FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PUBLIC MEETING ON BENEFIT-RISK FRAMEWORK IMPLEMENTATION

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P R O C E E D I N G S

WELCOME

MR. THOMPSON: All right. Good morning, everyone. I think there's a few more people out in the lobby. But we're going to go ahead and get started because we have a very full meeting today and we want to make sure we get through everything.

So, welcome to this public meeting on benefit-risk assessments in drug regulatory decision-making. My name is Graham Thompson. I'm from the Office of Strategic Programs in the Center for Drug Evaluation and Research, or CDER. So I'll be moderating the first session of this meeting.

Today's meeting is an opportunity for FDA and its public stakeholders to discuss a range of topics related to structured assessment of benefits and risks in drug and regulatory decision-making. It also satisfies an FDA commitment that's part of the fifth authorization of the Prescription Drug User Fee Act, PDUFA V, which wraps up at the end of this month.

As I mentioned, we have a very full agenda of topics to cover today. So I'll keep this brief. In a

few minutes, Dr. Rich Moscicki, who is CDER's deputy center director for science operations, will get us started with opening remarks. The format of the rest of the meeting will include a series of presentations on each topic, followed by a discussion and Q&A with panelists and audience members.

So the three topics we have here today are regulatory and industry experiences with benefit-risk assessment approaches; session two, approaches to incorporating patient perspectives into benefit-risk assessment; and, session three we're just calling special topics in benefit-risk assessment. It's sort of the more forward-looking session.

So following each session of presentations, we're going to have time for public comment. If you want to sign up to speak during the open public comment period, you can do so at the registration table outside. There is a limited capacity for people to speak. So if you'd like to do so, you should do so during the break.

I do want to mention, though, that in addition to this meeting and the public comment of this meeting,

we'll have a public docket that will remain open until November 18th, providing plenty of opportunity for anyone who wants to submit comments in more detail to do so.

I have a few housekeeping things to go through. But while I do that, can I have the topic one or session one presenters come up and take your seats up here? So while they make their way up here, a few housekeeping things.

We'll have a 15-minute break at 10:15 and then we'll have an hour lunch break at noon. We have food and beverages available for purchase at the kiosk outside. You can also preorder lunch, which I recommend because there's often a line at lunch time. And then, you can just pick up your lunch at noon.

Bathrooms are down the hall on the right. And if you're looking for Wi-Fi, you can find it at the front desk in the lobby. There's a simple password for public access. I'll now turn it over to Dr. Moscicki for opening remarks.

OPENING REMARKS

DR. MOSCICKI: Thank you, and I want to

welcome everyone to our session today. We're very excited to convene this meeting on benefit-risk assessment approaches.

As indeed Graham told you, we're wrapping up the fifth authorization of the Prescription Drug User Fee Act, or PDUFA V. So FDA does perform an essential public health task by ensuring that safe and effective human drugs and biologic products are available to improve the health of the American people.

In an executive quick summary of today's meeting, we're going to reflect on the progress in implementing the benefit-risk framework. We're going to hear perspectives from industry, other regulatory agencies and patient stakeholders. We're going to discuss the incorporation of patient perspective in benefit-risk assessment. And we'll explore the possible ways to further advance FDA's benefit-risk framework.

Okay. So that's the quick overview. Now, tell them what you're going to tell them. So let's delve juts slightly more. So FDA's primary mission is to determine whether a drug is safe and effective for

its intended use.

Now, the meaning of effectiveness is in fact specified by statute and I'll read this for you: "Evidence consisting of adequate, well-controlled investigations on the basis of which it could fairly and responsibly be concluded that a drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling."

Now, while that is prescribed, it does leave room for some flexibility in thinking and we have over the years under special circumstances certainly applied that kind of flexibility in our thinking around effectiveness.

Now, the meaning of safe, however, is not explicitly defined in the statutes or recognized or regulations. So recognizing that all drugs have some ability to cause adverse effects, the safety of a drug is assessed by determining whether or not the benefits outweigh those risks that will certainly exist. Thus, benefit-risk assessment is the basis of FDA's regulatory decisions in the premarket and post-market

review process.

Let's delve into that just a little bit more. Full assessment of a drug's benefits and risks is indeed a complicated task. So those assessments must be informed by science, medicine, policy and judgment in accordance with legal and regulatory standards. We also have to consider how well the outcomes that were studied translate then to meaningful clinical improvements in how a patient feels, functions or survives.

We also have to think about the safety signals that we might see during a premarketing program are often quite small because the number of patients studied may be too small. We must also consider how people will actually use the drugs once they're marketed.

So critically then, every decision must also be made in the context of the disease that is being treated, how severe is that disease and how well do available treatments currently meet the patient's needs.

So all of that comes into benefit-risk

decision-making. Now, that decision-making has always been at the heart of what we do. But it is when stakeholders started asking for greater clarity and transparency of FDA's benefit-risk assessment in human drug review that we initiated back in 2009 a structured approach for drug benefit-risk assessments that could serve also as a template for product reviews, as well as a vehicle for explaining the basis of FDA's regulatory decisions in drug approvals.

So PDUFA V commitments included this development and implementation of the framework and also §905 of the FDA Safety and Innovation Act required FDA to implement a structured benefit-risk framework in the new drug approval process.

So this meeting allows us to reflect on what FDA has accomplished and learned over the past five years in developing and using more structured approaches to assess and communicate benefit-risk assessments.

We have determined over all that time and all that consideration that we must use a framework and not a simple formula for the determination of benefit-risk.

FDA's efforts to implement a structured framework for benefit-risk assessment has also coincided with efforts elsewhere at other regulatory agencies as well as in the regulated industry. So today, we will also hear from international regulators as well as representatives from pharmaceutical developers.

The two top -- excuse me. The 2012 PDUFA V letter, under the heading of benefit-risk assessment, also included an FDA commitment that launched FDA's patient-focused drug development initiative, or PFDD, as we call it around here. This allows more systematic and effective approaches to enable patients to have a meaningful engagement and input into drug development and drug review.

This meeting will also give us a chance to reflect on FDA's and stakeholders' experiences and key learnings in this important and evolving area. We have now had I believe 25 of the PFDD meetings. Theresa is nodding her head. So I think the number is about right. And they've been quite successful in giving FDA insight into patient views on the burden of disease, the adequacy of current therapies, desired outcomes for

benefit and tolerance of risk.

We now need to move forward with broader methods to gain input on so many more diseases than what 25 meetings could provide.

And finally, this meeting recognizes that there are even more opportunities in the years ahead in terms of exploring more formal quantitative and semi-quantitative approaches to benefit-risk assessment, rooted in the decision science disciplines that may add further value to FDA's most challenging regulatory decisions.

So we wish to continue to strengthen the benefit-risk framework as a communication tool to interested patients, healthcare providers and others in the public health and hence, I believe we're in for a very good day. Welcome.

(Applause.)

SESSION 1: REGULATORY AND INDUSTRY EXPERIENCES WITH BENEFIT-RISK ASSESSMENT APPROACHES

MR. THOMPSON: All right. Thank you very much, Dr. Moscicki. So now, we'll move into the first session of presentations and discussion focusing on

regulatory and industry experiences. We're going to kick off this session with some presentations from my FDA colleagues.

A quick reminder for all presenters, including ones later in the day, we have a very full agenda. So please make sure you stick to the 15-minute limit. And if I need to interrupt you, I'll do so. I'll turn the mic over now to Sara Eggers, from CDER's Office of Strategic Programs.

OVERVIEW OF FDA'S BENEFIT-RISK FRAMEWORK AND ITS IMPLEMENTATION

DR. EGGERS: Maybe I'll go long just to see if you'll stick to this. Do I -- okay. Good morning, everyone. I'm Sara Eggers, in CDER's Office of Strategic Programs on the decision support and analysis team. I'm very excited to talk about the benefit-risk framework, building on what Dr. Moscicki has said, and to talk about its implementation, more of the nuts and bolts. All of my comments are mine alone.

As Dr. Moscicki mentioned, that for a drug or biologic to be approved for marketing, FDA must determine that the drug is effective and that its

benefits outweigh its risks to the population.

And as he also mentioned, this is a very complicated assessment that is informed by an extensive body of evidence on the underlying treatment -- underlying condition and treatment options, uncertainty about how the clinical trial extrapolates to the real world setting, what is -- what are tools available to help manage or mitigate those risks, what is the dynamic nature of the drug's life cycle beyond marketing and then, of course, the laws and regulations which guide our decision-making.

And so, in 2009, we did begin the effort to develop a structured benefit-risk framework for human drug review. I'm bringing in some of the historical context to set the stage of what we were thinking and saying and doing five years ago when PDUFA V kicked off.

Our goals were twofold for the benefit-risk framework: one, externally better communicate the reasoning behind CDER's decision; and two, there was an internal goal to ensure that the big picture is kept in mind throughout these complex detailed reviews.

So at the time, FDA determined that a structured qualitative approach best fits its drug regulatory decision-making. There was a lot of talk about what the best path forward was.

And at that time, it was clear that the reality is that benefit-risk assessment is a qualitative exercise that's grounded in the quantification of a lot of data. And what we needed to focus on was how to more rigorously communicate the basis for those decisions in words.

The framework, though, we wanted to make sure was flexible to accommodate more complex supporting analyses that could aid expert judgment if the time -- if that was useful.

So this is a picture of the benefit-risk framework. I think you'll see it throughout the day. There are a few enhancements to this figure that, I apologize to all of the other folks who have -- who have this figure in. These are changes that we made in just the last rollout of the framework just to clarify what you're looking at here.

So you're looking at the shell of the

framework that has shown here on the bottom the dimensions -- the benefit-risk dimensions, the analysis condition current treatment options, which sets the context, and then the benefit-risk and risk management, which looks at the product that is the subject of the review.

The table asks for two types of inputs to each of those dimensions. What are the facts? What's the evidence and what are the data gaps? What are the uncertainties? And then, what do you make of those data? What are the conclusions? And what are the reasons, what are the implications on the regulatory recommendation or decision?

And then, what's shown here at the top of the framework, although you complete it last, is the benefit-risk summary and assessment or the benefit-risk integrated assessment, which is tying all the pieces together into an overall summary of the decision.

Okay. The framework has guiding questions to help account for the important considerations. I've put a few of these up as samples about the analysis of condition, really looking at what is the unmet need in

the population by looking at the severity across demographics.

Are there some demographics that are -- that have a greater progression of disease or have greater impacts on functioning or quality of life? The current treatment options wants to know how well is that population's medical need being met by those currently available therapies.

When we get into benefit, we are trying to look at the data, but also at the meaning of those data, the clinical relevance of the endpoints that were used to measure the drug's benefit and how clinically meaningful the efficacy results have been shown to the overall population or to any particular subset.

In risk, we're looking at characterizing the safety concerns that are identified, looking at the safety profile in the post-marketing setting and then looking at uncertainties and how the implications of those uncertainties -- what are the concerns that come out of those uncertainties.

And then, risk management asks what can be done and what would be a reasonable -- an appropriate

strategy to manage the risks.

Okay. What we specified in -- early on in PDUFA V was that the desired benefits -- what we wanted the benefit-risk framework to do was to provide a clear and concise snapshot of the decision, highlight the aspects of the important data most relevant to the decision, faithfully capture the team's careful deliberations and do so transparently, including differences of opinion and then provide an accessible record for reference and future reviews.

As part of our commitments in PDUFA V, we committed to publishing an implementation plan and, as part of that plan, to revise the templates that guide the reviews of our market -- of our applications, conduct two workshops, develop an evaluation plan.

And then, we also included here, as Dr. Moscicki mentioned, the 20 -- at least 20 public meetings for patient-focused drug development. I'm not going to focus on that. Dr. Mullin will do so later in the day.

Okay. So here is an overview of what we have accomplished in PDUFA V to address these commitments.

We published a plan in February of 2013. In May of 2013, CBER, the Center for Biologics, integrated the benefit-risk framework into the review templates for the original BLAs and BLA efficacy supplements.

In September of 2013, CDER established a benefit-risk implementation committee and began the process to revise the review and memo templates. In February and then May, because there was a snow cancellation, if you may remember, of 2014, we had our first public meeting that really focused on characterizing uncertainty in the assessment of benefits and risks.

In March of 2015, CDER was ready to implement our new template into the review process and that's when you start to see frameworks coming out at the time for new molecular entities and original BLAs submitted after March of 2015.

In September of that year, we initiated our evaluation and then, in September of this year, we completed that evaluation project and Valerie Overton will summarize the key findings of that. We have just broadened the implantation of our templates to a wider

set of new drug applications. And we are now conducting our second meeting today.

I just want to show you, we always show the blank framework. And now, we can show a completed framework. So it's not just a blank table. This is an example of one, a snippet of one. You can find these in the reviews when you -- for new molecular entities and original BLAs at Drugs @ FDA, if it's been approved since -- in the 2016 range. You can look for the frameworks.

How CDER has implemented the frameworks is by having a framework at each level of clinical review starting with the primary review, the cross-discipline team lead, division director and office director where the office director is considered the agency's final framework.

And then, now moving ahead into PDUFA VI, we're very excited. That should begin in a few weeks now. What we've specified in the letter is to update the plan for implementing structured benefit-risk assessment into the PDUFA VI timeframe through 2022.

That seems hard to say, 2022, but it's going

to come up quickly -- to draft guidance that really looks at how to articulate FDA's decision-making framework in context throughout the life cycle, discuss appropriate interactions with sponsors during drug development to really understand how the therapeutic context is coming into play and to discuss appropriate approaches to communicate to the public FDA's thinking on benefit-risk such as during advisory committee meetings.

We have another evaluation coming up that will use what we've learned in this current evaluation in PDUFA V as our baseline. And we will revise manuals and standard operating procedures, MAPs and SOPs as we call them, to incorporate the framework.

There are other opportunities that we can continue to explore and to try to move forward, continue to make benefit-risk frameworks more easily accessible on the FDA website, to explore the use of more technical approaches within the qualitative framework to inform benefit-risk assessment in targeted cases like Dr. Moscicki mentioned.

Examples could be structured techniques to

characterize uncertainties inherent to the assessment. We find that it is often what makes these decisions challenging before you ever get to the benefit-risk tradeoffs is to truly understand what the uncertainties are when you are getting at the limit of what more data you can have in place to make this decision. What are those uncertainties and how do they really play into our decision-making?

And then, as we will talk today and then continue to talk into the future, more effectively incorporate the patient experience data into drug development evaluation and benefit-risk assessment. Again, there's a whole session on that this afternoon to talk about that.

And with that, I will complete my presentation. There are a lot of acknowledgements. This is a huge undertaking at FDA. Theresa Mullin and Patrick Frey have been working on this since the beginning, since 2009 or maybe even a little before.

There's our decision support and analysis team, which is those of us that are sitting up here who are helping to run the meeting. And then, there's a

benefit-risk implementation committee who has been many medical officers who have to -- who have to work on what we give them for the benefit-risk framework. And they've been a tremendous guidance throughout this process. And of course we've had a lot of buy-in and support and engagement with CDER and CBER leadership.

So I thank you very much for your time and I look forward to the rest of the presentations.

(Applause.)

MR. THOMPSON: All right. Thank you very much, Sara. We'll turn it over to Mary. Do you want to take it?

REGULATORY CASE STUDY

DR. HAI: Good morning. I'm Mary Thanh Hai. I'm the deputy director in the Office of Drug Evaluation II in CDER. And I was invited to provide to you a cause study of one of CDER's benefit-risk framework. And I'm going to do this by actually doing an overview of the benefit-risk framework from its concept to present day because how did we get to where we are today, we kind of have to discuss a little bit about the beginning.

The concept case will be actually of liraglutide and then the present-day case study will be on nusinersen. You saw this slide in Sara's presentation. I'm going to refer back to this slide to kind of keep us focused on what CDER's goals were when this framework was implemented.

Again, it's better communication, keeping the big picture, that the determination was that this was going to be a qualitative approach. Embedded in it would be quantitative analyses as well.

And while we today have a structured benefit-risk framework, we have to keep in mind that benefit-risk assessments had always been done. So it's not like this is a novel concept. But how it was done is what the team needed to understand before kicking this off.

So in about 2009, the FDA team that Sara had actually already pointed out in her acknowledgement slide actually undertook the task of interviewing a lot of FDA reviewers across several applications which were approved or not approved to understand what were the thought processes in the benefit-risk assessment that

led to those regulatory decisions because there was going to be a foundation from which they were going to build on. And one of those applications, or one of the teams that they interviewed actually happened to be the one that reviewed liraglutide.

And I picked this one for a variety of reasons. One, I'm familiar with it because I was the division director overseeing this NDA review at the time. Liraglutide is a GLP-1 receptor agonist approved for the treatment of type 2 diabetes. It was not the first in class approved. There was actually one that was approved before it.

But what made this one different from the other one is that it was a longer duration of action and it was approved in 2010, again before the implementation of benefit-risk framework.

I also chose this one because it was an extremely challenging regulatory decision. While the drug itself was very effective or was effective at lowering hemoglobin Alc, which is an established measure of glycemic control for diabetes, that benefit was counterbalanced by some safety concerns.

And what's interesting is that these were not safety concerns where you could put an incidence rate on. You couldn't say that it was 1 in 10,000 patients would develop x, y or z.

There was a lot of uncertainty around these safety concerns and they included a concern for cancer, a type of thyroid cancer called medullary thyroid cancer, that was observed in animal models, not in the clinical studies.

On top of that, this application was submitted right before the agency published a guidance on cardiovascular safety assessments of all type 2 diabetes therapies. Some of you may recall the agency was under quite a bit of challenge about adequate safety assessments of a lot of therapies, particularly diabetes drugs.

And so, the benefit and risk of this application was taken before a public advisory committee and thinking that the expert -- the panel of experts could also help us in this. But they actually made it challenging for us because they rendered a split vote, six to six, for or against approval.

To top that off, we had two experts on the panel who were thyroid experts and they had different views on whether or not the risk of medullary thyroid cancer was real.

So no surprise, the benefit-risk conclusion for this application differed within the agency. There were some staff members who didn't recommend that this could be approved and some who actually recommended it should be approved. As you know, it ultimately did get approved.

And there was a benefit-risk assessment outlining why that was the case and it existed throughout several memos.

So from the public perspective, if you want to read the agency's thinking of how we got to this decision, you could go to the 17 pages of the office director, the 45 pages of the division director's memo, the 63 pages of the cost discipline team members' memo, over 500 pages of the medical officer's memo, over 700 pages of the pharm tox reviewer and also, on top of that, you could also read the advisory committee transcript.

I think you get the picture here. It wasn't entirely transparent. It's available to the public. But it wasn't easily accessible. And I have to admit, when the team came by to interview us, I was a little bit, well, we do our -- we already do benefit-risk assessment.

Why do we have to do this? I understand why we have to do this. Well, we actually did have a much more succinct benefit-risk assessment that was conveyed to the public in the form of a four-page New England Journal perspective published by the office director and myself two months after its approval.

And that would have been nice to be actually part of the action package because five years, 10 years down the road, anybody who is interested in liraglutide's approval and they go to Drugs @ FDA, they won't see that. That's not part of the administrative record.

So where are we today then? Well, as you heard, in 2009 was when they kicked off this trying to establish the framework. And so, that was under PDUFA IV and it was rolled out in stages throughout PDUFA V.

And last year, the agency received 41 applications for new molecular entities. They received and filed 41 applications for new molecular entities, of which 22 were approved.

Now, all 41 had benefit-risk frameworks in their reviews. But only 22 would be available to the public because only the approved ones are available to the public. And these 22 approvals were actually quite unique.

They differed from past approvals because the majority of them actually had some component of the expedited programs that FDA would do -- expedited programs including things such as fast-track designation, breakthrough designation, priority review or accelerated approval.

A large proportion of these applications were also for rare diseases. These are your orphan indications. And those are always challenging because by the nature of these conditions, you have small numbers of patients affected, widely dispersed geographically.

So the kind of data that come out of these

programs are not as broad as your typical gold standard large placebo-controlled, double blind, multicenter, clinical outcomes trial. You have to be very creative and flexible as to what you would accept as substantial evidence for effectiveness and for safety.

Now, I actually had an opportunity to review all 22 benefit-risk frameworks in 2016 because I had to give a presentation earlier in the year. For purposes of this presentation, I'm only going to present that on nusinersen. This application was approved in December of 2016 and it had already gone -- we had already gone through one public workshop. We've had two revisions to the reviewer template.

There was already an externa evaluation of the benefit-risk framework implementation. And the signatory was -- I think he's also a member of the BRC and so there was a lot of knowledge as to how CDER's benefit-risk framework should be implemented.

I focused on -- well, I read all of the benefit-risk framework. I'm going to call it BRF and hopefully I won't say BFF. I focused -- I focused on all the BRFs. But for purposes of this presentation,

I'm only going to discuss the office directors and the division directors. And what I noticed immediately was that these BRFs are encountered first in their reviews.

And these are posted within 30 days of approval of an NME. On top of that, these BRFs were four and five pages respectively, not your 72, 68, 400-plus. You didn't have to wade through a lot of material to get to the heart of the matter.

I also selected the -- well, there were two reasons why I selected nusinersen. The first one was that this was not in my office. So I knew absolutely nothing about the discussion, development plan, the clinical trials, even the condition.

And so, I was clearly an outsider reviewing this benefit-risk framework, which really is what this is meant to be, communication to the public.

Now, I acknowledge I have some advantages because I can navigate Drugs @ FDA. I can look at reviews that are not necessarily available to the public. And I did have a conversation with the signatory on it. But for purposes of this presentation, I'm only focusing on what's available to

the public.

And I also thought that it captured very well the concepts that Sara had mentioned in this slide here, better communicate the rationale behind CDER's decision, ensuring that the big picture is kept in mind.

And so, what did I learn about this application by just looking at the benefit-risk framework? Well, if you recall that grid, the first row is the analysis of condition.

So what did I learn about the analysis of condition? Spinal muscular atrophy, or SMA, is a rare and serious disease resulting from a deletion or mutation of the SMN-1 gene which codes for a protein that helps maintain motor neurons.

These patients have severe motor disabilities and there's clinical heterogeneity. I'll get to that in a moment. There's also a related gene called SMN-2 that can also produce this protein that can compensate for the SMN-1 defect.

But most copies of the SMN-2 pre-mRNA -- so DNA, as this goes through the process of transcription

and translation to production of the protein, going to the pre-mRNA, it actually lacks a critical portion of genetic material called exon7 which will lead to a shortened protein that is easily degraded.

So it's not a functional protein. But the more copies of SMN-2 hopefully you'll have more ability to produce more of the functional protein and that's what speaks to the clinical heterogeneity in SMA.

If you have only one copy, death shortly -- occurs shortly after birth. Two copies, these patients are unable to sit unassisted and survival is typically under two years. If you have more than four copies, you can have normal life expectancy and mild muscle weakness.

The second row in the grid talks about the treatment options. And I immediately learned that there are no approved therapies for SMA. There's just supportive care. Those first two rows, by the way, are not describing anything inherent to the drug application. It's just talking about the disease.

If you go and look at any benefit-risk framework, that's what it's focusing on. It's not

until you get to the third, fourth and fifth row that it becomes particularly to the application. And so, in the third row, now we talk about benefit. So now, we talk about nusinersen. It's an antisense oligonucleotide that would bind to the pre-mRNA and it will allow the inclusion of that genetic material, exon7, for the production of functional protein.

What was -- how was benefit established? It was established based on an interim analysis of a control trial in patients with the infantile onset SMA-2. So these patients actually inherited two copies of SMN-2. Remember, these are patients who are unable to sit without assistance. I think that was what it was.

And the finding, it was at 40 percent of these patients on drug met a motor milestone development responder definition versus nobody in the sham control arm, highly statically significant and impressive enough that the trial was stopped early and all patients were switched to active treatment.

In addition, there were other data that supported the benefit finding. There were topline results from another control trial in patients with

later onset of SMA. These patients had inherited three copies. And this trial was also stopped early based on a highly statistically significant effect on a functional motor scale assessment, highly statistically significant with a lot of zeroes behind that decimal point.

And then, there was a third set of data, open label trials looking at the less severe form of SMA, which also suggests that there was a benefit in those patients.

Oh, I want to point out that for the topline results there, that's what FDA -- the review team received was the topliner results. They actually did not get the datasets to review.

It was considered so impressive that it wasn't something that they felt was -- they were willing to accept those results as opposing to prolonging the review, waiting for the datasets to come in and review. And Bob Temple is in the office -- in the audience, so he can correct me if I got that one wrong.

Safety data, so this is the fourth row now of the grid, talks about risk. As I mentioned earlier,

the orphan indications are always very challenging with respect to data supporting safety and efficacy. Safety, there's just a limited number of patients exposed.

For this application, there was some leveraging of what we already knew from other therapies in this drug class and those concerns included thrombocytopenia, bleeding, proteinuria and effects on growth.

I don't know to what extent that was actually observed in this program. I don't think there was much observed because it was such a small database. But the team felt that these concerns here could be managed under risk management through labeling. There was no REMs associated with the approval of this product.

So in the end, there was a favorable benefit-risk assessment for nusinersen. The signatory authority did specifically say that there were characteristics of this program of an adequate and well-controlled study that provided substantial evidence of effectiveness.

And what you also saw in this application

review was that it was a rare disease, unmet medical need and you saw regulatory flexibility played out here. There was a willingness to accept interim analyses from a pivotal trial, topline data without the data analyses, datasets in hand, open label studies.

And this program -- this application actually received a full approval not just for the patients that were studied in that pivotal trial, but all of the patients with the diagnosis of SMA in pediatric and adults.

So finally, I want to go back again to this particular slide from Dr. Eggers' presentation to talk about qualitative versus quantitative. There's been a lot of discussion about that throughout the process of designing CDER's benefit-risk framework.

And you know, clearly it was decided that it was going to be a qualitative approach. But embedded in it would be quantitative analyses of various data. And this is the reason why I wanted to pick nusinersen because I felt that the office director's benefit-risk framework did actually capture this.

With respect to the quantitative, you already

heard about the evidence for benefit. Clearly it was statistically significant and an endpoint where patients were being evaluated with respect to certain milestones for their stage of development, 21 patients out of 51 versus none out of 27, 41 percent over zero percent, highly statically significant.

However, the qualitative analysis puts these numbers into a clinical context. And that's what I highlight here. These are all drawn from his benefit-risk framework, again four pages long. And he states in considering the benefit, it is important to convey realistic expectations with respect to the effect size.

Although a 41 percent response rate compared to zero sounds impressive on face, it means that 41 percent of nusinersen-treated patients had some response.

Although the response was clearly important, perhaps life-changing in a few cases, 6 percent of patients gained the ability to sit without assistance, a feat that almost never occurs in individuals with only two copies of the SMA-2 gene. The majority of patients had a modest response or no response at all.

He goes on to say, but it should be kept in mind that the vast majority of patients did not achieve this milestone and no patient became able to stand unassisted or walk. One patient was able to stand with assistance. Thus, although the drug represents an unprecedented advance for individuals with SMA, it does not represent a cure.

I didn't take these words here as intended to deflate our expectations of what this therapy could offer. In fact, it was approved and it wasn't withheld. It was approved for the entire spectrum of SMA.

But what these words conveyed to me was that this is benefit-risk. There was a regulatory decision with respect to benefit versus risk. But that assessment goes beyond the regulatory decision.

This is about communicating to the care provider, the physician, the patient because in a patient where there's no response, as he had pointed out that for some of these patients there was no response at all, that means that there's no benefit. And that's where the risk side of the drug tips the

scale.

So in conclusion, CDER's structured benefit-risk framework over the past five years has actually led to more transparency in regulatory decision-making process, balanced communication to the public of what to expect from the approved therapy.

And this last bullet here, I just -- you know, it's something that I always want to remind people, that while we strive for transparency in our regulatory decision, the benefit-risk framework is only available to those applications that are approved.

As you recall, the applications that were submitted and filed, they all had benefit-risk framework. But only 22 were available to the public. So when a decision is made that something is not ready for primetime, that benefit-risk assessment is not available for people to understand why. Thank you.

(Applause.)

MR. THOMPSON: Thank you very much, Mary. Now, we're going to hear from Valerie Overton from the Eastern Research Group. They're going to discuss their assessment of the benefit-risk framework.

ASSESSING THE IMPLEMENTATION OF FDA'S BENEFIT-RISK FRAMEWORK

MS. OVERTON: Thank you. So my name again is Valerie Overton. I'm with Eastern Research Group, the contractor that conducted the independent assessment of the FDA's implementation of the benefit-risk framework.

So the purpose of the assessment was twofold. One was to fulfill FDA's commitment under PDUFA V to conduct such an assessment.

And more importantly, the purpose of the assessment of the implementation of the benefit-risk framework was to examine the usefulness of the framework in facilitating consistent, balanced considerations of benefit-risks -- of benefits and risks, training, communications and decision-making within FDA and communication of benefits and risks to external audiences.

So as others have described, there's really both internal and external purposes for the benefit-risk framework and we were looking at both.

So the approach that we took to our assessment was to define a cohort of novel drug applications.

They were 43 applications that FDA received between March 1st of 2015 and February 29th of 2016. And so, we looked at those applications that received a first cycle action, whether it was approval or non-approval.

We reviewed all of the benefit-risk frameworks in the review documents for those applications. As Sara mentioned, in CDER, there are four review documents that are produced that included a benefit-risk framework. And in CBER, for biologics, there is one primary benefit-risk framework that's produced.

So we reviewed all of the benefit-risk frameworks and all of the review documents for these 43 applications, looking at the content, format, clarity and understandability of those benefit-risk frameworks. We also conducted interviews with both internal and external stakeholders for the benefit-risk framework.

So internally within FDA, we interviewed FDA staff, primarily those involved with the reviews at different levels ranging from medical officers, the primary clinical reviewers, the cross-discipline team leads, the division directors, the office directors and so forth. We interviewed 104 staff for those 43

applications.

We also interviewed applicants, the representatives from the drug developers who submitted the applications for drug or biologic approval. So we interviewed 45 representatives from applicant companies.

We also interviewed 154 other external stakeholders. Those included patients and care partners, health organizations and healthcare providers, including primary care physicians and nurse practitioners and specialists for the therapeutic areas that the products were relevant to.

So we interviewed a lot of people, both internally and externally, to get feedback about the content, format, clarity, understandability and the usefulness of the benefit-risk framework in communicating FDA's reasoning for making the decision that they did on these products.

So I'm going to talk about some highlights of the results that we found. We have a tremendous amount of data. So I'm going to kind of skim the surface of the data that we generated. So first, looking at FDA,

of the hundred or so FDA staff that we interviewed, about 75 percent said that the benefit-risk framework is useful in one or more ways.

So those include organizing their thinking about benefits and risks, reminding the reviewers to cover key points in their benefit-risk assessment, training newer reviewers in how to think about weighing benefits and risks and documenting their thinking and communicating their benefit-risk analysis in a concise standardized fashion up the review chain so that each level of the review process would receive a concise discussion of the thinking for the benefit-risk analysis. And that would also be available for others in management or elsewhere within FDA.

So there was a lot of positive comment, particularly from the newer reviewers, who felt that this was particularly useful in helping them understand kind of how to present their thinking and cover the key points in a stepwise, logical, concise fashion.

About 25 percent of the FDA staff who we interviewed felt that the purpose of the benefit-risk framework was not really for internal benefit, but for

external benefit. So their feeling was that the purpose of them spending their time working on these benefit-risk assessments was really to communicate the analysis and the reasoning behind their regulatory decisions externally rather than internally.

So among the applicants who we talked with, the applicants were overwhelmingly positive in their responses to our questions about the benefit-risk framework.

They overwhelmingly felt that the benefit-risk framework is useful. They cited quite a number of ways in which it could be useful to them, both currently and potentially in the future as more benefit-risk assessments -- benefit-risk frameworks are developed for more products over time.

So first, in terms of the specific drug product or biologic that the framework -- that an individual framework was describing, they found -- the applicants found that the benefit-risk framework was useful in verifying that FDA's -- at least from the FDA's documentation, that FDA's experience aligned with their own experience of the review.

So they were appreciative of seeing in writing, in a concise fashion, that the way FDA portrayed the review in terms of what they thought about, how they thought about it, what the discussions were, reflected their own communications with FDA during the review process.

They also said that they find the benefit-risk framework to be useful in communicating a summary of the product review to management and partners because it is such a concise way of presenting FDA's perspective on the drug application. It was a useful way of passing that along to other stakeholders to the applicant such as the upper management and investors and other kinds of partners.

They also thought, interestingly, that seeing the benefit-risk framework not only for their own products, but for other products, enabled them to glean insights about FDA's thinking, what FDA's concerns were, what FDA thought of as kind of the key factors in their decision so that they could apply those lessons learned and that thinking to their own development programs to ensure that those development programs are

as effective and focused as possible to generate the results that will be useful to FDA in making decisions on future products.

So the thinking that was represented in the benefit-risk framework helped them to think about their applications for future products and also to focus their post-marketing activities for products that were approved to ensure that they reflect FDA's concerns as documented in the benefit-risk frameworks.

I think that one of the presenters already mentioned that currently the benefit-risk framework is available to the public for applications for drug products that are actually approved.

Applicants generally responses that they would like to see the benefit-risk framework for non-approved applications as well and that they would like to see those privately, not published on FDA's website for obvious reasons.

So in terms of the other external stakeholders, these are the patients and care partners, the health organizations and physicians, including general practitioners and specialists. These external

stakeholders also overwhelmingly expressed positive opinions about the benefit-risk framework.

They stated that the benefit-risk framework is useful to them also in several ways. One is that they greatly appreciated the transparency that the benefit-risk framework provides in understanding FDA's reasoning and decision-making about particular products.

In terms of the product for which an individual benefit-risk framework was constructed, they also said that the benefit-risk framework helped them understand the therapy better and decide whether to use or to prescribe it, depending on whether they're a patient or a physician, and also to interpret and share information about the new therapies.

There are -- in addition to physicians, the health organizations are often interpreters of information that is published by FDA and others. And even patients often are advocates and support group leaders and things like that who also help interpret and share information and the benefit-risk framework they said is very useful for those purposes as well.

For those involved in policy, advocacy and research, they said that the benefit-risk framework is helpful in that fashion also, similar to what the applicants said in that the lessons learned about the thinking of FDA about these products enabled them to glean insights that would help shape their programs for the future.

And also, many of these external stakeholders said that they appreciated seeing the opinion of credible, objective experts at FDA. A lot of them pointed out that when they read information about new products, they're seeing -- you know, some of them will actually go to the literature and look at FDA's website and so forth for the more technical and the lengthy explanations of the product.

But it's rare to find a concise explanation of how and why a particular product was approved. And it's even rarer to find that from an author that has the credibility and the objectivity that FDA has. And so, they were very appreciative of having that available to them as well.

So I think Sara mentioned that the agency is

planning on expanding the benefit-risk framework to other types of applications and the external stakeholders also suggested that that be the case so that the benefit-risk frameworks are available for efficacy supplements and just more types of applications in general, not just the new molecular entity NDAs and original BLAs.

They also stated that they would like the benefit-risk frameworks to be easier to find. So currently the benefit-risk frameworks are inside the review documents that FDA posts on its website for drugs that have been approved.

And almost all of the folks that we interviewed indicated that they would not have known to look there to find the benefit-risk assessment. And so, what they suggested is that FDA publish these as standalone documents that are easily searchable and findable through Google or through a search of the FDA website.

So as I mentioned, we looked at content, format, clarity and understandability as well. So in terms of content, these comments reflect the opinions

of folks that we interviewed across all of the groups, FDA interviewees, the applicants and the other external stakeholders as well such as patients, health organizations and physicians.

So about the benefit-risk frameworks that they read, the interviewees said that the main topics are the correct ones to cover so that in terms of having in the table the analysis of condition, the current therapies, the benefits, risks, risk management and then the integrated summary at the top, that those represent the topics that are most useful for them.

They also said for those who saw the full review documents, that the content accurately -- and the benefit-risk framework accurately reflects the content in the full review document. And in terms of suggestions for improvement, they also indicated that the consistency in the level of detail in the benefit-risk frameworks could be improved across benefit-risk frameworks for different drugs, that in some cases, benefit-risk frameworks were at a more summary level and were, say, one or two or three pages.

And in other cases, the level of detail was

quite greater than that and that then resulting in frameworks that could be 10, 15, 20 pages long. And so, improving the consistency in the level of detail would be useful as a reader of the benefit-risk framework.

When you interview about 300 people, you're bound to get a lot of different opinions. And so, we did. So we had all sorts of opinions about the content of the framework. What I described above is kind of the large majority of people said those things.

In terms of less common opinions, there were people who thought that the benefit-risk framework has too many details and redundancies. There were also those who said that the benefit-risk framework should have more details and more kinds of content.

Particularly there were people who thought that it would be useful for the benefit-risk framework to include more patient perspectives, particularly from the patient-focused drug development meetings, although those who brought that up recognized that at the time that they were reading the benefit-risk framework for a particular product, the patient-focused drug

development meetings were just then happening.

And so, it was more of a wish that for the future that the benefit-risk frameworks reflect those discussions, acknowledging that it would be difficult for the benefit-risk frameworks to include the results of those kinds of discussions before they had really matured.

Some folks also said that the benefit-risk frameworks could include more clinical considerations, more review issues, particularly to identify when there were differences in opinion among reviewers. And there were a small number of people who also felt that the benefit-risk framework could contain more quantitative information and perhaps even focus on quantitative benefit-risk assessment rather than a more qualitative approach. That was a very small number of people out of the 300 however.

MR. THOMPSON: Sorry, Valerie. Can you move to some concluding thoughts?

MS. OVERTON: Yes.

MR. THOMPSON: We're running low on time. Thanks.

MS. OVERTON: Okay. So in terms of the format, again, people were very appreciative of the format. They felt that it was very effective in organizing and presenting content and that the format itself made the content more digestible and easy to follow.

As I said, there are a lot of different kinds of opinions as well. Most people thought that the benefit-risk frameworks were clear and understandable and even the non-technical readers who sometimes had to read the benefit-risk framework a couple of times or more to understand it nevertheless felt that it was worth the effort and that they could understand it with a little bit of effort.

So our findings, the benefit-risk framework was successful in communicating the reasoning behind FDA's regulatory decisions, useful and worthwhile to the various audiences and were clear and understandable to most audiences.

In terms of potential refinements, folks were interested in having benefit-risk frameworks for more types of applications, to have them be more easily

findable as easy-to-find, standalone documents, improve the consistency and the level of detail and to refine the template in ways to enhance the presentation of content.

And these are not kind of foundational changes, but rather kind of tweaks and refinements to, for example, add a concise, well-structured conclusion statement to bring everything together in one or two sentences and some kind of formatting, for example, bold, lead-in headings in the narrative summary at the top and so forth.

So overall, the results were quite positive and the feedback was quite constructive and kind of focusing in on the more minor rather than foundational ways that the benefit-risk framework could be enhanced to further improve its usefulness to the various audiences. Thank you.

(Applause.)

MR. THOMPSON: Thank you very much. A reminder for all the audience, you can save any questions for any of our presenters for the panel discussion which will be at the end of this session.

And now, we'll welcome Patrick Frey, who will talk a little bit about ICH efforts with benefit-risk.

INTERNATIONAL COUNCIL FOR HARMONIZATION

MR. FREY: All right. Morning, everybody. I'm happy to come to you this morning to talk to you about what we did at ICH in the context of a benefit-risk assessment over about a timespan of a year-and-a-half. So a pretty quick turnaround for ICH standards.

Some of the background for this presentation and for kind of like that was the context of our discussions at ICH had to do with the fact that regulatory authorities -- we approve drugs that are demonstrated to be safe and effective for human use.

However, while effective and effectiveness is defined in statute, determining whether or not a drug is safe is not defined. But it's historically been interpreted as the benefits outweighing the risks of the drug. So recognizing that the benefit-risk assessment is the fundamental basis for regulatory decision-making, in the last several years what we've seen is an effort across the ecosystem of drug development, whether it's regulators, companies,

patient perspectives and those groups being incorporated as well to provide more structure to the benefit-risk assessment continues to be an important topic.

We had general guidance in M4E revision one, which has been replaced now by our new version. That general guidance, I have a slide later showing exactly how general it was. But it gives some indication about what the expected content was of §2.5.6, which is entitled benefits and risk conclusions.

But there wasn't really additional guidance to aid industry in further structuring that benefit-risk assessment. So the discussion in the field of benefit-risk assessment kind of was moving in a certain direction. And what we did at ICH was recognize that the ICH documents needed to keep up with that.

So here is the M4E R1 that was recently replaced. It's basically three-quarters of a page, and with credit to Francesco Pignatti, from EMA, he did a word cloud of the previous version of benefit in the §2.5.6 and you see that there and you see which words, particular word shows up most prominently. I'll come

back to this later in my presentation.

So here's the representation on our expert working group at ICH. We began meeting in the fall of 2014, I think it was, and then finished in the early summer of 2016, so pretty broad representation across regulators, industry and other health authorities.

So when we first began meeting in the fall of 2014, we pretty quickly reached consensus on general principles for what a revised guideline should look like.

We had also done, at least at FDA, an analysis going into the start of those discussions to show the group in an anonymized fashion just the level of variation that we were seeing and what companies were doing with §2.5.6.

And it was pretty extreme in terms of some companies who are often part of the benefit-risk structured framework conversation had created their own structured framework within §2.5.6 and that would wind up being several pages in their CTD. And then, other companies, you would see a minimal treatment of §2.5.6. It might only be half a page.

So we reached an agreement on these principles that the revised guidelines should be pretty concise and not prescriptive. You know, we had a focus on suggesting elements for consideration by an applicant in the benefit-risk assessment, but tried to avoid a lot of language using the word should.

We felt that the new guidelines should not specify methods for the benefit-risk assessment nor methods for how a regulator should think about the benefit-risk assessment to kind of maintain that autonomy on behalf of the regulator and recognizing that other ICH guidelines speak about benefits and risks, we did have a principle and a focus that the new §2.5.6 should be consistent with those other documents, which was a little bit of a challenge.

We also reached consensus on principles for what a submitted §2.5.6 should look like from industry, that it should represent the thought process that the applicant went through in weighing the benefits and risks, communicating that to the regulator and it should be really an analysis of information that already exists elsewhere in the CTD, not a presentation

of new information.

So this is the revised structure that some of you are probably familiar with, seeing as ICH posted our revised guideline I think a little more than a year ago and I think we recently put out our own guidance to implement the ICH guideline. I'll talk a little bit more about the specific changes in each of these sections.

So for the new §2.5.6.1, the therapeutic context, this section is very consistent with, you know, how at least FDA structures the benefit-risk framework here and as well as other -- how other regulators think about the benefit-risk framework, that these decisions are not made in a vacuum.

There is some context that we have here that kind of frames how we weigh the benefits and risks against each other. And with the therapeutic context really including two areas, information about the disease and information about the current therapies that are used to treat patients in that particular population.

Consistent with other sections in the revised

2.5.6, we asked that any limitations or uncertainties in these areas should be discussed if they're known. And information about disease severity and subpopulations, that should be considered and, to the extent that it's known, communicated to the regulator because that's certainly something that we think about.

In the benefits and risks section, so 2.5.6.2 and 2.5.6.3, we continued use of the terms key benefits and key risks to keep it consistent with the PBRER. We provide suggestions in the ICH guideline for the types of benefits and risk to consider when identifying what is key.

This is not about, you know, a laundry list of benefits and risks. There's a pretty extensive conversation in our expert working group about that aspect and that the benefits and risks should be a subset, the key benefits and key risks should be a subset of everything that was found in the product.

We also give suggestions for the characteristics of those benefits and risks to consider when identifying and describing the key benefits and key risks. So it's -- you know, when you fill out

§2.5.6.2 and 3, it's more than just listing out the key benefits and key risks. It's really about discussing why you think they're key and pertinent to the benefit-risk assessment.

And then, of course, any strengths, limitations or uncertainties of that information should be considered and discussed because we do that here.

Did I go too fast? Okay. Moving on to §2.5.6.4 and the benefit-risk assessment, as I said before, there's no prescribed approach for the benefit-risk assessment that we put in the guideline. But I think I tend to think about it in terms of we kind of had a permissive approach into the revision of the §2.5.6 rather than a proscriptive approach.

So we allow for things, but we don’t require it because some companies, you know, they want to -- they're a little bit more forward-thinking in the benefit-risk assessment area and they were interested in putting additional elements or analyses that they go through to think about the benefit-risk assessment and to reach a conclusion there, that there was an allowance for that. This seems to have a mind of its

own here. There's no keyboard.

Okay. We acknowledge then that a descriptive approach will generally be adequate, that that at the base level, that's what an applicant should be doing and if they want to go further than that, they can do that if they wish.

And if there are additional analyses done by the applicant that maybe perhaps are of a more quantitative nature or a visual display, that those analyses can be submitted in an appendix to 2.5.6. I think that's 2.5.6.5. But you know, how you analyze that information and draw conclusions from it, that should show up in the benefit-risk assessment in 2.5.6.4.

And about patient perspectives, there was a lot of discussion in the working group about the inclusion of patient perspectives and any information or analysis that a company does to glean this information to help frame and inform the benefit-risk assessment, that that information may be included in §2.5.6 as well.

So this can include descriptive information on

patient attitudes or preferences or even more quantitative information that can be gleaned directly from patients or indirectly from other stakeholders such as caregivers.

So I talked about that word cloud. So I'll move back to it right now. And this is the same word cloud that you saw earlier representing the revision one moving to revision two. You see there's a bit of a change.

So while we didn't go into these ICH conversations expecting to create a more balanced document in terms of benefits and risks, that wound up happening. So risk seemed to be a focus of revision one, at least in terms of what the guidance that is provided there. And now, it's more of a benefit-risk 2.5.6, and I think that's a good thing.

So in terms of our outlook, I think the ICH working group recognizes that this is still a rapidly evolving field with variations in experience and expertise both across regulators and across companies.

The new 2.5.6 captures a wide range of thinking on the content format and the flexibility that

can be permitted in providing different approaches to the benefit-risk assessment, that no one approach, you know, is considered superior. And we in the expert working group look forward to seeing how this is implemented in regulatory submissions.

So having said that last bullet, I was watching the Packers lose last night and looking at these slides and realizing, well, this guidance has been out for, like I said, a little over a year. What are we seeing?

So I went into our databases and pulled up a couple of applications, which then led to a couple of dozen applications, to see what are we actually seeing. And about half of the submitted NMNDAs and original BLAs -- I just looked at them -- year-to-date used the new guideline with the clinical overview total length being about 30-odd to 150 pages and §2.5.6 falling in that range.

So in average, what we have seen so far is that §2.5.6 represents about 10 percent of the clinical overview. And this was one of the concerns in the expert working group because we were going from one

page of guidance to like five or six pages of guidance.

Some folks on the group were worried about the §2.5.6 becoming very extensive because elsewhere in the clinical overview, the ICH guideline, I think there's a rule of thumb that the whole clinical overview should be like 30 pages. And you know, even before we revised 2.5.6, we were seeing clinical overviews well over 30 pages.

But I think if you would poll the members of our working group to say, okay, how much of the total clinical overview do you think §2.5.6 would be, it wouldn't surprise me to think that we would have landed mutually on or around 10 percent. So I don’t think we're seeing tomes being written about §2.5.6.

So I think so far so good on this. And those who do use the new guideline, there is still variation. There must be discussions that go on in companies about creating additional substructure even within the revised 2.5.6 structure that we did. So while we have 2.5.6.1 or 2.5.6.2, I was seeing 2.5.6.1.1.1. So for some, there was a fair bit of detail.

And this is my pictorial acknowledgement

slide. This is the group that engaged in about a year-and-a-half of discussions and thanks and kudos to them who participated in this. Okay. It looks like I was perfect. Do you want me to sit up here?

(Applause.)

MR. THOMPSON: We're going to break for now.

MR. FREY: Okay.

MR. THOMPSON: All right. We're going to move to a 15-minute break. Let's aim to be back by 10:35. And remember, for people that want to have lunch later, you can preorder it now. It will save you time later. Thanks very much.

(Whereupon, the foregoing went off the record at 10:22 a.m. and went back on the record at 10:38 a.m.)

MR. THOMPSON: If I could have the industry and -- oh, they're not here -- the industry and other regulatory agencies people have a seat up here if you're going to present, so Becky and Tarek and Clause? Yes, they'll be first. I guess we'll give them a second. That's all right. So we're going to kick off the second part of session one with perspectives from

international regulatory agencies followed by pharmaceutical industry. And our first presenter is actually joining us remotely. Francesco, are you there?

DR. PIGNATTI: Yes.

MR. THOMPSON: Okay.

DR. PIGNATTI: Hello, Graham.

MR. THOMPSON: So we're going to start you off with your presentation. And when you need to advance slides, just let us know. All right.

INTERNATIONAL REGULATORY AGENCIES

DR. PIGNATTI: Okay. Thanks a lot for allowing me to participate remotely to this meeting. Unfortunately, I wasn't able -- I would have liked to, but wasn't able to come in person. Can we go to the first slide, please?

So over the next 15 minutes, I'll tell you a little bit our story, how we came from concept of quality, safety and efficacy to benefit-risk assessment, how we developed our framework, how we dealt with possible implementation of quantitative methods and then some of the things that we are working

on at the moment trying to further improve the current framework.

Moving to the next slide please, I will show you probably the first drug which was ever approved by EMA in '95 was an important anticancer drug. Docetaxel now has broad indications everywhere. And I went recently to look at how we worded the benefit-risk assessment for this important drug. It was a difficult assessment, improved on the basis of surrogate endpoints and a number of Phase II trials and so on.

And what I found was this laconic paragraph saying basically that the application contained sufficient clinical data to support clinical safety and efficacy. Now, how -- it's probably clear, short and sweet, you might say. But how well does it convey all of the uncertainties about this approval?

Next slide, please. I have a slide where I am showing you how we have worded the benefit-risk assessment for a recently approved drug. This is now a broad section, highly structured and contains tables -- a table with the effects, good and bad, of the drug.

What has changed? Next slide, please. Well,

if we talk about how the decision is actually made, often perhaps one could say that nothing really has changed, nothing major has changed. Decision is still done largely intuitively and based on expert judgment.

Next slide, please. But like others, we have come under scrutiny about being more transparent about the rationales and reasons that play a part in our decisions. And so, we have tried to work on a framework basically driven by communication objectives. But there was also another question, which is by doing all of this sometimes difficult decision-making intuitively, are we making the best really of the methods which are out there?

And we started our research led by Professor Larry Phillips, from the London School of Economics, who came to EMA and worked for us for a number of years looking at opportunities for trying to be more systematic about benefit-risk assessment and communication and also looking at possible implementation of some of the more quantitative methods.

Next slide, please. What has changed also was

in the primary pharmaceutical legislation, initially applications were to be reviewed if efficacy was lacking because only 10 years later in 1975, when the concept of benefit-risk was more or less introduced but only in the preamble to the regulation, it is only in 2004 that we have this term benefit-risk really prominent in pharmaceutical legislation.

Next slide, please. So lots of changes happened in these years. What did our work with Professor Phillips come to? Well, the first opportunity for improving our communication was to adopt a framework.

This was loosely based on a general decision-making framework developed by Hammond, Keeney and Raiffa called the PrOACT-URL framework, which basically consists of decomposing the decision problem into its various components.

This per se had a major impact in the sense that people were much clearer when discussing what we were actually talking about rather than dealing with the issue in a whole sort of compound, complex concept.

Next slide, please. And we translated the

framework into the benefit-risk assessment template where our reviewers really write the evaluations. And this is more or less the structure that you have now. There are some introductory parts which deal with the therapeutic context. I'm not going to mention them here.

But the heart of the template is benefits and their uncertainties, risks and their uncertainties. We have then an effects table, which is really trying to convey as clearly as possible what is depicted from the drug in terms of efficacy and safety. And then, the more value judgment parts on the importance of the effects and the actual trade-offs.

So this -- next slide, please. This is the template that we have implemented now since a number of years. One of the questions as we were working on this was, okay, so we have now this descriptive framework.

In the meantime, others had mapped the whole spectrum of methodologies that could be used to do something slightly more sophisticated. For example, we considered using multi-criteria decision analysis for certain situations to have a proper quantitative

framework to deal with those.

Next slide, please. Now, to make a long story short, there were lots of different opinions about the possibility of using a more structured framework. And to be -- to be short, basically in the regulatory setting, this was seen as too complex an environment.

Next slide, please. In fact, this might be particularly acute in Europe where we have to deal with a number of committees, which assessment teams which are in the different countries. And so, introducing really a sophisticated methodology would require the whole network to be really knowledgeable about it.

Next slide, please. So in short, there were different views. And today, these methods are not used by the regulators, certainly not systematically. There are a few who think that might be used in certain situations. But we still lack examples.

But we do recommend to companies, if they think it's useful, to use such methods and then we would all gain experience form this. There are a number of reasons, some more valid than others, why people think these methods are not useful. One of the

perhaps more interesting things is it has opened the debate on when recognizing that there are subjective elements and there are value judgments to be made. And then, this begs the question as regulators, how good are we making those value judgments.

Next slide, please. Well, we have been interacting with patients over the years a lot and this is an activity which keeps increasing. But this resulted in including patients' representatives, for instance, in certain discussions, even early giving advice to companies and so on. But it's always a couple of representatives that you would get in those meetings.

Now, we all agree that benefits and risks have something to do with patients. So the question is aside from inviting a few advocates, which is an excellent thing in many situations, is there a way that we could have a more systematic approach to incorporating patient preferences in our decisions.

And to quote a recent CDRH guideline, in fact if you are able -- recognizing heterogeneity of patient preference, if you're able to identify a subgroup with

certain preferences, this should be taken into account perhaps in the benefit-risk assessment.

Next slide, please. So what we are doing at the moment is really with others in Europe, there is a consortium on this and I'm sure you'll hear about it in later presentations. But we're looking at ways in which we could use stated preference studies when assessing the benefit-risk.

This could be, let's say, used in specific situations. There is in fact a number of questions that arise around these studies, around the validity, when to use them, when it's most efficient to use them and so on, that is actually -- are still open questions.

But let's say the avenue looks promising and if you want to look -- if you want to know what we've been doing recently with a cohort of myeloma patients, I invite you to look up the references that re in this slide.

Next one, please. And another question which we are working on at the moment is this concept of uncertainty. It's a word, a term which is ill-defined.

But for us, it can be understood that the interesting part is understanding it's something, perhaps lack of information, which blocks the reviewers from taking a decision and then looking within our framework how we -- what are the uncertainties that emerge and how we deal with them.

And then, when looking at this -- next slide, please -- we actually found that we were lacking a proper framework for looking at uncertainties in the first place.

So from a review of the literature, we found a paper by Lipshitz and Strauss of 1997 already contained a very good framework that we felt we could adapt for our situation. It has three elements basically. What is the source of the uncertainty that causes this uncertainty? What is the issue we are uncertain about? And then, what are we going to do about it in terms of coping strategy?

Next slide, please. So we adapted this framework a little to suit our purposes and we found that sources of uncertainty are not enough data, unreliable data, conflicting data or lack of

understanding of the data, for example. And you can read all the other categories there.

We found this was useful in, for example, distinguishing between orphan cancer product compared to non-orphan cancer product, so quite a sensitive framework.

And we are now looking at other types of validation of this and also looking longitudinally how we deal with uncertainty during the assessment perhaps to identify strategies, if there are certain problems with the data, perhaps certain strategies are better than others and what are the situations, for example, when the efficacy data is very clear.

Perhaps there is the ability to deal with more uncertainties for example in terms of safety in some situations again. So I think this would be an interesting tool and today we are rather informal when we describe in our framework uncertainties. Perhaps in the future we will see even there a little bit more structure on how we word this.

Coming to my last slide now, next please, we are quite happy with the structured benefit-risk

assessment framework that we introduced a couple of years ago. There are perhaps improvements that we can make. When I heard the previous speaks, the pros and cons of using a framework, the experience, it's pretty much exactly what we've heard from people here. But still, it's a big step forward I think from where we were 10 years ago.

The role of quantitative approaches is still unclear and one of the few persons let's say in the system who thinks that there is a role in perhaps certain challenging situations.

But in many situations where benefit and risk is totally clear, we probably do not need those roles. Nevertheless, companies are encouraged to explore such methods and we will all gain experience and for sure it may help communicating with the regulators.

Lastly, we are very interested in exploring alongside the traditional way of gaining patient input like advisory roles and so on.

But to look at the patient preference studies in the form of stated preference studies or similar studies, but there is a lot of work to be done to be

let's say comfortable with all the different methodological questions that these studies pose.

Thank you very much for listening. I will not be able to take questions efficiently. But please, you have my contact details. If you want to continue any of these discussions, please contact me. Thank you very much.

(Applause.)

MR. THOMPSON: Thank you very much, Francesco. Our next speaker will me Clause Bolte, from Swissmedic.

DR. BOLTE: Thank you very much indeed for inviting me. I'm honored to be here, trying to outline a small to midsized regulator's perspective. Quite a nice juxtaposition perhaps compared to Francesco's elegant presentation you just heard. So you'll see that our approach to evolving this concept is a very pragmatic one.

In trying to outline what I'm hoping to convey to you, on the left-hand side is our questions around the purpose. Is it -- is the structure, more or less structured benefit-risk framework a decision tool aiding decision-making internally? Does it serve to

document these decisions or to communicate these decisions as part of an assessment report to also the external audience?

This is what I will focus on predominantly. Then, I will hint -- only hint -- at some attempts to advance the concept, to develop the concept in terms of the format. Can we quantify? To what extent can we? Do we need to break it down by therapeutic area, by subpopulations, different age groups perhaps as well? And do we also have to consider the application type?

And then, in our outlook, we come to this, this afternoon. We will probably be able to just scratch the surface in terms of patient preferences, patient-reported outcomes, fact boxes and the life cycle approach and perhaps even cost. I put it in brackets and parentheses. This is quite a heretic statement to make, I'm quite aware.

Now, how did this all come about? How was this all triggered? Swissmedic is an independent, fiercely independent agency, I should add. And we're not reporting to a ministry or a politician, for that matter.

But we are reporting to a council, to an institute or agency's council. And one of our councilmembers, Reto Obrist, he published, well, about two-and-a-half years ago, all the conflicts of interest by pointing out some conflicts we are encountering in terms of the quality also of the data we see.

You can perhaps read this on your own time. Highlighted are the most important ones that served as a wake-up call for ourselves, starting to revise our approach to benefit-risk and how we document it.

There are different agents at play and eventually there's always a third party at risk. That is something we have to be aware of. He also quotes Nassim Taleb, who you probably know from the Black Swan and Antifragile publications or books.

And he is quoted saying the relationship of a scientist to a scientific truth, be it an academic scientist or someone in industry, is that -- it's somewhat politically incorrect to state, but I guess we can do this here now on this side of the Atlantic as well -- is reminiscent of a relationship of a prostitute to love. So there is always a conflict of

interest we have to consider.

In terms of a broader, 360-degree context, if you follow me around from 12 o'clock, interconnected world, post-trust society, there is not a single source of truth anymore, leading on to what Reto published two-and-a-half years ago.

In fact, it was quite an eye-opening moment for me when I was confronted with a lot of media queries after Cochrane, the Cochrane collaboration published their assessment of the Tamiflu dossier. It was in fact the very first time that regulatory documents were assessed by a third party, by a different group, Cochrane in this case.

And then subsequently, media were asking me and I had to appear on primetime television as well. Now Clause, that Cochrane found out that Tamiflu is not only not efficacious but also not safe, how did you ever -- why did you ever approve this drug. And Swissmedic was one of the first agencies to approve it. And subsequently, the stockpiling story unfolded which was a political decision predominantly. So we are, and you are probably as other regulators and monopolists in

your jurisdictions, but our authority, our value is increasingly questioned. And maybe this framework can help us as we are able to communicate our decision, if we can do this with this framework.

I focus on -- sorry. It's too loud or -- okay. I focus on -- thank you very much, Pujita. So we can leave out those I marked in black. But as you can imagine, as you know probably, personalized, stratified healthcare, precision medicine needs to be considered as well as new facilitated pathways, accelerated or conditional approval, for example. We cannot just leave it out.

New-try concept, randomized controlled trials, as to the old standard compared to real-world data, master protocols, basket trials, but also different age groups. If you look at 7 o'clock, pediatric and different geriatric age groups, as by ICH age brackets. HTA I won't get into yet. And then, of course, there are empowered patients, social media and transparency. I didn't quite get the equator right. But these are all factors within a broader context that have to be factored in.

Now, what we accomplished, and Patrick already summarized that, this is basically what M4E, the second revision of that part accomplished in a nutshell. We took the patient perspective into account, explicitly also the severity of the disease, context, which can be mitigated to some extent also in the way we develop a drug label. And the drug label can be quite an extensive or comprehensive document.

As you all know, risk mitigation, risk management and, as you know, we did not mandate, we did not prescribe a particular way in terms of assessing benefit-risk. It can be quantitative as well. It can be qualitative or semi-quantitative.

Now, I promised you a very pragmatic approach. At our agency, this is how we have been doing this until quite recently. How do our clinical reviewers assess benefit-risk?

Basically, if you look at the last bullet, this sums it up quite nicely. Authorization should mean on a population basis that potential risks are judged to be acceptable given the specific conditions of use, the target population and alternatives

available at the time of approval. It's only a snapshot.

But authorization does not mean that an individual patient will necessarily benefit or the other way around. We did reasonably well with this descriptive approach. And what you had in our assessment reports was quite a lot of heterogeneity. All free text. More or less drug should be based on this internal guideline.

Then we came back from the first workshop here and we refined it in order to clarify some guiding principles and key objectives, key objectives in our mind. And I think we have to narrow it down, are mainly arriving at a decision, at a reproducible decision and to have it documented predominantly for internal purposes. So we refined it on the left-hand side. You'll see part of our SOP, which we implemented after the first workshop one of my colleagues was able to attend.

Now, as I mentioned earlier on, if you look a little bit more broadly and internationally, one reason why I'm here as well, you will see that I cannot

properly point this out to you on the second display from the right. Swissmedic, we increased -- in fact, we doubled our number of priority or fast-track reviews in the last four to five years since I arrived.

As a small or midsized, fiercely independent agency, how can we muster that? How can we shoulder this responsibility? In fact, just to point it out, in about 11 percent of new drug applications, new active substances, we are number ones, the first approval or the approval occurs within a very narrow time window compared to larger reference agencies.

This in fact was some benchmarking done by the CIRS group, so a third party, pretty independent. We achieved this predominantly by playing -- trying to play a very active role in ICH, but also within our ACSS, or ACSS consortium together with Canada, Singapore and TGA Australia.

Now, this consortium came up with a very quantitative, fairly sophisticated, comprehensive tool. In fact, it's an electronic template and tool. I think it's going to be available online as well, driven by Stewart Walker of the CIRS group or agency, a template

by which you can assess and quantify benefit-risk and then come up with a score. You can even weight certain components thereof. It's pretty sophisticated. It allows you to clearly, transparently display what factors went into it and how you calculate a benefit-risk ratio.

There's a manual for that as well, a pretty comprehensive manual. And with all that at the time, our next step in the evaluation, if you like, of the benefit-risk approach, with all that, it was so comprehensive that we decided to opt out. Don’t get me wrong. The initiators and participants of this template and the framework should be congratulated. It has evolved since.

But at the time, as a small to midsized independent agency, this was a duplication of the standard assessment report we would otherwise provide. So we opted out. It was simply not pragmatic enough, not practical enough for us.

We refined our internal guidance, our SOP. It incorporated -- in fact, I mandated this incorporated the nice framework we learned here and from other

parties involved. And in fact, I mandated that this framework should be considered. It doesn't have to be completed for each and every indication, but should be considered. And this is how it looks like on a street level view. This is one example. I tried to anonymize this example as much as possible.

On the left-hand column, you see the different review teams, clinical pharmacology review, CPR, CR is clinical review team and PCR is the preclinical review team. They all come up with a succinct description, some bullets or keywords in that table based on the framework we adopted and also tease out -- I think this is the most value or the highest value in this table -- some uncertainties which I highlighted.

So in this case, we are dealing with a direct acting antiviral against hepatitis C and they clearly teased out something they probably would not have done without the framework.

So it serves as an bête noir. There were no data on co-infected patients, HIV or hepatitis B co-infected patients. There were no data at different stages of liver decompensation, cirrhosis or fibrosis

and were no data for certain age groups as well.

So this was in that case already a value in itself. This table had to be generated manually and it required a lot of extra time as well.

Again, it served for internal communication purposes only and it helped us to issue the list of questions very similar to what EMA does to the applicant, to which the applicant then subsequently submits replies. And at the bottom, you see the benefit-risk assessment for different genotypes. And you see that for some genotypes, at that time point, no assessment could be made.

Now, there is a new way of -- not so new anymore -- to also communicate risk -- benefit-risk posed by Gerd Gigerenzer, who works out of Berlin, also had an academic stint in Chicago and Virginia. And he basically shows -- he depicts data that often healthcare providers don’t very well understand. He calls us statistically illiterate, statistically illiterate.

So how can we then explain a benefit-risk assessment to patients, insurance providers, for

example? So he proposes a graphical display. In this case, it was an ultrasound screening for ovary cancer, all published quite recently in The British Medical Journal.

And you see basically what he depicts is relatively easily to grasp. And the topline already indicates the outcome, that patients do not benefit from this screening. In fact, a number of patients had ovaries removed unnecessarily. So just the way to communicate. This is not for decision-making or documenting internally, but to communicate what has been decided upon to different stakeholders.

Now, not our remit, my last subtopic, called at ASCO, this year's annual meeting of the American Society for Clinical Oncology and I have to throw it in here. In fact, these are just photos I took myself because there is no presentation as yet that I know of.

You see the time lag between the regulatory approval and subsequently a proper health technology assessment. At the bottom line on the right-hand side, you see lines. So it takes another one-and-a-half years almost to get reimbursement as well. After many

years of drug development, our review cycles and then you undergo HTA and eventually you get reimbursed in the monolithic NHS.

And that's my very last one. I propose to you as almost a segue to our discussion this afternoon, a value-based framework, not our remit, not our mandates strictly speaking, also from this year's ASCO meeting. And you can see what they tried to integrate. They look at the evidence generated, also the quality of evidence. Are we dealing with randomized controlled trials, real world evidence?

At endpoints, they look at quality of life and patient preferences, very similar to what we are now documented in M4E. And they look at cost, something we obviously don't do. And also, out-of-pocket cost and offsets thereof, so health resource utilization, something that could be taken into account.

And you see there are different frameworks. The first one is the ASCO framework. Then there is the National Comprehensive Cancer Network framework, ESMO, the European counterpart. We have the ICRE value assessment and they take patients' perspectives into

account and cost or not in a different way. And then, you have Emmy Morris, Sloan Kettering algorithm or drug abacus, as they call it.

So this is my last slide. I know we're moving into the next PDUFA cycle. Not our mandate, cost, but probably something we cannot keep out. I think we need -- for a long time, we need an integrated approach.

It can still be sequential and we have to consider pilots going on, providing scientific advice based on regulatory comments and input as well as HTA. And in the end, we also have to, I think -- we can't avoid combining integrating all this in order to advance a concept. Thank you very much.

(Applause.)

MR. THOMPSON: Thank you very much. Now, we're going to hear from a few members of pharmaceutical industry. And our first presenter here will be Tarek Hammad, from EMD Serono.

PHARMACEUTICAL INDUSTRY

DR. HAMMAD: Hello, everyone. I will start -- let me just make sure I have this. I will start by saying that my comments reflect my personal opinions,

not my employer. This is an outline of my presentation. I will start by visually showing you the complex context that we are dealing with and that this was behind the reason for why we needed a more structured approach. And then, I will share with you some of the conceptual challenges when it comes to two of the multiple changes in the ICH updates, which is the quantitative aspect and component and the patient engagement.

So if you think about the context, there is actually for the benefit and for the harm, there is a local context that when we are trying to evaluate and think about, we talk about how plausible the situation, the actual harm is, what is the actual evidence, what's the magnitude, how severe it is and so on and so forth, can it be mitigated and the like.

But then, when we talk about the benefit, there is -- it has its own local context about the extent of benefit and of course being cognizant that we are collecting it from trial data, so how different are these patients from the real-life patients. That's another thing to put in mind. And of course, the

quality of the evidence, it plays a role here.

But then, there is a global context that revolves around the public health interest. Talking about, for example, the disease itself, how bad the disease itself, the expected extent of use, if you're talking about a rare disease versus a disease that is going to explores a very large portion of the population. It makes a difference, and so on and so forth. What are the alternatives to the drug that is being examined, and so on?

So after that, an action can be taken either by a regulator or can be proposed by a company. But regardless, what will happen eventually, there will always be remaining unknowns. There is potential for latent risk or some subgroups that are not really non-elate.

So that's the complex picture that we are dealing with. And because we are a firm believer in Lincoln's code, the best way to predict your future is to create it, this is exactly what we did with the ICH group. And actually, I am repeating the picture because I like it. Actually, it's very high quality.

This was Pujita's camera.

So because of that complexity, we felt we need to come together and do the revised guidance and I know Patrick spoke about this in detail. So I will not belabor that. I will just focus on two aspects and I will try to link them together. The patient perspective and the quantitative component or quantitative approach.

So what about the quantitative approaches? Now, if you think about the whole process, you will find two logical pieces. You have the identification and then the assessment. But in reality, the assessment itself has its own components. One has to do with the actual weighing of the benefits and risks and the second has to do with characterizing the profile, the visualization, the tabulation and the like.

And for this way to happen, it can happen explicitly or implicitly. Now, I make a distinction between what is a quantitative metric and what is a quantitative assessment because this is a cause for confusion when people talk about the same thing but

they mean -- use the same terminology but mean different things or vice versa. So I figured I'd better define my own terms when I am talking about this.

But the metrics will be utilized mostly for identification and the assessments will be utilized for weighing benefits and risks. So what does this mean? What does it entail to explicitly weigh various events?

Now, it takes us to the question about where should we go, qualitative or quantitative, and what exactly is that. When I was trying to examine this, I'm like -- I mean, when I talk to even different people, they gave me different kind of opinions. So I figured the best way is to define my own realm, if you would.

So if we are talking about collecting and identifying the benefits and risks and then doing the assessments, if in the assessment you are asking something like that needs a value judgment, like asking a diabetes expert, for example, what do you think should you go for A1c or hypoglycemia as a metric, that's qualitative. And I even have a question mark

here because even that, you know what happens. The expert is internalizing their quantification.

So I believe actually there is really no qualitative anything. It's all quantification. But it's just different level of quantification, if you would. And some are explicit and some are implicit.

But if we are using judgment and then using quantitative metric, that's what I would call quantitative -- a semi-quantitative approach. And that's using risk difference, no major harm and the like. But then, that's where there are outcomes.

I mean, when we use complex modeling -- now, people hear that and they think that we want to replace the judgment with the modeling. But the reality is in addition to the judgment, we're basically guiding the judgment.

You're using more sophisticated modeling and that's where the weighing of the benefit and the risk takes place and the tradeoffs. And that's where the more explicit weighing of benefit and risk takes place and that's the most controversial. And that's -- and hence, that's where the guidance is needed. This is

the missing piece that we need to talk about and have a discussion around it.

Now, there are many other methodological aspects to resolve, like how many times have you heard about being terminated prematurely because we thought the efficacy is really out of this world. But then, later on realize that there might have been some safety issues missed.

Why not then use benefit-risk as the metric for terminating trials instead of just efficacy, as happens now? So what about the threshold discussion? What would trigger revamping or revisiting various experiments or risks provides? That's not an easy thing to do. But we need to have a discussion. And what is the realistic goal for the quantitative approaches I spoke about? That's something that we don’t have any guidance about.

So there are so many other things that we have to consider. I'm not going to go into every single point of this. But there are methodological challenges that industry is facing and there is a need for guidance and discussion.

Now, the last piece I will talk about has to do with the patient engagement in -- now, you know how -- I feel actually guilty because I know lunch is coming. So I should not be showing pictures like this. However, sometimes you look at something. It looks perfect. But then, the reality is usually much more missing.

So let's examine the reality of patient engagement and what exactly is that. Again, when I tried to look in the literature and speak to people, assuming different vocabularies, people say the same thing and mean different things and so on and so forth. So I figured let me define my own and then take you through the challenges and what is missing from the picture.

Now, if you think about it, I'm defining it as engagement has three different dimensions: perspectives, preferences and choices. Now, if you think about it, the bigger domain has to do with the indications, everything that we are dealing with when it comes to disease, all the unmet needs, all the patient struggles and so on and so forth.

And then, within that, you have a smaller circle which has to do with applications submitted for approval because whether we like it or not, we don't have a solution for every problem out there in healthcare. And then, you have a smaller circle that represents whatever gets approved and passes the bottleneck of approval process.

Now, what I call the patient perspective is that it only covers the outer circle. That's what I mean when I talk about patient perspective. These were the unmet needs, perhaps what is the outcome of interest, what's the minimally important clinical difference the patient will be happy to live with. What is the delivery mechanism the patient will be happy with and so on and so forth?

But, and that's what mostly the patient-focused drug development is focused on. So basically this is capturing whatever is out there that needs to be addressed. But it's not so -- let me say it. It's actually a very magnificent effort. It's very necessary. But it's not sufficient.

So, and I will try to make the case now for

why we need more than that. Now, what I call preferences has to do with the bottleneck, the actual deciding on whether the drug goes to market or not. And currently, both regulators and payers are playing a role. The patient does not play any role at all when it comes to this particular prat of the patient engagement.

And then, you have the patient choices, of course, after the drug gets approved and of course the patients, together with the healthcare practitioner, they decide on what is the best course forward. However, I say this is too late. The bottleneck is what matters, at least at this stage of discussion. So what's missing is actually right here at the point where something is being decided to go to the market or not.

What we are missing is a way to identify, capture and integrate the patient preferences in the process where somebody is going to decide whether a drug goes to market or not. And here is the challenge. The data collected is a group data. To be able to find meaningful, useful information, we have to use data

that are compatible with this group data. That's why I was saying the previous -- the PFDD alone is necessary but not sufficient because it does not collect information in a way that is compatible with the group trial data that are being collected later on.

Then, there is also of course the issue about the patient understanding -- how much they understand really what's going on with their disease and the whole issue around literacy and then empowering their choices by doing some comparative work between various alternatives.

So we have some missing pieces when it comes to the patient engagement that I'm hoping that by the end of today we'll get some kind of plan for to address these moving forward.

Now, as if this was not complicated enough, what we are really still missing is to be able to appreciate everything I mentioned by the life stage, because younger patients might respond differently than older patients, and also by the disease stage.

Perhaps when patients are still at their mildest stages, their thinking will be different than

when the disease has already progressed. So that's another complication that has to be collected. And that's -- what I'm sharing with you today actually is all the conceptual struggles that as industry we are facing and we need guidance in.

So the question that emerges then, should we redefine our targets when it comes to drug development. Now, what happens now as this goes is that the patient population, when the benefit-risk balance on average is positive, that's when the drug gets to the market.

But in the spirit of the -- but of course the hope is that the premise here is that we are trying to maximize the benefit for patients while offering more choices. How can we go about doing that? That's the goal, but how can we achieve that?

Now, in the spirit of the precision medicine initiative that was initiated I think last year or the year before, if you think about it, at least phenotypically we should be able to identify a subgroup of patients that are really benefiting more than others.

And that's where actually I have an issue with

people saying, well, the majority of situations are qualitative. We only talk about quantitative in the very small scenarios. The reality is even when you have a major situation where qualitatively the drug clearly is superior, there is a chance that we might be missing opportunity to identify the subgroup of patients that really can benefit more than others.

So the question is what should be our objective. Should the objective be to find benefit-risk that is acceptable or that is favorable?

Now, if you think about it, the acceptable scenario, which is the green one, reflects the patient willingness to accept certain -- to play a central role, basically how much benefit are they willing -- how much risk they are willing to accept in exchange for how much benefit. That's the central facts we need to collect.

But when you are talking about how favorable something is, well, the regulator would play a central role in this. And the implication would be that if you go with the green scenario, then we will try to find predictors for what the characteristics that the

patient preferences actually -- what can predict the patient preferences and also understand patient attitudes towards the disease.

It's like a totally different and whole different endeavor that we have to embark on and we have to be able to justify it for our development teams.

But if we go to the other route, then what we need to do is find predictors for what characterize patient response to treatment. But that's it, without any patient input to what they perceive as what is worth the risk for what kind of level of benefit.

Now, of course, the challenge -- so you don’t think I'm just pushing for one thing without appreciating that it is challenging, the challenge for the green scenario has to do with the fact that what about at the point of care.

Suppose a patient drug was approved in a market because the patient preference studies showed that there are some subset of patients that are going to accept this kind of risk for the benefit. How would you know that the patient coming out of the door at the

point of care belonged to which group? So that's the challenge. That's not an easy challenge to address.

But then, on the other hand, for the other scenario, how can we find the patient that fits the correct pattern, basically that we figured out in the trial at the point of care? So I mean, both scenarios and both choices are not easy.

So in conclusion, the context itself is very complex. And that's why there was clear need for a structured approach. So the value of that structured approach is almost like no-brainer.

However, there is a lot of knowledge gaps when it comes to what we need to do for the patient perspective, what we need to do for the quantitative approaches, what is appropriate -- what is actually the appropriate timing to approach the agency when it comes to suppose we are trying to figure out whether we need some kind of quantitative approach or not.

What is the best time to approach the agency? And then, what we really look for is some kind of targeted feedback, meaning I know companies have already done some quantitative assessments. But they

submit to agency, but then they do not hear back. What is the contribution of this submission and this effort and this piece towards the overall decision, whether it was favorable or helped at all because without that, quite honestly, this field will not go anywhere without people knowing what is the impact of the efforts that are already being done now on a voluntary basis.

On the overall picture, this field will not go anywhere because, if you think about it, this requires a lot of delay, a lot of effort and time and money also goes into building up that quantitative piece. So it's very crucial to appreciate that this is -- targeted feedback is needed. That's it.

(Applause.)

MR. THOMPSON: Thank you very much, Tarek. Our next presenter will be Becky Noel, from Eli Lilly.

DR. NOEL: Morning, all. So first, as Graham said, I'm an employee of Eli Lilly & Company and, similar to others, I just need to declare that the thoughts and opinions that are represented in today's presentation are solely mine and not those of the company.

So I have two disclaimers for you above and beyond the first one. And that is that I am going to recover some of the ground that's already been covered this morning, but hopefully from a slightly different perspective.

And the second is that my slides are nowhere as pretty or vibrant as Tarek's. I have found myself now a number of times following him and we just need to get it out of the way upfront. Mine are plain, boring, heavily text-based and, you know, I'm a Luddite. What can I say?

So as Sara mentioned this morning, we started down this path to structured benefit-risk assessment because we realized that we needed a decision aid and a communication tool. But you may be thinking, okay, so now we have structured benefit-risk assessment. Do we still really need to keep pushing the topic of structured benefit-risk assessment forward? And I would say the answer to that is yes.

And the reason for that is laid out hopefully in an entertaining way here on this slide. There are multiple reasons that benefit-risk decision-making is

hard. Often, we're faced with a lack of clarity, a lack of certainty, a lack of structure and judgment and that comes along with an overwhelming complexity as well as volume of data.

Paired with that, as we see so nicely in John Jenkins' slide below, here is just a sliver of some of the things that a regulator must keep in mind as he or she is trying to weigh the benefits and risks and reach a benefit-risk decision.

So we do need structured benefit-risk assessment and we need structured benefit-risk assessment because it offers us a way to make higher quality decision-makings. I think Mary said it quite nicely this morning. We've always been making benefit-risk decisions.

So benefit-risk decision-making is not new. What is new is this approach to it in which we're trying to promote higher quality decision-making. And one of the ways that we can do that is through the use of these benefit-risk frameworks.

So Sara presented the benefit-risk -- the FDA benefit-risk framework this morning. But we'd also

like to remind you, as Clause did and as Francesco did, that there are multiple frameworks to support benefit-risk decision-making, some of which you may be familiar with.

The question then that comes from this multitude or this abundance or this alphabet soup of frameworks is which one. And I think Patrick did a very nice job of laying out this morning how the commonalities across these frameworks were brought together and harmonized under the ICH guidance.

One of the things that Patrick didn't elaborate on, although he briefly alluded to it when he talked about some of the sizes of the clinical overviews that they were seeing, is that one of the purposes -- actually the primary purpose of the clinical overview is to provide a critical analysis of the safety and efficacy data as well as a critical analysis of your benefit-risk assessment.

But like all good things, things can sometimes go astray or not really work out the way that you think that they might. So what are some of the challenges to achieving what's been laid out so nicely this morning

in terms of what we would like to achieve through the use of benefit-risk frameworks?

Well, one of the primary challenges to achieving our objective is something that I like to call the tyranny of the summary of the summary, not only in the clinical overview but in also other deliverables and documents that we may prepare. And this tyranny of the summary of the summary is not only an industry problem, I would argue, but it's a problem that we find across our fields, both for regulators and for industry.

So in the second half of my presentation, I would really like to focus on how do we take advantage of the excellent progress that's been made to date through PDUFA V, hopefully through PDUFA VI and ICH and move even further.

So I have three themes or three broad areas that I'd like to briefly touch on to outline what we might need to do and how we might move further. And that is really looking at what goes into the benefit-risk assessment and looking beyond that, so understanding what good looks like and how we get

there, looking at the topic of capacity building and then lastly thinking about really the value of all of this, which is in collaboration, connection and communication.

So Patrick didn't touch on it or Clause or Francesco, but for those of you who want to know more about ICH than you had ever hoped to know, expert working groups can go on to become something called implementation working groups. And implementation working groups are usually formed when it's thought that the guidance might be thorny, might be too strong a word, but that the guidance might need additional elaboration.

One of the ways that this additional elaboration comes about is through a Q&A document. §2.5.6 did not get a Q&A document because the expert working group consensus was that industry and regulators would benefit from living with the update for a short interval to better identify the types of questions and pain points that companies were experiencing. And there's been no change in that position since the workgroup concluded that summer.

So my provocative question for today is that if you look at 2.5.6, you'll see that 2.5.6 provides the what. Remember, this is the format and structure of benefit-risk information. But we're still faced with the question of how.

So the reason that I raise this question of how is because mutual increased clarity on what good looks like supports the likelihood of us being successful.

So we know from the PDUFA VI goals that we will be excepting guidance in 2020 and so one of the suggestions that we would like to make is that FDA collaborate with patients and with industry, both of whom have gained significant experience in the development and application of benefit-risk assessment, to inform what this guidance looks like. And we believe that MDIC offers a very positive role model for us in this regard.

When we turn our thoughts to capacity-building, so I think we saw that approximately 50 percent of NDAs, BLAs were using the guidance that came out of the ICH update. When we look at the topic of

capacity-building, what do we need to do to go further? Well, there are three things. The first is that we need to progress the FDA framework. There are ways that we can do this. We've made an excellent start. And we should celebrate the achievements that have come from working together. But there are ways that we can go further.

So how do we advance the baseline? Well, we might consider the use of data summarization and visualizations that are supportive of the decision. We could consider a methods toolkit or a methods catalog, again, similar to what came out of MDIC, standards for methods applications. So if we do have folks who want to use more quantitative approaches to benefit-risk assessment, again, how should they be doing that? What does good look like?

Understanding how we can achieve alignment on the assessment of outcome importance and then adaption and application to post-marketing assessments.

The second large area that I think we might have an opportunity for capacity-building is in his topic of patient perspective methods. So we certainly

need to increase our understanding and build our capacity both on the industry side and on the regulatory side in the use of patient perspective methods and perhaps even going so far as including that information as a communication tool for patients in labeling.

And then, last but not least, when it comes to the topic of qualitative and quantitative benefit-risk assessment, again similar to MDIC, developing a methods catalog along with documentation around best practices.

This is a topic for capacity-building that doesn't get as much play when you go to benefit-risk meetings or you hear benefit-risk presentations. But it's one that I think is critical and that not only do we need to build knowledge and experience with preferences and quantitative benefit-risk assessments, but we also begin -- we need to begin building capacity and increase understanding of things such as quality decision-making, judgment-based decision-making, because these are the -- this is the science which really gives insight into the principles and processes of both qualitative and quantitative benefit-risk

assessment.

So this slide is again intended to sort of reframe our thinking, push us a little bit further. Many of us know -- hopefully all of us know of the Apollo moon program. If you're more technologically inclined, and I most certainly am not, but my 17-year-old niece was more than happy to educate me, if you're a techie, a moonshot, you know, Google for example says, you know, how can we be transformative in 10 years. This is really about being adaptive and exploratory and collaborative in an open way.

So this is my benefit-risk moonshot thinking. And that is that both here and at other forums, you'll see individual standalone discussions around real-world evidence and big data, PFDD, methods and tools, training and education, policy and reg science. But they're siloed. But yet, when you look at them in this context, in this way, we see that they are very much interrelated and very supportive of this overall idea of integrated benefit-risk science.

So what's needed here? What's needed is connection, collaboration and communication. So as we

move forward under PDUFA VI and coming out of workshops such as these, I think this is the real challenge that we have before us, to think about not only what do we need in terms of blue sky or moonshot thinking, but how do we connect all of that to drive us towards an integrated use of this information. Thank you.

(Applause.)

PANEL DISCUSSION AND Q&A

MR. THOMPSON: All righty. So we're finally going to stop having a lot of presenters talk at you and give you an opportunity to ask some questions and for the presenters to ask questions of each other as well.

Jeff, if you want to come up here and join us? So our panel will consist of all of the presenters who have spoken previously, as well as Jeff Roberts, from CBER.

So I'd ask that if you're going to ask a question, that you can just line up at one of the mics. We'll have one at the front and one at the back. And we'll try and get to you before lunch. Jeff, do you want to do a brief introduction and say a few words?

DR. ROBERTS: Sure. Jeff Roberts. I'm a clinical branch chief in the Division of Vaccines in CBER. And just a couple of thoughts to start us off, from my perspective anyway.

To go to the internal issue of sort of helping us think through things, I can report that at least from my perspective, the use of the framework has been tremendously successful. We were in the process of rewriting the clinical review template at around the time that CDER was developing the framework.

We took that and put it right in the clinical review template and started using it right away. And it has been very helpful for our medical officers to think through the bigger picture.

So I think the other element of that is it's been -- it's been reassuring to see that from our perspective where we're reviewing vaccines for the most part, which have a slightly different benefit-risk perspective because, as you can imagine, our risk tolerance is very low when we're considering licensing a new product that might be used by the entire birth cohort of healthy babies.

So we've seen that the framework can work well even with a fairly different benefit-risk perspective. So it's kind of a good news story in terms of the internal goal from someone close to the ground.

And I guess my other thought is looking forward, what are we going to need to think about. And I mainly think about the issue of thinking about benefit post-marketing. We've talked about integrating this into these update reports.

What does that mean exactly? You can imagine from our perspective it's very important because think about the FluMist example. I don't know if you all have seen the flu vaccine that's meant to be administered intranasally appears to have been less effective over the course of several years in the past several years.

What does that mean post-marketing? How do we integrate that into our thinking of weighing benefits and risks? We're very good at thinking about risks post-marketing. We've done less of that sort of thinking. So that's one thing I anyway would like to hear more thinking about going forward.

MR. THOMPSON: All right. Thank you very much, Jeff. All right. If anyone has a question, you're welcome to line up now. You can break the ice for us. Thank you.

DR. CRAIG: Yes. Well, that's part of my job. I'm Benjamin Craig. I'm chair of the International Academy of Health Preference Research. We represent the majority of health preferences researchers in the academic setting. And I really do appreciate the work that's being done by -- between these collaborations, both here and abroad, MDIC, PREFER, et cetera.

But listening to these presentations, I'd like to hear more about what you think the role is of the academicians who are trying to drive these methods to understand how to both qualitatively and quantitatively assess preferences so that we can collect the evidence necessary to inform regulatory decisions.

So far in the presentations, I haven't heard mention of the research being done and we have meetings. We're having our seventh meeting in Glasgow coming up in November focusing on preference heterogeneity. But that type of methodology isn't

being represented yet. So how do we merge these different organizations to bridge so we can promote patient preferences for regulatory evidence? Thank you.

DR. EGGERS: So first of all, I think that it's time -- I'll take the opportunity to thank the methodologists who have -- who have come along the way and helped us in this effort. Dr. Phillips was mentioned earlier today. I think Baruch Fischhoff and we have other -- Steve Woloshin and Lisa Schwartz, who continue to help.

One slide I give when I have given a talk similar to this was directed towards the toolmakers developing these methods. And I think it's come a long way. I don’t even give the slide anymore because I think it's come a long way in the toolmakers really appreciating the complexity of the regulatory context. That goes without saying.

But when I was working with Baruch in the early 2000s, it is hard. We don’t -- to develop a method that we thought would help FDA. It is hard to really put ourselves in the shoes of the regulators.

So one small suggestion I would have is how do we get the doctoral students and the postdocs and the others to become embedded in the regulatory world and become -- and to learn how -- to learn how these decisions, how complex they are, to bring it a little bit out of the academic setting and hypothetical setting and to come in.

It wasn't until I came to FDA that I said, okay, I really get it now. And I wonder if there's some sort of programs that could help with that.

DR. NOEL: Ben, thank you for your question. I think you're aware that there are several very strong regional programs in place to bring together regulators, drug developers and academicians. So the IMI projects, and you mentioned PREFER, is a clear example of this.

I think one thing that we may wish to consider is how do we replicate something similar to that in other geographic regions. But I think really, you know, the last slide is it or my last slide, it is it for me. And that is connection, collaboration and communication. So figuring out the correct ways, as

Sara mentioned, in which we can all work together collaboratively and productively to begin to address some of these questions and to better understand the methods and how we can make them fit for purpose, both for drug development and for regulatory decision-making is one of those moonshot goals that we should be working towards.

MR. THOMPSON: Dr. Temple?

DR. TEMPLE: Hi. Bob Temple. There were hints of discussion of this. But I'm interested in whether people want to talk more about the fact that people in a trial -- that people don't have the average effects seen in a trial.

There's a distribution of responses and I presume our benefit-risk calculation takes into account the fact that some people have a bigger response and a smaller response.

There is one classic case of that where the drug flibanserin, for sexual dysfunction in women, was approved I believe at least partly because a fraction of the population, about 10 percent, had a really big effect compared to the rest of the people. And that

overcame the fact that they would fall over and hurt themselves. So any comments about how to consider the distribution of effectiveness in trials?

DR. HAI: I guess I have to ask a clarification on that. Bob, are you asking with respect to incorporating that into the benefit-risk framework --

DR. TEMPLE: Yeah.

DR. HAI: -- or as part of our analyses of the efficacy results in the trials in the program?

DR. TEMPLE: Well, we have to have it as part of the effectiveness results and we all too often do not. But I'm asking about how it gets incorporated into the benefit-risk analysis.

In the case of flibanserin, I think if there hadn't been that subset, I'm not sure people would have voted for approval. But given that there were some really very nice responders, they thought it was okay. But all treatments have variable responses.

And so, you're not interested only in the risks versus the average response. You're probably also interested in people who have a very good

response.

The other thing I will throw out is a major interest for drugs that are toxic should be whether it works in people who don't respond to other therapy. Something that has been tested exactly four times in all of history and we've approved drugs that were extremely toxic because of that.

Clozapine is approved even though it causes agranulocytosis because it works in people who fail on other things. We had a calcium channel blocker that killed people with torsades de pointes but worked in people who failed on diltiazem. So that kind of study is almost never done but could be very interesting for a drug that's toxic.

DR. HAI: I think what you touch on is actually something that Tarek actually mentioned in his presentation, is looking at the subgroups.

I'd have to say that when I looked at those 22 NMAs that were approved in 2016, I did have an opportunity to see the decision-makers in that setting there actually looking at subgroups and looking where the response was really driven by particular areas.

And it didn't necessarily change the indication. But in some cases, it actually changed the signatory authority's decision to approve over when in some cases the team felt that they really wanted to see the average effect to be much more meaningful.

So there were situations where -- and it was actually in your ODE. I can't remember the name of the drug. But it was a situation where both the division director and the office director felt that in that subgroup it was such an impressive finding in this responder analysis that the application should be approved. So I think that is actually being used more often in our benefit-risk assessment.

MR. THOMPSON: Yeah. You want to comment, Tarek?

DR. HAMMAD: Yes. I would like to add that the challenge that -- the challenge that comes with finding a subgroup that most likely it's supposed to have kind of finding and that's why we don’t tend to believe it.

However, what I find contradictory is that, okay, say we have a hundred patients. Ten percent felt

really, very good. So we agree on the whole drug to be approved with all patients being treated and not agree to identify the subgroup and characterize it and perhaps alert the patients to those subgroups because we don't believe the finding.

So there is some kind of contradiction in that we have findings in the way we are handling perhaps some of these aspects.

DR. TEMPLE: Lots of times, when you look at the responders, you don't know how to define the subgroup that responds well.

DR. HAMMAD: Sure.

DR. TEMPLE: You just know that they do.

DR. HAMMAD: Sure.

DR. TEMPLE: So one of the things that we've been urging since our guidance on §14 was put out in 2006 is showing the cumulative distribution of responses or showing bar graphs showing what the range of response is.

DR. HAMMAD: Yeah.

DR. TEMPLE: And it can make a big difference --

DR. HAMMAD: Absolutely.

DR. TEMPLE: For flibanserin, it did.

DR. HAMMAD: Yeah.

DR. TEMPLE: The average effect was half an event per month, everybody, you know, said who cares about that. But in 10 percent of the population, there was one event per week.

DR. HAMMAD: Yeah.

DR. TEMPLE: And I think that's probably the reason people recommended approval. So there's always a distribution of responses.

DR. HAMMAD: Yeah. But your -- yeah.

DR. TEMPLE: It's worth looking at and should be looking at more, I think.

DR. HAMMAD: Now, you are referring now to the efficacy alone. What about the safety component? I think it should always be viewed in that context, the safety.

DR. TEMPLE: Same. The same deal. Not everybody has the adverse effect. Right.

DR. HAMMAD: But then, when it comes to the patient at the point of care, say the example that Mary

mentioned, about 40 percent -- 40 percent of responders. Now, when it comes to the patient at the point of care, he doesn't know -- he doesn't know where they will fit.

So there has to be some kind of extra effort, extra step to garnish their preferences. What is the level of benefit they are willing to take for the level of risk that they have no idea where they will fit in it, which is I think much more challenging. But it needs a paradigm shift in how we are approaching the whole thing.

DR. TEMPLE: For symptomatic side effects, you know, they can tell whether they're having them. So maybe that's okay.

DR. HAMMAD: Yeah.

DR. TEMPLE: But for other bad outcomes, like having a stroke, you do want to know who's at risk and who's not.

DR. HAMMAD: Yeah. Exactly.

DR. TEMPLE: Right.

MS. OVERTON: One comment that I would add to that is that in talking with about 300 people about the

benefit-risk frameworks, what we found is that, as you indicated, sometimes there is a well-defined subgroup. And so, communicating that provides some kind of assurance to the reader that they do or do not fall into that subgroup, either for a benefit or for a risk. And in other cases, there's not a clearly defined subgroup.

And so, in those cases, I think that what the readers were interested in is kind of what -- how can you frame the uncertainty around that to be meaningful to them so that they can understand kind of what the uncertainty is around the non-identified subgroups and understand both kind of what that means for benefit to them and what that means for risk.

So in some cases, there are just those unknowns and it's about communicating them effectively.

MR. THOMPSON: Bennett, you have a question?

DR. LEVITAN: Yeah. Bennett Levitan, from Janssen R&D. First, a quick note to Bob Temple -- Bob's question. There are -- benefit-risk can get hard enough alone when just dealing with the average effects alone, which is probably one reason it's predominantly

been the way a lot of analyses have been presented. But there is a lot of machinery that's in development, particularly with a group called QSPI where they're looking at distributions and joint distributions and particularly for on the simple level, do the people who get the benefits also get the risks.

Do the people who get the benefits don’t get the risks? And it totally changes the way you might consider an approval. It's just that the machinery hasn't necessarily been brought into play. But the wherewithal is there.

All right. My question is really picking up off on what Becky mentioned. So Becky did suggest in her moonshot slide the collaboration and communication concept. And I know from my participation in the Medical Device Innovation Consortium, or MDIC, the collaboration between academics, regulators, industry and patient groups really worked hand-in-hand.

And we developed a framework which turned out to be pretty well-accepted and had a basis in supporting future FDA guidance. Do you see a potential for a similar public-private partnership or

collaborative approach for the upcoming benefit-risk guidance that is mentioned under PDUFA VI? This is to the FDA folks on the panel.

DR. MULLIN: (Off mic) -- so I mean, what do you guys -- when you say that, that you -- you know, you're thinking there's going to be a different -- I mean, MDIC has a lot of very useful tools in it. I don't see us reinventing what was a good collection of a lot of the tools that are out there that are usable. I wouldn't see reinventing that, you know, repository of information.

I think we -- it's a little bit ahead of the game to be saying what exactly would this look like. I don't know. Did a guidance come out of that? There's a repository. Does the guidance that's a CBER -- CDRH guidance actually get developed?

I mean, we typically involve other stakeholders. No doubt we will have some workshops and meetings with other stakeholders there when we get further along with the intent of that guidance. I don't think we're looking at developing a new framework. I thought I heard Becky say that the

benefit-risk framework was pretty good.

Let's not stop in terms of further evolving or doing more and making sure it's used and not siloing things. But I mean, I don't think we were going to go off, you know, in some dark corner of the White Oak campus and try to come up with that guidance in a few years.

I do really think there's a lot to do. You know, and Tarek has raised a whole bunch of new issues today. I mean, I don't think we'd even get them addressed by 2020. And so, I mean, I think we very much expect to involve the other stakeholders in this.

And it's -- you know, saying collaboration, communication and whatever the other C word was sounds great. But you know, in fact, it's hard to do that well too and also keep all the other work going. So we'll try to figure out how to modulate this and involve other stakeholders further downstream. But I wouldn't want to reinvent.

I mean, we'd probably be going into the cupboard and using a lot of what's in the MDIC repository because there are a lot of useful tools in

there. I don't think we need to redo them.

But you know, I think it's -- I think we haven't really figured that out in terms of what we're going to do with that yet. We have a lot of guidances that will be in flight soon, as I'm sure some of you know.

And so, we'll be working on a lot of that and trying to figure out how to interleave it, figure out how to interleave and come up with protocols so that we really can integrate these different new sources of evidence into decision-making in an appropriate way.

And it'll be a challenging -- even more cognitively challenging task than maybe what we're already dealing with. So I think we respect that.

DR. LEVITAN: Well, thank you, Theresa. That's wonderful to hear. I actually was not impersonally thinking about replicating the MDIC work where the benefit-risk framework there really focused on the use of patient preference studies, which is only one piece of many.

What I had in mind is more what Becky referred to as the toolkit, a variety of qualitative, semi-

quantitative and quantitative techniques that could be chosen from and applied to particular benefit-risk assessments, depending on need.

And there are tons of techniques and what we thought -- what I thought would be wonderful is to have a set of standards, that if you pull this technique from your toolkit, what are the requirements for it to meet regulatory needs and what does that -- what's needed to communicate it. And it's much more than preferences, what I had in mind.

DR. MULLIN: (Off mic.)

DR. LEVITAN: Without question. All right. Thank you.

DR. NOEL: Bennett has some free time, I hear.

DR. LEVITAN: One to two a.m.

DR. SAHA: Hi. Annie Saha, from CDRH. I just wanted to clarify a bit about the role of what we did with MDIC and the CDRH CBER guidance. Just sort of clarifying this also help spur discussion in terms of what, you know, could potentially happen.

So with the MDIC work, the catalog and framework that was created for how to incorporate

patient preferences in regulatory, primarily in devices but certainly applicable across medical products, is really the regulatory science aspect, so focusing on the science, the methodologies, what are the questions from the regulatory science aspect.

And that was helpful for us as we internally within the center or across the centers developed our guidance. So we used the science to help inform our policy decision-making.

So if there are these larger regulatory science-type questions that were really beyond any one group or, you know, beyond any one stakeholder take-on, that's where something like a public-private partnership model and developing that larger framework or catalog could really be of potential benefit if there is that need. So that's what I just wanted to add.

DR. NOEL: Yeah, and that really was the point of I think that slide, is that not that we would redo what's been done for preferences through MDIC, but that that offers a model for us as we move forward in trying to consider what we do with semi-quantitative, which is

actually not a term I really like, but what we do with semi-quantitative and even quantitative benefit-risk assessment.

So it's that what does good look like. And I'm not sure that any of us really know. And I think those are regulatory and policy science questions that we need to consider and perhaps even address before we can move towards any sort of wholesale use or wholesale implementation.

MR. THOMPSON: Okay. We're about out of time. We're about to have lunch. So if there's one final question? Sure.

MR. FURMAN: I was interested in how this framework that we've been discussing today affects clinical decision-making because obviously a risk-benefit assessment has to be done by prescribers particularly in cases where significant and troubling safety information emerges post-market. And you get into the question of how best to educate prescribers or change prescribing behavior.

Does this framework instruct us on any strategies or give us any ideas on how to handle that

situation? Thank you. Oh, Jon Furman.

MR. THOMPSON: Thank you.

DR. HAI: Thank you for that question. I think that for me, the benefit-risk framework, the two areas that probably would address your question would be that row where they talk about the current treatment options and then the last row which is risk management.

As I'd mentioned, benefit-risk has always played a role in regulatory decision as far back as I can remember joining the FDA, which is a while ago. But to have a section where the clinical reviewer is tasked or asked to think about current treatment options really means that when you look at the data, you're not looking in your little sphere of the drug application.

You have to step beyond that and think about all of the other available therapies. So if you're challenged with a unique risk in this product, then you go to what the current treatment options are. And what are those risks there? What are those benefits of those therapies? Where could this product actually fit into the overall available therapies, the niche that

you can identify?

And from there, then that would go into a decision about with respect to risk management, including the label. So the label itself for what the company has proposed may actually be evolved and modified based on a determination of where the benefit of this product and this risk fits in the whole sphere of all the other available therapies.

MR. THOMPSON: Thanks very much. I'm sure we're all very eager to get to lunch. I'd like to have a quick round of applause to thank all of our presenters.

(Applause.)

MR. THOMPSON: And we will return at 1 o'clock. So enjoy your lunch.

(Whereupon, the foregoing went off the record at 12:07 p.m., and went back on the record at 1:00 p.m.)

SESSION 2: APPROACHES TO INCORPORATING PATIENT PERSPECTIVE INTO BENEFIT-RISK ASSESSMENT

MS. VAIDYA: Good afternoon, everyone. I hope you all had a good lunch and also got some time to

network with some of your colleagues. My name is Pujita Vaidya. I am in the Office of Strategic Programs in the Center for Drug Evaluation and Research. I will be your moderator today for session two, which is going to focus on approaches to incorporating patient perspective into benefit-risk assessment.

Before we get started though, I do want to mention that in addition to those of you in the room, we have a pretty good Web participation as well. We have 400 participants joining us on the Web. So definitely an interesting topic.

So for today, we will start off the discussion this afternoon hearing perspectives from our FDA colleagues from the three medical product centers. This session will provide an overview of FDA's ongoing efforts to incorporate patient experiences and perspectives to support regulatory decision-making. Followed by that, then we will open it up to other stakeholders and hear their perspectives.

Without further ado, now I'd like to turn the podium to Dr. Theresa Mullin.

FDA EXPERIENCES AND PERSPECTIVES

DR. MULLIN: Thank you, Pujita. Good afternoon. Glad you could make it here today either in the room or the many of you who apparently are on the webcast. So that's great. And so, even though we now have Pujita, and Graham's not sitting here, we were told to take 15 minutes and no more.

So I will do my best to take 15 minutes and no more than that so we have time for discussion. And so, we pared back this talk. And this, from the Center for Drugs' perspective, is really saying more about this patient-focused drug development initiative. You probably heard it mentioned earlier. And it's gotten its own commitments, set of commitments going into PDUFA VI.

But we began this effort by really thinking back in 2012 again with the -- in terms of our reauthorization of the user fee commitments at that time and what to do with our benefit-risk framework. And again, this is a variation on what you've heard before from the speakers earlier this morning, that we now have -- we basically work with a qualitative

approach.

But it's grounded in the quantification of various kinds of data, evidence of safety and evidence of effectiveness. And we evaluate that at the population level in order to make a decision about whether or not it can be approved for marketing.

And benefits typically measured as efficacy endpoints from controlled trials, harms, what's been observed during those trials and what maybe has been observed in other regions if the drug's already available elsewhere. And then, as more information comes in regarding the benefits and the harms, that calculus of benefit-risk will change and it can change over time, and so, as we learn more.

And so, we understand that it's a dynamic process. Yes, it has a lot of uncertainties associated with it and we make these decisions, not only bringing that available information to bear, but really weighing in societal expectations, which may be changing over time, and the personal values and perspectives of the persons who are involved, the humans involved at FDA and also trying to gain the perspectives of patients in

terms of this and applying statutory standards.

So here, we have this benefit-risk framework. And just to orient you, you saw that this morning. I'm going to talk about the yellow highlighted area here. That's the place where we started with this patient-focused drug development initiative, the idea that patients' information could help inform that therapeutic context that you heard about earlier today.

But I think what I'll get to hopefully later is to say that based on what we learned during the patient-focused drug development initiatives and the meetings that we've had -- and we've had a number of meetings. We've had 23. We're going to have -- we committed to have 20.

As of last Monday, we had -- or the 11th, we had 23. And the Center for Biologics will have its final meeting on the 25th, next Monday. And then, we'll have conducted as an agency 24. There's also been about eight led by external patient groups that we set up a process for externally led groups because there were so many groups that wanted to have a meeting about their disease area that we extended it in that

way.

But what we want to do over time is really take this very rich narrative that we're getting and figure out how to in the most straightforward way possible turn that into evidence that can be used as a basis for decision-making, evidence regarding the benefits and the risks experienced during trials with a particular drug.

So we started this initiative, as I said, in 2012 based on the observation that patients were uniquely positioned to inform our benefit-risk decision. They're the ones that are going to take the drug after it's been approved. They're the ones who will experience any benefit or harm that will come from it. And we didn't have a systematic way to do that at the time.

We have a very good patient representative program. But you have to -- you weigh in on individual product matters. So you have to be screened for conflict of interest. It really does narrow the possibilities to people -- for people to participate and those decisions usually need to be made within a

particular timeframe and that also is another constraint.

So we thought we would try this as a pilot effort to see how it went with 20 diseases in different -- each in a different disease area. So we spread that out across the divisions of the Office of New Drugs in CDER and CBER spread it across its therapeutic divisions as well.

Quickly, you can see, if you'll glance across this, the variation. So we really had a wide range of disease areas that we took a look at. We tried to focus on ones where there were no really good therapies, maybe no therapies at all. There's a certain number of these that are rare diseases.

A good fraction of them are for rare diseases. They have typically feature very important symptomatic components and maybe loss of functioning over time. And so, it was really -- these were ones where we knew -- we were hoping and we certainly found that we got a very strong, insightful information from patients.

Just a sense of the numbers, actually we had even more participants in our meeting on alopecia

areata on September 11th who came in person. But we have a lot of participation, as you can see, a lot of webcast participation. That makes sense because a lot of people can't get to White Oak who have a disease and they were able to effectively participate on the Web, which was wonderful.

We also got a lot of comments in through our docket. And we tailor some questions for each meeting. But we also had a set that we used every time I'll say more about in a minute. We also took the opportunity and the review divisions took the opportunity in these meetings to ask questions that they also wanted to hear from the patients about, maybe having to do with participation in trials, their willingness to accept risks.

What about the certain endpoint? Would they find that acceptable? And so, this was also information that was very useful. And here's a golden opportunity to ask the patients what they thought.

So we got panel information. We got the webcast and we had the discussions in the room and we also get information from the docket. And this goes

into a report. Now, here's the kinds of questions we would ask for that top row of the framework, if you think about.

The types of questions we would ask include of all the symptoms that you experience because of your condition, what are the one to three that have the most significant impact on your life.

Are there specific activities that are important to you but that you cannot do at all or not as fully as you would like to because of your condition? Has your condition and its symptoms changed over time? What worries you the most? We asked other questions as well. But these are -- typically every time we ask these questions.

And they always get a very strong response of resonance with people in the room. What about the burden of treatment? What do you currently do to help treat your condition or its symptoms? How well is that working for you? And what are the most significant downsides of your current treatments? How do those affect your quality of your daily life? And assuming that there's no cure, but what would be some of the

characteristics of an ideal treatment for your condition? Again, people found these questions to be very relevant and we had very robust discussion.

So after these meetings, after the docket closes and we're able to analyze everything we've received from every source, we develop a Voice of the Patient report. You can Google Voice of the Patient, or whatever other search engine approach you want to take, and you will be taken to our website and see these reports. We do our best to use the words that patients use to tell us about this to make it as authentic to what they told us as possible.

We try to structure a synopsis of that information in the benefit-risk framework, that top two rows to facilitate its use by reviewers. We encourage reviewers to go and look at the reports if they have a drug that's for that indication. And we also have found that this information sometimes prompt further discussion, further exploration by the review division or companies will come in and talk to us more about their programs and other things.

We've also identified patient groups who have

come in and used this information to start -- jumpstart their work on trying to develop patient-reported outcome measures.

As I said before, we have this externally led option as well if people are able to have this meeting. They can tell us about it. We have a lot of materials on the website that allow them to use the same approach we have if they'd like to do that with their meetings and have them facilitated. And if they hold them in the Washington area, our review division folks will try to get there and our office we try to have somebody go and participate or listen in on what happens in those meetings.

And the success of any of these approaches and these meetings really depends on how much participation they get. And it does really require the stakeholders work together. And sometimes, it means multiple disease advocacy groups working together and trying to bring in participation and so on.

What have we learned from this? Well, that patients are experts. They're a type of expert and they're an expert in what it's like to live with this

condition that they're living with. Their chief complaints, and what we heard about in these meetings are often not factored specifically into drug development programs.

These things are not being measured necessarily in terms of the benefits or even the burdens of treatment. And for a degenerative disease, often patients or their parents would say that just stopping progression would be ideal for them. That would be a very desirable outcome. They want to continue to be active in trying to move things forward in their area.

So they'd often ask us what next. What are you going to do now? We are engaging the broader community. We are now going into this next set of commitments that we made beyond into PDUFA VI. You've heard some people from industry here talk about PDUFA VI today.

And so, we're really working there develop a set of guidances that's going to systematically build from these qualitative, rich, important meetings that we have early on to something that could be used in

that as evidence for decision-making ideally in drug benefit-risk assessment. And that guidance would be written so that not only industry could make use of it but also these communities could be involved heavily and make use of it.

Quickly there, what are we talking about? We have four guidances that we're teeing up for this commitment. We actually have more than that we're working on now because we have some additional requirements that Congress included in the 21st Century Cures Act of 2016. So there'll be more like five or six guidances that will be developed overall in this area.

But the ones that we're talking about to do that bridge from a qualitative early discussion to tools that can be used or measurement tools and trials that can collect evidence that can be used in decision-making start with collecting comprehensive patient community input.

What do you need to do to engage patients to collect meaningful input and what other considerations should you address? For example, how do you make sure

you have a representative cross-section of patient input early on? And then, developing a set of holistic impacts that include both the burden of the disease and burden of treatment since both are extremely important.

And beyond that, how do you then turn that and distill that into measures that are going to actually change with treatment and be useable to measure the improvement or worsening of a condition? And finally, then how do you turn those kind of measures into endpoints that can be used in trials?

And so, we need to start early. The things that I've just described is here, on the left here. Early on, upstream you might say of some of the other presentations you may hear, there are a number of places that I think FDA, the three medical product centers want to see patient -- integration of patient input.

And what I've been talking about is early stage. It might be activity that has to go on early at the translational stage, certainly before you go into trials so that you're able to take those usable instruments into data collection and clinical trials

and you'll have the evidence available for subsequent use. You'll also better identify the kinds of impacts or measures that might be useful and meaningful to patients in subsequent benefit-risk tradeoff studies. So with that, I'll end. And, thank you.

(Applause.)

MS. VAIDYA: Thank you, Theresa. Next, we have Dr. Telba Irony.

DR. IRONY: Good afternoon. I'm Telba Irony and I'm currently at the Center for Biologics at the FDA. I used to be at the Center for Devices. So I'm going to talk a little bit about both and how they intersect.

Just to give you an idea of what the Center of Biologics regulates, it doesn't regulate all biologics. It regulates some. But it's basically blood and blood components, blood derivatives, cell therapies, gene therapies, tissues, some devices related to blood, vaccines and other products.

The whole story that I'm going to tell starts with the guidance that was issued finally in 2016 by the Center for Devices and Center for Biologics on the

factors for benefit-risk determinations.

So these factors include, of course, the benefits and the risks. But it adds what we call additional factors that mean reflect the context in which the benefits and risks are being evaluated, including uncertainty. But of importance for today, now is a factor that relates to patient tolerance for risk and perspective on benefit.

So the guidance says that the risk tolerance will vary among patients and FDA would consider evidence related to patients' perspective on what constitutes a meaningful benefit and risk.

So at the time that we worked on the guidance, we actually had this in mind. But we had not -- we did not know how to consider evidence on patient preferences.

So we decided to see, okay, let's go into a pilot study and see ways in which we can get evidence on patient preference. And that gave origin on a proof of concept study on devices to treat obesity. And the objectives at that time were to explore how to elicit patient perspectives and how to incorporate them into

regulatory decision-making.

So devices to treat obesity, they involve very difficult benefit-risk tradeoffs and we found that that particular area was very convenient for these kind of studies.

We had at that time a broad array of devices in the pipeline and basically we couldn't approve any devices because they involved sometimes not so high benefits. In other words, the weight loss was not so high and they were considerable risks involved.

We wanted to assess the feasibility of eliciting patient preferences and the feasibility of using quantitative patient perspectives in the regulatory decision-making.

So the question was the following. You have the graph of benefits and risks and you consider low benefits, low risks, high benefits and high risks. But if we did have a new treatment that has an intermediate amount of risk, how much benefit we would require to get approval for that particular treatment.

So of course, as I mentioned before, based on the guidance, it will depend also on the context. If

it's an unmet medical need, maybe we will tolerate more risks. If it's something that's very common, we would be more restrictive on what kind of risks we would tolerate. More importantly, what would patients prefer? Would they tolerate risk? How much risk they will tolerate?

So we decided to go on this obesity study. We partnered with RTI and we collected a sample of 650 subjects with BMI greater than 30 and who were willing to lose weight. And we used a discrete choice experiment as a quantitative way to elicit patient preferences in which the respondents evaluate choices between pairs of hypothetical weight loss device treatments.

So each treatment is defined by its attributes and levels and the pattern of choices will review the patients' preferences. For instance, in terms of quantitative terms, we could say that patients would tolerate two more months of adverse events or diet in exchange of losing 24 more pounds.

So these were the attributes and levels we considered in obesity study. We considered the type of

surgery, the diet restrictions, how much weight loss will be accomplished, how long it will last, improvement in comorbidities such as diabetes and cardiovascular disease, how long the side effects will last, the chance of a serious side effect requiring hospitalization and finally, the chance of death for receiving the device if you are a really obese patient and you go under surgery. You have risk of death. So that was considered in the study.

This was the type of choice question that we used in the study. If you have two devices, A and B, with several attributes and levels, patients will -- all respondents in the study will select which one they would prefer. Each subject in the survey had to make eight of such choices. And based on these choices, we could calculate what we called preference weights.

So these are some results very briefly. You know, how we depicted the preference weights, you know, higher bars means higher preference. The negative values are bad things. The positive values are good things. So better outcomes have significantly higher weights and mortality risk and weight loss and weight

loss duration were the most important attributes for the respondents in the survey.

So as a result of the survey, we could get a quantitative decision tool that would calculate the minimum benefit patients will require in exchange for certain risks and other attributes for devices or calculate the maximum risk that patients will tolerate in exchange for a benefit.

The results could be reported for various levels of patients' risk tolerance and risk aversion, reflecting the heterogeneity of the patient population. And the tool would calculate the proportion of patients who would choose to get a device instead of remaining obese.

And what's very interesting, we could estimate what would be -- or values that could inform the determination of what will be the minimum clinically significant -- clinically significant benefit or weight loss that will be used in a clinical trial for that treatment and, you know, in the design and analysis.

What was the regulatory impacts of that study? You know, the study was published in Surgical

Endoscopy. The method can be adaptable for other products. DCE is not the only method. There are several methods that are listed in the medical device innovation -- medical device, MDIC catalog. You know, there are 14 methods listed there.

One obesity device called Maestro was approved based on some information derived from the decision aid tool, not only but some of that information. That study helped to develop the patient preference information guidance document that was released in 2016. It's subscribed by Center for Devices and Center for Biologics.

And it motivated the development of a project or several projects at this point by the Medical Device Innovation Consortium.

So these are the impacts. It's a publication. It's the catalog from MDIC and the guidance on patient preference information used for medical decision-making for medical devices and some biologics.

Now, what's the Center for Biologics initiative on the science of patient input? So we have a group that's involved in developing patient-reported

outcomes and recognizing them and validating within CDER and also patient preference information. The initiative supports the whole agency efforts to capture and to incorporate patient perspectives into a regulatory framework.

We are advancing the science of patient input within CBER, building internal review capacity for patient preferences studies and PROs. We are collaborating with other FDA colleagues. We are exploring existing and new ways to integrate the science of patient input information into our regulatory decision-making and we are tracking our experience to inform continuous improvement.

So we have some other activities. We have studies in hemophilia. We are providing education and training to our reviewers. We are assessing the understanding of our reviewers in their regulatory decision-making and we are reviewing patient input studies that are submitted to the Center for Biologics.

So one of the examples of preference sensitive studies that we are conducting is in hemophilia in which there are two different treatment options. You

can treat hemophilia by prophylaxis using the patient weight or using the pharmacokinetic profile. Both have benefits and risks.

For instance, if you use a prophylaxis using body weight, it's a less invasive way of treating. But the patient will have more bleeding episodes whereas if you use a PK/PD profile, it's more invasive because you have to collect blood from the patient to construct the PK/PD profile.

The patient might require more infusions. But they will reduce the frequency of bleeding. So these kind of studies is -- and these kind of choices are preference-sensitive and we are studying that within CBER.

So finally, my takeaway message. Patient preference information is a very important supplement to clinical and statistical evidence and can enhance the benefit-risk assessments for regulatory decision-making. The evidence in patient preference can be scientifically obtained, as proved by one of the DCE methods that we conducted and other methods listed in the catalog.

Patient preference information can provide insights. For instance, we see within CBER that for rare diseases, our clinicians didn't have any contact with patients because the diseases are so rare. There are very few patients in the U.S. So providing that information is very important for the clinicians when they make regulatory decisions. And of course, the science of patient input is evolving. Thank you very much.

(Applause.)

MS. VAIDYA: Thank you, Telba. Next, we have Martin Ho.

MR. HO: Good afternoon, everyone. First, I want to say thank you to Telba for doing the heavy lifting of explaining the benefit-risk guidance of CDRH and CBER. She did a very nice job of explaining the quantitative approach of using patient preferences in informing our regulatory decision.

So therefore, I will take advantage of that and I will rather focus on some big picture items so that we will keep on track of why we are here and why we are doing that.

As you may have heard from both Theresa and Telba, Theresa had mentioned that she had been working hard to try to turn collect patient voices into evidence. And that is a qualitative effort. On the other hand, Telba has showcased some efforts in trying to measure patient preferences quantitatively and also presented it as evidence to inform our decisions.

So I'm very, very glad to hear that because it's for all across all the medical product centers, we are working very hard to achieve one goal, which is assist the meta-collection of evidence so that the patients will be heard -- and could be heard unbiased and in a valid manner.

First, I want to introduce my center, Center for Device and Radiological Health. We are at the FDA regulating more than 5,000 unique types of medical devices and we also actually regulate diagnostic tests. There are not that many people who would be aware of the medical tests that are also regulated by the FDA.

And as you can see, the patients are at the heart of what we do. In fact, I mean, patients come first in our CDRH vision, which is patients in the U.S.

have access to high quality, safe and effective medical device of public health importance first in the world.

I'm pretty sure that my center director would love to see that because he likes this vision very much and he mentioned it many times in front of us.

Next, we are -- I want to talk a little bit about why we are here. And I mean, from the very beginning, on the left-hand side, you can see that in the traditional way of delivering medicines, it's mostly determined and led by physicians.

And then, during the '80s, we have seen some emerging disease situations that basically pool patients together and form groups and they have provided support to each other and they also felt that perhaps it's a good way for them to influence the medical product development.

And then, through sharing information, perhaps thanks to Internet, people are getting more and more -- feeling more comfortable to share information and their opinions. And then, that further employs the power of patients. And now, we are here, that the patient-provider partnership is very important in terms of

shared decision-making setting, even though I think we still have a long way to go. But the will is there and I think the patients are looking forward to that.

So I talked a little bit about hearing patients' voice. What does this exactly mean in the context that we have talked about collecting evidence? So therefore, we wanted to be careful about using terms. Here I hope to provide some clarification. Here we see that there are three different types of patient voices.

The first one is patient inputs which is the widest type of patient voices that range from anecdotal comments from patients to qualitative measurements.

And then, a more specific type of patient input would be a patient perceptive, which our guidance referred to a type of patient input that patients -- reflecting the patients' experiences with a disease and condition and its treatment and management. It can be very useful for us to understand the disease or condition and its impact.

Also, it will also be informed about the relative importance of outcomes to patients which

Theresa had mentioned about in the PFDD effort. And then, we understand the benefit-risk tradeoff for treatment, which Telba has mentioned very nicely in the previous presentation.

So I wanted to put a little context here in terms of where the patients' input in terms of regulatory impact.

Of course, I mean patients' voices can be used in so many different stages in the medical device total product life cycle from the idea conception to the design of clinical trials and development of patient-reported outcomes and then helping us to conduct a benefit-risk assessment of the medical product.

And of course we also need to communicate correctly and unbiasedly the to the benefit-risk information to patients so that they can use the information. And finally, the patient-centered outcome can also inform us in post-approval surveillance context.

Seeing that patient preferences or patient information can be so informative, it has a very big role to play in the benefit-risk frameworks that the

medical products center has been using. As you see, we have two different types of frameworks. The left-hand side is CDER's and CBER's benefit-risk structural assessment and then on the right-hand side is our benefit-risk guidance.

I want to comment that structurally if you pay attention to both, they look very similar and they are trying to assess some very similar things, which is trying to get a better understanding or systematic understanding of benefits, risk and the impact to patients.

And a little promotion for my own center's benefit-risk guidance, I think it comes with a very nice worksheet that is a requirement for all the post-, pre-market approval applications files to be filled out by our medical officers. And in that worksheet, it talks a lot about in details about the benefits, the risks and the patient perspective.

And in each factor, we have asked very detailed and layered questions to help guide the clinical officers' thought process in terms of determining the benefit-risk ratio of the product under

investigation.

And I also wanted to highlight that one of the unique places that I'm quite proud of our worksheet is that we have a very detailed, you know, description or questions about patient preference information.

Here is just a highlight of some of those questions. In terms of patient-reported outcomes, we ask how does the benefits and risk include effect on patients' health-related quality of life, which Theresa had alluded to earlier. And then, we talk about the benefit-risk considerations.

So which one -- which benefits and risks are most important to the patients. Are those tradeoffs acceptable to them? Are there any clinically relevant subgroups that would accept a particular benefit-risk profile over the other alternatives? And finally, what other PPI -- the patient preference information -- can capture a diverse preference across a spectrum of indicated populations, which is implications of generalizability of the results.

As we have talked about before perhaps this morning, we know that the patients' opinions and

preferences can be very diverse. And therefore, being able to capture such distribution is very important. And I'm a statistician by trade. So therefor, whenever we see a distribution, I love to hear that.

So therefore, if we have a way to capture that and compare them I think is a leap forward for us in terms of science to understand patient preferences as an outcome.

In addition to the science side, my center has also been working very hard to have a cultural change within our center. The first trial of our center structurally or center-wide effort is our strategic priorities for the last two years. We intended to interact with patients as partners and work together to advance the development and evaluation of devices and monitor the marketed devices.

So it's a cultural change by encouraging 90 percent or more of all the center staff to interact with patients at least one time in one year. And we also have increased use and transparency of patient inputs in our regulatory decision-making. That includes patient-reported outcomes and patient

preference information.

So I would like perhaps to give a review about -- I mean, our use of patient preference information. We have a few submission in-house and we have been considering them. So very carefully work collaboratively with the sponsors.

So hopefully not too far in the future, it will be some results can be shareable and then people would have a better understanding of how patient preferences can be used in different types of devices and regulatory decisions.

Last but not least, I think we have a great patient engagement advisory committee. I want to applaud my colleagues who moved mountains to make it happen because, as you can imagine, we have never had or organized an advisory committee based on patients.

And so, the date -- the inaugural meeting will be October 11th and 12th and the focus of the conversation will be on my favorite topic, which is design of clinical trials. Again, I am a statistician. And going forward, we are really committed to the science of patient input, just like our sister centers.

In fact, it has been shown in our user fee agreement in terms of our commitments of deliverables, we will commit to build capacity, to build scientific evidence of patient input. We create -- we will create a PRO evaluation framework.

We will conduct demonstrative studies that are adapting existing PROs and using -- and also on patient -- on patient preference information studies as well, which will be focused on the preference-sensitive conditions. We will hold workshops to talk about PROs in regulatory decision-making.

And then, most important thing is this year -- by the end of this year, we will -- I mean, across all three medical product centers, we have organized the FDA patient preference public workshop, which will be on December 7th and 8th. I have seen a lot of my partners in crime here. We work very closely. So I'm very glad that we've made significant progress. And I hope you can save the date for that.

In conclusion, I think that structural benefit-risk framework has been proven to be a very important tool for us, not only for systematic

assessment of medical products but also for us as the reviews and staff to communicate the files with the major stakeholders because everyone now, they are facing this same set of framework.

And also, I think both qualitative and quantitative PPI can inform medical product development in one way or another. And more importantly, the qualitative part can also help us to evaluate the benefit-risk profile of the product.

And we have been working very hard and we will continue to engage patients to inform regulatory decisions.

But one thing I didn't mention here is that because of patients, I see that in my nine years of working at the FDA, during the last few years, we worked closer than ever between different medical product centers to talk about how we can listen to patients consistently and scientifically.

And we have held regular meetings with Theresa and others and Telba and we exchange notes and compare our review experience. So I think it's very valuable. Thank you.

(Applause.)

MS. VAIDYA: Thank you, Martin. And thank you, Theresa, Telba and Martin for talking about our FDA efforts. Now, I'd like to ask our other stakeholders -- so we have Brett Hauber, Leah McCormick Howard and Alicyn Campbell -- to please join us on the panel.

We're going to move on to the next session and hear from our other stakeholders on ongoing efforts to incorporate patient experiences and perspectives into drug development. So I'll turn the podium over to Brett.

STAKEHOLDERS' PERSPECTIVES

DR. HAUBER: Thanks, Pujita. I'm Brett Hauber, from RTI. This presentation was a little difficult to put together because we've covered a lot of area already today. So I'm going to do my best.

One of the things I wanted to start with, which I think is already evident from what has been discussed before, is that incorporating the patient perspective into drug development and regulatory approval is a hot topic. A lot of effort is being put

into it by a lot of different types of stakeholders. I actually -- this slide here was inspired by Rachael di Santo-Stefano, a colleague of Bennett Levitan's, who had a similar slide.

But we can't fit all of the logos of everybody who's working in this area onto this particular slide. So I just grabbed a couple. I mean no offense if I've skipped somebody who happens to be in the room. That's always the risk of doing something like this.

So when thinking about what matters, or patient input in general, I always go back to -- or I should say I have recently always found myself going back to an article in The New York Times two years ago and there is a rare genetic disorder called RCDP. I'm not going to try to pronounce it because I am not a medical professional by training.

But it's a rare form of dwarfism. And this was a great article that I think really brought home to people, to me in particular, what it really means to think about the patient perspective and unmet need in drug development and as a patient preference researcher, this is kind of an important starting point

for thinking about how to incorporate the patient perspective into benefit-risk decisions.

So one of the things that comes out in the article was that there is no treatment for this rare disorder. There wasn't, at least at the time.

But there was a great theory about how this disorder might be treated. And there was a biological endpoint that had been identified that could in fact potentially be an endpoint in a clinical trial.

But during one of the patient group meetings in Alabama that happens pretty regularly, apparently a couple of the researchers in this field actually met with the families of the children with this disorder.

And they basically conducted an informal patient preference study, which I just kind of thought was really cool because what we do systematically and often quantitatively in patient preference research is a very natural thing for people to do.

So this particular clinician asked, you know, what kind of improvement would you like to see in your child. And that is basically the foundation of everything that we do in preference research. And

then, you get answers such as stronger respiratory system, stronger immune system. We'd like our child to be able to talk to us, to hug us, to tell us that he or she is in pain, not having to second-guess every decision as we go along.

These are the types of things that I imagine FDA is hearing in the PFDD meetings in different areas. We're hearing from the patients that, look, we can have a clinical endpoint. But really what matters in the end to us is how does it affect our day-to-day lives and fulfill these needs that are currently unmet.

So essentially, without even knowing it, or at least not doing it in quite the way that I would necessarily do it, this particular doctor was actually doing a preference study.

And I think the key in doing -- using this example is before we can measure that matters, we need to know what matters. And that's a really important starting point for all of the work that we do.

So there are three types of patient preference information that can be used to inform benefit-risk assessments and I'll kind of lay out what these three

types of information are and then talk about kind of where patient preference information might fit into a benefit-risk assessment.

The first is what matters. These are the attributes. What are the things that can be affected by treatment that are important to patients? What matters? Then, how important are these things? What is the relative importance of each of these things?

And I think in one of the recent presentations, this concept of how important are these things came up because not everything is equally important. And then, then the tradeoffs.

What tradeoffs are we willing to make between the benefits and risk to determine whether, as Telba was able to demonstrate in the studies that she had shown, what the minimum important clinical difference is and what the risk tolerance is.

Those are tradeoff concepts. But before we get there, we need to know what to measure, how important it is and then we can start talking about the tradeoffs. One of the challenges is methodologically the beginning is fairly easy and that's the type of

informal, qualitative-type stuff that this doctor who was at the patient group in Alabama and maybe even through some of the patient-focused drug development stuff we can get qualitatively. What are the attributes that matter? Then, we can get into the more quantitative approaches.

So there are essentially three, four -- there are three basic approaches to incorporating patient preference information into benefit-risk assessments. There are actually four. One of them I've divided into an A and B. So I'm kind of cheating a little bit.

I'll show you four different ones under three different categories. But when we think about benefit-risk assessment, and this is similar to a graph or a figure that Tarek had shown earlier today, there are kind of three steps.

First is to assess what do we know about the benefits and the harms. Then, either implicitly or explicitly, what are the weights that we put on those benefits and harms? And then, how do we use those weights to interpret the benefits and harms to come to a decision? And as you've heard a lot about today,

this can be implicit, this can be explicit. It can be qualitative, it can be quantitative.

But this is the general framework. Where patient preference information really focuses on is in this middle section. And all of the methods that -- I'll show you the list of methods from the MDIC catalog later in this presentation. But all of these methods essentially focus on that middle point.

But the first approach to doing this is to look at the question as a whole. And this is where something like multi-criteria decision analysis might come into play. And as part of multi-criteria decision analysis, there is this idea of weighting and often it's swing weighting or other types of weighting that can be used for this middle component.

But part of multi-criteria decision analysis is to define the problem, apply the weights and come to a decision or facilitate a decision.

And a good example of this is an EMA pilot study that was conducted and published last year in which EMA actually went out to regulators, patients and careers and healthcare professionals in the fields of

myeloma and melanoma to get input on what matters, to use swing weighting to determine how much it matters and the tradeoffs that patients are willing to make between improvements in progression-free survival and overall survival and toxicities.

And then, to look at the results and then the interesting thing about this study is because it was a pilot study, they then followed up with people to ask them about their input and kind of feed it back to them and see exactly whether they were -- the agency or the researchers were interpreting it correctly.

And the conclusion that came out of this was, hey, this could in fact be a very useful tool. And earlier, one of the representations showed what I believe is the next iteration of this particular study beginning to look at individual patient responses and the distribution of those individual patient responses.

The second way to do this is just to zero in on that second section. And this is a lot of the type of thing that Telba and Martin were talking about. And that is to elicit weights directly for the outcomes of interest. And the first way to do that is to elicit

one weight at a time. So once you've determined what matters, you've identified your attributes, get an individual weight on each of those attributes.

For those of you who might be familiar with cost-effectiveness analysis, this would be that type of thing where you have an outcome. You have a weight for that outcome. You multiply them together and then you can kind of come up with your relative importance.

There's a current study ongoing. I wish Martin were still here because he's an integral part of this study with the CDRH, the Michael J. Fox Foundation, MIT, the Medical Device Innovation Consortium and a group of us from RTI in Parkinson's disease.

And it's a multiphase project and really it's part two that I am mostly involved in. And that's a patient preference study. But that's where we'll get to. But I think this warrants kind of showing the whole arc of this study. I can't claim to have designed this study myself. I wish I could because I think it's absolutely brilliant.

It started with going to patients, and not

only patients but also to reviewers within FDA to determine what is important. And that work in aim one has been completed. And the learnings that came out of that, from getting the input not just from patients but understanding from the reviewers, hey, this is the information that I need when I'm looking at clinical data, was just really revealing.

Our job then is now to work and develop a patient preference study to understand the relative importance of each of these particular endpoints and the tradeoffs that patients are willing to make to do that and incorporated in that we have two patient scientists from the Michael J. Fox Foundation who are working with us.

And every time we have a conversation, I come away having been scolded by the patient scientists who tell me that I'm not getting it. And that's an important thing as a researcher for me to hear is that I need to understand what it is that matters and understand it in a way that it matters to patients.

Then eventually, once we complete this study -- this is what's really interesting -- is we'll take

some of these preference weights, share it with a group of researchers from MIT who have developed a model to look at optimization of clinical trials, incorporating the patient perspective to look at the levels of uncertainty that patients would be willing to accept in order to have a product on the market sooner. Really a terrific and novel concept.

So this is a longer term thing. What we're really focusing on is aim two currently. And what we will do is we will use the threshold technique and I mention that even though it may not have meaning to a lot of you. It's different than a discrete choice experiment because we are estimating tradeoffs.

But we are using those tradeoffs to get one value at a time and there are a number of reasons why we're doing that instead of something else here.

But these are actually the endpoints, the outcomes that came up during the patient and reviewer interviews that are important that we will be measuring in that study.

The other way to get -- to zero in and get on the -- get to the weights that matter to people is to

estimate the weights simultaneously. And the best example of this is the example that Telba showed earlier, which is the discrete choice experiment approach used in obesity that was then subsequently used to provide evidence to inform the decision to approve the Maestro device.

And then, finally, we could look at the actual decision in the end, expose people to both technologies in a two-arm trial and then see what they would actually prefer. And a recent example of this was a study sponsored by Genentech to compare subcutaneous and IV rituximab in the treatment of particular forms of non-Hodgkin's lymphoma.

So all three of these particular methods have been used. Remember the first is to look at the whole decision framework together. The second is to zero in on the weights in the middle and then the third is to kind of look at that decision at the end and work your way back.

Here's the list of preference methods from the MDIC catalog that has been mentioned quite a few times today, actually more than I thought it would be

frankly. You can find the framework report online at MDIC.org. I'm going to make a plug for that.

Go to the patient-centered benefit-risk work stream and in there the first thing that probably will pop up, I think, is the framework report and the catalog of methods is actually an appendix in that framework report.

But there are a whole list of methods out there for eliciting preferences that could be used in benefit-risk assessments. They come from different theoretical foundations. They come from different academic disciplines. They have been used for different reasons in the past and are currently being used for different reasons.

But there's a whole host of options out there and I think when we talk about toolkits, one of the things that we really need to keep in mind is that there are a lot of tools out there. And what we need to learn to do is apply the appropriate tools in the appropriate context.

And that's what we're trying to work through now, I think, in a lot of different ways from a lot of

those different groups that I had shown upfront.

So if you only remember a couple of things about this presentation, these are my opinions. That's why I think they're important.

So I really do believe that before we can measure how much something matters, we really need to think about what is it that does matter. And that's where the patient-focused drug development initiatives really, you know -- I think really do a fantastic job because the whole idea is to begin to understand what in fact does matter. What are we trying to impact here?

Preference methods, as Telba and others have shown, can really have a tremendous impact on informing decisions. They are not necessarily decision tools in and of themselves. But they can provide information.

And I think, if I'm interpreting what Theresa said correctly, one of the things that we want to do here is to begin to say how can we use this and other types of information as credible evidence. And I think we're in that development phase right now.

But there are precedents for doing this and

some of them have come from industry sponsors and some of them have come from private and public partnerships. Some of them are in development by patient groups. Everybody who has a stake in this is actively involved in this type of research.

And then, finally, I want to go back to the point that I raised earlier. Right now, there are lots of tools in the toolbox. And what I think our biggest challenge is right now is to understand how these different tools perform under different circumstances in informing decisions and will those decisions stand the test of time. And that's a really big challenge.

But I think it's a challenge that people are already undertaking that we need to continue to undertake as we develop this whole concept of approaching benefit-risk assessment. Thank you.

(Applause.)

MS. VAIDYA: Thank you, Brett. Next, we have Leah Howard.

MS. HOWARD: Great. Thank you. Good afternoon. My name is Leah Howard. I'm the vice president of government relations and advocacy for the

National Psoriasis Foundation. The comments that I make today are mine alone and I'll disclose that I am an employee, as I said, of the foundation and the foundation works with all of the developers in the psoriatic disease space.

So the National Psoriasis Foundation's mission is to drive efforts to cure psoriatic disease and to improve the lives of those living with both psoriasis and psoriatic arthritis.

The NPF was founded 50 years ago in Portland, Oregon by this little ad actually that you see up there on your screen. So a gentleman whose wife had severe psoriasis, as a gift to her for her 30th birthday, put an ad in the Oregonian, the local newspaper, and simply asked do you have psoriasis, do you want to connect with others that do, call this number. And from this ad in the Oregonian newspaper, our organization was formed.

In that first week alone, she received a hundred phone calls and finally felt like there were other people that knew the pain and challenges she was experiencing and felt that there were people she could

help. So over the last 50 years, our foundation has served the more than 8 million people living with psoriasis and psoriatic disease. And we touch about two-and-a-half million of those folks annually through our website and programs.

As we talk about patient preference, I think it's helpful that you understand a little bit about the disease our community is impacted by. So as I said, there's more than 8 million people living with psoriasis and psoriatic arthritis. Up to 30 percent of those folks will go on to develop -- up to 30 percent of the folks living with psoriasis will go on to develop psoriatic arthritis.

And we also see very high rates of co-morbidities. So there's a strong connection between psoriasis and psoriatic arthritis and heart disease, cardiovascular disease, diabetes and other inflammatory health conditions. Beyond those conditions though, there's a very strong connection between psoriasis, psoriatic arthritic and mental health.

And so, I just want to note as we talk about this topic that when we talk to our community, what we

hear is that approximately two-thirds of people living with psoriatic disease express that they feel angry, frustrated and helpless. Greater than 50 percent talk about the way their disease impacts negatively their ability to enjoy life and nearly 30 percent suffer from depression. What we also hear is that those same impacts extend to the family members living with the people with psoriasis and psoriatic arthritis.

So about 88 percent of family members living with someone who has psoriatic disease expressed that they have those same levels of anxiety and depression. And we know that in many cases unfortunately individuals living with moderate to severe psoriasis as well as psoriatic arthritis are not treating up to the levels appropriate for their disease.

So about 45 percent of folks with moderate to severe psoriasis and 59 percent with psoriatic arthritis are not treated up to the level that their physician feels is appropriate based on the severity of disease. And there's a lot -- certainly a lot of reasons behind that, many of which the NPF tries to serve.

So we have heard today quite a bit about the evolving landscape when it comes to incorporating patient preference. And I'll say from the patient standpoint and patient organization standpoint, we've certainly been pleased to see the increased interest and emphasis on understanding patient perspectives by both industry as well as regulators.

We've seen patients respond very favorably to the increased opportunities that go along with that for patients to share their own experiences of living with the disease, the challenges that they have felt, both the needs as well as the frustration and what we're looking for in new therapies and new treatments coming down the pipeline.

From a psoriatic disease community's perspective, certainly the PFDD meetings that have been discussed today have been a big part of that. But we know from others in the chronic disease community as well as beyond that that's not the only opportunity and patients are enthusiastically embracing other opportunities to share their perspectives.

Ultimately, this open dialogue is what has our

community and others so excited. We are pleased to see that as part of that evolving landscape, that's also meant that there's a more accurate understanding of patient perspectives being discussed and considered in advisory committee hearings and other contexts by regulators.

And so, the result, of course, is that the patient community feels more empowered going forward to engage with drug developers and regulators, something we certainly have been pleased to help support.

A few of the lessons learned that I'd like to share as we've gone through this evolution. So first is who. So we've talked about the diversity of patient communities.

And the chart that you see up on the screen was put together by myself and my colleagues as the PFDD for psoriasis was planned back in 2016 to ensure that we -- as we thought about our community, we're really capturing every segment of that community. So this chart, which I understand is illegible, is just meant to visually demonstrate to you that even in a community like ours where we have a broad understanding

of that diversity, when we actually sat down and wrote out who all the different subpopulations were of our community, what we realized was there were a lot more folks that we were going to need to tap into in order to try to help the FDA hear from that very diverse community.

And so, thinking about who those subpopulations are, and not just who they are, but how to access them was a key part of how the NPF supported the planning for that 26 PFDD meeting. We know as an organization that's been around for 50 years that our community has very strong perspectives. And we've heard that from them ourselves over decades of annual surveying and our registries.

But knowing exactly what data regulators and industry are looking for is often a challenge. And so, helping to think through as the PFDD meeting was planned some of how to ask those questions to get at exactly the data that would be most useful to regulators and to industry is something certainly we encourage folks to do.

As I said, I think that patient advocacy

organizations have a broad reach into the communities that they serve and certainly have the trust of that community built over many years. And they can be a great partner. Patients are partners, absolutely.

But the patient advocacy organizations are also great partners, as you think about how to elicit patient perspectives.

So engaging patient communities and patient subpopulations through each of those outlets, the patient organization, the physicians as well as other tools such as social media, is a really important way to ensure that as patient perspectives are brought in, they truly are reflective of the diversity of the perspectives of the community.

It is important that as patient perspectives are elicited, that there's an emphasis placed on explaining the value that the patient perspectives will bring to the conversation, whether from a regulator perspective or an industry perspective.

And I think it's often forgotten that patients sometimes need explained to them why their perspective is going to make a difference. How it'll be used

certainly, but what value it brings. And so, that's something that the patient advocacy organizations can help with certainly, but also regulators and industry explaining that is helpful.

So going forward, from an opportunity standpoint, regulators can now access more accurate, timely and current patient perspectives and decision-making and that's something we've all been very pleased to see from a community standpoint as this evolution has occurred.

As I said, partnership opportunities abound with patient advocacy organizations. We can assist with that information-gathering. We can also assist with the dissemination on the backend as well of information. And the patient community, I think you'll see from an opportunity standpoint, really embraces the opportunity to share their perspectives when they know, as I said, that doing so will make a difference.

Of course, there are challenges on the flipside. So as we've heard today, there's been much evolution in the last five years and I won't really touch on that. But I think there are from a patient

and patient community standpoint a number of questions that remain as we move ahead. And those include understanding how as this paradigm evolves patient perspectives will be incorporated into the risk-benefit framework.

Determining what actions they can take both individually and as patient advocacy organizations in collaboration as well as independently to capture relevant information and to bring that back to regulators. And then, knowing how these inputs are being considered as part of our product reviews.

As we think about going forward and hat success looks like, a few patient perspectives on that.

So certainly one measure of success will be that more patient perspective data is gathered and utilized by all stakeholders, that patient perspectives are incorporated more and more into the regulatory decision-making process and that patient representatives have a meaningful place at the table particularly in advisory committee meetings, but certainly other settings as well.

And finally, that patient and patient

representatives feel valued by regulators and product developers, remembering that patients are more than just a trial participant or an end-user.

A few final thoughts and observations. So from a patient community standpoint, I think we've all been very pleased to see how far we've really come in the last five years on incorporating patient perspectives.

Congress and the FDA, as well as patients and industry appear to be committed to the tenets of patient engagement and patient-focused drug development, including the risk-benefit context.

Patient perspectives we certainly understand are not a suitable substitute for solid scientific evidence. However, when the case is close, when the call is close, scientifically rigorous patient perspective data must be considered to inform a decision.

I think the era of big data brings with it tremendous potential for the field, as it will hopefully become easier and more cost-effective to collect relevant input. We've been pleased to see that

we now have tools at our disposal that allow us to gather patient perspectives on a whole host of symptom and challenge issues for patients in an ongoing way through an online registry platform. And I think that's really supplemented our ability to share information even beyond things like traditional surveys.

I would just add we applaud the FDA for moving ahead on implementing key provisions such as the guidances called for in 21st Century Cures and hope to see additional clarity and direction to ensure patient perspectives is a key element of the risk-benefit framework.

I want to just close with a quote from one of the public comments that was submitted to the docket for the 2016 psoriasis patient drug development meeting.

The NPF was pleased to support more than a hundred patients registering to participate in person in that meeting and more than double that online. And as part of our outreach to our community, we encouraged those folks who could not be there on March 17th to

share their perspectives with the public docket.

And this was a comment, part of a comment offered to the docket by a woman who I don't know. She didn't have a lot of advocacy experience with the foundation, if any that I'm aware of.

But I thought it was very interesting that as part of her comment she specifically called out that desire as a patient to engage with regulators as well as with industry and offer her perspectives. Thank you.

(Applause.)

MS. VAIDYA: Thank you, Leah. And next, we have Alicyn Campbell.

MS. CAMPBELL: Sorry. It was a bit of a long walk from over there. Hi. Let me make sure I do this correctly. Hi. So for those of you I haven't met, I'm Alicyn Campbell and I'm the global head of patient-centered outcomes research for oncology at Genentech, which is a member of the Roche Group.

So I'll be talking a lot today from the oncology perspective and also just I'm not a preference person, although I was part of the -- he gave me a

really nice setup with that Rituxan preference example. We didn't conspire beforehand.

But I'm definitely a social scientist and I've been in outcomes research for almost 11 years now. And I'm going to be talking about patient-reported outcomes and clinical outcomes assessments and how those can help with the FDA benefit-risk framework. And my disclaimer is my thoughts are my own and they're not those of Genentech or of Roche.

So whenever I talk to folks about the patient voice, I always like to talk or start with a scan like this because I think when we talk about benefit or treatment benefit, we tend to look at objective measures. And so, for those of you who aren't oncology people, and I'll forgive you -- just kidding -- this is a scan showing progression-free survival.

And so, you can clearly tell that the patient's having benefit and the tumor's shrinking. But if you think about the FDA definition of clinical benefit, which is impacting how a patient feels, functions or survives, I would argue what this scan is telling us about how this patient feels or functions or

their symptom burden. And so, when we talk about efficacy or benefit, we tend to use examples like this.

On the flipside, when we think about safety or risk, this is a common toxicity criteria for adverse event table that's commonly used in oncology. And you can see it has a long list of adverse events, from highest to lowest frequencies across the two treatment arms.

And so, for this session, when we talk about benefit-risk, I'd argue in the last two examples I've shown you, we don’t see the patient voice. It's really absent. And I think we know that although adverse event tables are great for characterizing the risk associated with laboratory values, it's been well-documented by Ethan Bosch, Amy Abernathy and others in the patient-reported outcome community that it definitely tends to underrepresent or undercut the patients' impact.

So we've talked a lot today about how it would be great to have systematic inclusion of the patient perspective. In particular, I really liked Tarek's slide where he had a patient with all the different

semantic word clouds for the ways we can talk about the patient voice. And so, I would posit we already have some pretty good quantitative methods we can use to better understand the patient impact that I think would be helpful for risk-benefit assessment.

So if we start on the right -- and I just want to make -- yeah, I knew that was going to happen when I tried to use the pointer. Now I've been fired. Sorry. I didn't have the pointer training here. I'll just -- I will not use the pointer.

If you start on the right, these are the types of measures we can use to systematically and quantitatively assess the patient experience of treatment and also of disease.

And so, first is the patient-reported outcome. And so, that comes from a patient without interpretation from anyone else. I think these are particular important in oncology when looking at adverse events because oftentimes patients are concerned with telling their provider about a symptom for fear of losing the medication.

And so, the confidential patient-reported

outcomes often give us a fuller picture of a cancer patient's experience with their disease. We also have clinician-reported outcomes. And so, these are measurements based on a report that comes from a well-trained health professional after observation.

These are much more common in areas like neuroscience, additionally sometimes in pediatric areas where patients aren't able to self-report, observer-reporter outcomes, this could be for a caregiver for a patient with Alzheimer's disease or autism. And then finally, performance tests. This could be a six-minute walk test.

It's essentially a test that requires patient cooperation to complete. And a lot of the digital health and mHealth applications we're starting to see could fall into this area.

And on the left, you can see the broad array of concepts these can measure. You can measure signs. You can measure symptoms, interference with activities of daily living, functioning and behaviors. So when we think about how do we document systematically the patient experience into risk-benefit, I think we have

some good tools by systematically including this evidence.

So when I think about the framework -- and remember, I'm a social scientist. I'm not as much of a risk-benefit framework person -- I think we tend to talk about them as separate. And that's something that always kind of stymies me.

You know, with the second word cloud someone showed earlier today, benefit and risk were there. And to me, it's really the same. To me, it's hard to really tease those out as mutually exclusive concepts. It's not always an either/or for the patient, especially depending on the type of disease it is.

And so, in oncology, the benefit-risk could really shift depending on your curability expectation. So if I have a hematologic malignancy and I know that I might have to undergo a variety of treatments that might have side effects for a finite period of time for a very high chance of cure, my benefit-risk tolerance is extremely different than someone with a metastatic solid tumor who doesn't have a very positive prognosis and might only have a few months.

And so, I think as we look forward to what do we need include in the benefit-risk framework, I think just something more formal and quantitative for evaluation of patient-relevant evidence would be helpful because we're systematically generating this data now. But we're not always sure how it's being included for decision-making.

Something I'd also like to suggest today is considering including an overall assessment such as a patient's willingness to continue treatment as part of benefit-risk.

You know, these are things we could routinely incorporate into real-world care or clinical trials in a simple way to really understand, you know, at the end, is it worth it because, you know, we've been talking about a lot of really sophisticated statistical and classical health economic methods. But sometimes when I talk to patients, what they say to me is at the end is it worth it for me. And so, it's something to keep in mind.

I'd also like to reference two of the patient-focused drug development meetings. I had the honor of

attending the breast cancer meeting in particular and this is very similar to what we heard from patients. You know, early breast cancer patients were much more interested in the impacts and the tolerability of a treatment because they didn't have disease symptoms and were looking at a cure rate.

And so, I do think there's a lot of opportunity there to understand the continuum of risk-benefit. And maybe in the future it will end up being a disease-specific or therapeutic area-specific framework.

And this slide should be familiar to folks. But I thought it was an important one to include today because when we talk about operationalizing patient-focused drug development, which I think, you know, I'd really like to congratulate the agency.

As an outcomes researcher for over 11 years, the way folks talk about the patient perspective now than before patient-focused drug development four years ago is huge. The patient's really at the center now and I really think the awareness that this initiative raised helped.

I do think we're doing a great job on the data gathering and patient-reported outcomes. But the piece that's still a question is on the right. The quantifying benefit-risks. And I think until we have further information about how exactly that's done, as sponsors and researchers, we're not going to be sure how to be generating the right data for decision-making.

And so, I think as we look forward to the PDUFA VI commitment, further information on exactly the type of patient-relevant data and what might be most useful for decision-making I think will be really helpful.

I also think, to reference the really wonderful presentation before me, I think we need to talk to patients about this because they might have a really different benefit-risk than we think. And I think their input's essential in the review and approval process and even in the risk-benefit process.

And so, considering how we better obtain data to include their voice, not just about their experience but from a preference perspective, as both my prior

presentees shared, I think is important.

So you know, this is something I think about a lot, is, is it time for a separate patient label. And I thought this might be a good place to bring it up because all the data we've been talking about is pretty descriptive, right?

It's descriptive. It's analytic. It's large. We kind of have a space problem. And so, to kind of illustrate that, I thought I'd show you a couple examples of some patient-relevant evidence because I just like to show data.

So here's an example of the patient-reported version of the common toxicity criteria for adverse events. I realize that's a really long acronym. And this is really the patients' experience of side effects. And this is just a dataset that hypothetically showed bar charts, because we know patients like bar charts.

They don’t like hazard ratios. Those aren't intuitive. And it just shows bar charts that talk about frequency and percent. And this is just for one symptom. So if we had 20 symptoms and you're thinking

about the size of a U.S. PI, you can imagine we'd run out of space pretty quickly.

This is some data that Dr. Amylou Dueck, from the Mayo Clinic, who is also a developer of the PRO-CTCAE recently published and here it shows the patient-reported experience of tolerability next to the CTC adverse event item, which I also liked.

But as you can see, this is just the maximum score. And we've already pretty much filled up a slide with three symptoms. And if you reflect back to the second slide I showed, you know, sometimes we might have 20 to 30 symptoms.

And then, here's an example of the patient preference data from the Rommel paper that was referenced and these were also presented at the advisory committee of patients' preference for preferring subcutaneous to IV administration.

And again, it's at two different time points. It's done in a bar chart. It has descriptive information. It's a patient friendly way of presenting data.

But as you can see, systematic inclusion of

the patient voice in the large amount of information we have creates a vast amount of data. And really, you need to present it at the item concept level because if I'm a patient who really cares about those side effects of interest, we do need to get into that level of detail.

And so, you know, the expectation I often here is that patients could download the manuscript. Well, there's a cost associated with downloading a manuscript. There's health literacy and understanding how to search PubMed. And also just the way we present data.

I really like hazard ratios too. But when we talk to patients, they tend to tell us it's not intuitive to them. And so, really thinking about actively finding out how patients like to see information and we've been doing wok in that area and the types of descriptive data I showed you previously is really what they prefer.

And so, it's just something to think about because we do need to have a better way as we collect more patient-focused data, as we will continue to from

a policy perspective, to communicate this to patients in a way they understand and not expect them, when they have a lot going on in their lives and a short amount of time to choose your treatment, whether it's after cancer or for psoriasis, to have the health literacy ability to really find and interpret a fairly academic manuscript.

And so, I think also with 21st Century Cures, we're only going to be seeing more information. And so, the data I showed you at the end on rituximab was actually included in the tradename Hycela label in a verbal descriptive format rather than in a bar chart format.

But it's just something to think about as we continue to collect this data. I think there needs to be careful consideration not only about how it's incorporated into the framework but also how we're communicating it to patients because, in the end, they're also making an individual risk-benefit assessment about the best treatment choice for themselves and their family.

So in summary, you know, from my perspective,

I think patient-focused drug development was hugely successful at demonstrating the value of the patient perspective for drug developers and drug reviews. It was a real privilege to be part of some of those meetings.

I think it's important for future frameworks to really think about the fact that benefit-risk might be -- there's some overlap. A more specific framework would be very helpful for sponsors to ensure that we're generating the patient-relevant evidence you need for decisions.

And I think as we look forward, I know Dr. Mullin referenced the four PDUFA VI patient-centricity guidances. I think it'll be really interesting to see what synergies are there between advancing this work and that work in tandem and as well as the expanded use of patient preference methods such as, you know, time tradeoff, standard gamble, patient preference studies, again, a variety of the health economic elicitation methods that were referenced I think will be really key to success.

But in closing, I think it's a really exciting

time for patients because I think they're really at the forefront and I think we're really close to being able to have really important information communicated to them in a way that they can understand to make better decisions. Thank you.

(Applause.)

PANEL DISCUSSION AND Q&A

MS. VAIDYA: Thank you, Brett, Leah and Alicyn. So that wraps up our presentations for this session and now I'll open it up to the audience to please come to the mic if you have any questions for our panelists today. Don't be shy.

Okay. So as you get your thoughts together, I will ask a -- I will ask a question to our panelists. So we've talked a lot about, you know, looking back at the past five years, what we've done so far.

Looking ahead though, you all briefly touched upon this, but what are the greatest opportunities you see in incorporating patient experiences into drug development and decision-making for the next two to three years or so? And I'll open it up to the panel. Anyone can take this question. Theresa?

DR. MULLIN: Well, I don't want to leave that question hanging, I guess. I felt before this meeting that we already had a lot of work ahead of us and I feel like people have been very generous with their ideas and opportunities and have come up with even more ideas.

I think that, you know, to the point Alicyn was just making, I mean -- and thank you to everyone for their very thoughtful comments too. I mean, I think if anything, it just really has kind of created -- I mean it -- more things that we need to be thinking about.

The first opportunity I guess out of the box for us, well, it's a couple-fold. But in terms of externally facing, I mean, we are hard at work trying to take -- yes, there is a lot of established information out there. But we're trying to really turn it into usable, applicable material to indeed start with what I think Brett said is the first question of what matters.

I mean, what matters to people? We do really want to make sure we don't skip that one because we're

not -- we learned a lot. One thing we learned in those meetings is that we didn't go in there necessarily -- sometimes we sort of had an idea and other times we really learned a lot about what was most important to patients.

So we can't assume we already know that or that we have the full range of the cross-section of that opinion.

So we're really going to have our first public meeting related -- it's a workshop related to that first guidance which is going to cover quite a bit, including -- Tarek, we're trying to cover terminology and see what we can do to wrestle down terminology and also that first set of questions about the early qualitative research to try to hone in better on what's most important in terms of the burden of the disease and the burden of treatment, which I think is a bit of what Alicyn was getting to.

We're calling it burden of treatment but we're saying that you've got to always consider both in order to see if it's really tolerable to use a treatment that's been developed. So that's our first

opportunity. And I think the other -- so the internal piece which is very challenging I think for us is that this is really a different way of working and it does require -- some people have mentioned a culture, I think.

And for a large organization of scientists and people who want to do the right thing and be very careful and be consistent, we want our regulatory decisions to be consistent.

We say that decisions are like our case law and we need to be consistent with past decisions. We have to look at the precedent for any of our decisions. We're really looking at I just would say something like trying to turn the ocean liner because we have -- we need to be consistent with the past. And yet, we're trying to get people to adopt new ways of working and being innovative and doing all these things that really maybe feel a little bit at odds with being consistent with the past.

So I think that will be a big challenge for us internally to do it well. And again, I'll go to Brett's point about being sure that when we put all of

these methods in front of people, that we don't sink this by having somebody start using the wrong methods at the wrong time and then this gets a bad taste -- people get a bad taste from it and then you don't want to do it anymore. So we're really conscious of trying to have people appropriately use new methods and so that we're building on successes and trying to minimize how much we're learning from mistakes.

MS. VAIDYA: Thank you, Theresa. Yes, Brett?

MR. HAUBER: I think there's a lot that can be done in the short-term. But I guess the way that I view it, there's lots of areas where work can be done. I think from my perspective, my personal perspective alone, the more I learn about PFDD and the FDA initiatives, I just have so much more respect for the people who have to steer that very large ocean liner in a different direction.

And I think that's a long-term proposition and would rely on the experts with the institutional knowledge to tell us how best to do that. But I think we also have other opportunities within early phase drug development, in real-world data and maybe a narrow

window to incorporate patient perspectives in products that are already in phase three. And I think all of those things need work.

And a number of -- I've been doing this a little longer than 11 years. That doesn't make me smarter. It just makes me older. So but I remember a time when everyone was really risk-averse. And I think that's changing now. And I think there are opportunities for people to explore some of these tougher questions at all of those phases.

And I think there's been a sea change not only within FDA but also within industry and in academia to say, hey, let's look at ways to do this. So I think there are lots of opportunities across the spectrum. Some of them are going to bear fruit pretty quickly and others are just going to take time.

So I think the short-term perspective might not be the right perspective. Maybe that's my point. I think it's a long road and we all need to work to go along that road.

MS. VAIDYA: Great. Thank you. Anyone else? Okay. Yes, go ahead, Telba?

DR. IRONY: Just something to add, I think. Added opportunities that we have and maybe things that we can do within the FDA is more like educating our reviewers.

It's very important to educate them and explain what can be done, what cannot be done, why is it useful, when is it important and building capacity within the FDA to be able to, you know, review the studies, learn how to use them and see the utility of them within the regulatory process.

And finally, you mentioned about the labeling and communicating the risks, the benefits and making sure that the patients, the people that are going to use the treatments understand the risks, understand the benefits and perhaps will have shared decision-making tools with their own physicians to be able to make decisions, particularly when it's a close call, when the decisions are very difficult because the benefits might not -- might be perhaps not total.

You know, maybe only a subgroup of patients would experience the benefit. There will be risks. But there is an unmet medical need. So how do you make

these kind of decisions? How do you communicate the uncertainty? Sometimes the benefit -- there was a discussion this morning. A subgroup of patients might experience the benefit but not all of them. We don't know who these patients are.

So the benefit is not a total benefit. It's the benefit of having a chance of having the benefit. So how do you communicate that to a patient? Meaning they will incur risks for a chance of experience the benefit. This is a very hard concept to communicate. So we probably have to together understand how to do it and learn how to do it.

MS. VAIDYA: Great point. Thank you, Telba. Could you take --

UNIDENTIFIED AUDIENCE MEMBER: So I should start off by saying that I spent the entire session formulating my question, which was answered in your last slide. So I'm going to reformulate my question because I think this is of maybe more interest to me.

So there's people -- there's politics out here in this city as well as regulation. And I'm sure you're aware of the people who say, you know, FDA

should not be so much worried about whether something works. But if it's safe, you should give people a chance.

So having worked at FDA many years ago, I'm inherently skeptical to that notion. But as I heard talk today about subsets and how some subpopulations have effect that may not be reflected in the population, I think, well, maybe that makes some more sense to me.

So I guess my question is do you see this as a potential opening to use these patient preferences and PRO and quality of life and all of that? I mean, I'd like to think of a day when, you know, an indication could be driven by some of these -- maybe not driven, but at least much more highly supported than just based on your population needs. Is there a chance?

And it also goes back to that slide I saw at the beginning about how to predict your future by making it. I don’t know how to make this. So you guys have to help me to understand. Okay?

DR. MULLIN: Well, I'll just say I think one of the reasons we're going to spend a bunch of time on

these guidances to make sure that we have rigorous enough methods so that we are not concerned about people's desperate patients being manipulated and, you know, willing to try anything and so on.

I think that the work Telba described, for example, is at the disease level. It's not about a particular product. I think that this work will be better supported if we don't get into the potential conflicts that would almost be inevitable if a product sponsor were doing it at the product level.

But if you can work at the disease level and the people with that disease and the tradeoffs they would be willing to make, kind of absent a particular -- maybe you're taking the characteristics, the operating performance characteristics you would expect might be typical in that class.

But you know, you're not getting in there. And all of the time we're spending on trying to make sure that we give rigorous enough methodology to go from what people report in a very open, qualitative way, but a very compelling way to something that actually can be reliably measured and consistently

measured and thus used in clinical trials. We're very concerned about the same things.

So we want to develop these methods, not make the perfect the enemy of the good and so that it's -- we think that they're reliable. Our reviewers will consider them to be reliable methods that have been used and so we can go forward and feel pretty confident about the quality of the evidence. And that's exactly where we want to be.

MS. VAIDYA: Thank you, Theresa. Yeah, Sara?

DR. EGGERS: Yeah. I have a question for Leah. Sara Eggers, from FDA. I'm part of the team that does the patient-focused drug development meetings. And before the question, a thank-you to your group and others because when we are preparing for our PFDD meetings, we rely heavily on the outreach and the capacity that patient groups have to do that.

Maybe my colleagues have seen your rubric, your stratification rubric. I hadn't seen it. Did you do that -- so you -- if I understand correctly, you stratified and said there are particular characteristics of patients and was it that you wanted

to make sure that you had reached out so that they knew about our meeting? Can you explain a little bit more about that and what you did with it?

MS. HOWARD: Sure. Sure. Yeah. So I'm happy to. So, you know, over the course of the NPF's history, we've spent a lot of time talking to our community and, you know, to the conversation here.

What we've heard is different things from different subsets of our community about what they're looking for when it comes to treatment, what risk they're willing to tolerate, what their expectations and hopes are. And so, one of the things that we really wanted to do to assist you with hearing about all those same things that we had heard about was ensure that we had identified kind of the various subpopulations of our community.

So we know, for example, that folks that live in rural areas face different access challenges than those in urban areas. Folks that work have different demands on their time than people who are at home. And so, that limits or not their ability to pursue different treatments and kind of on down the line. And

so, one of the things that we did was sat down and said, okay, across our community, who are those different populations that have different needs and different expectations. A pregnant woman is going to have different options than, you know, a health male in the middle of their life.

So what we did was literally wrote out kind of who all those different voices were and then spent time reaching out to those different subsets of our community. We did that through our own networks. My colleagues that are on the ground across the country talked to different people in these different populations and encouraged them to participate in the meeting in whatever capacity they were available.

We also did that through different other organizations. So for example, the dermatologists that serve pediatrics have their own group. So we specifically contacted those folks and said, you know, here's this opportunity for you or your patients to share their perspectives. And then, you know, we used social media and kind of other outreach opportunities to remind those folks that this opportunity existed for

them to come and share their perspectives.

You know, I think ultimately, as you saw at the meeting, we had a lot of different voices, which was our main goal. And we didn't want, you know, a hundred patients with severe disease who were all looking for, you know, the next something.

We really did want the agency to be able to hear from people with mild disease who were just trying to address, you know, this particular symptom, you know, on down the line. And so, being able to acknowledge that our community isn't always after the same thing was really important for us and we wanted to use that grid to do it.

DR. EGGERS: Well, that's commendable because it is -- when we have a public meeting here in White Oak, we know -- we know that that means the docket is very important because not everyone can come to White Oak to be at the meeting.

MS. HOWARD: Right.

DR. EGGERS: So thank you for that.

MS. HOWARD: Sure.

DR. EGGERS: My final question is then you

also encouraged people to submit to the docket. And I'm going to assume it's the people that are harder to reach. I mean, if you -- if the same factors make it difficult for you to access one treatment, it probably makes it difficult for you to access FDA to give your voice.

Did you find in your outreach to people on the dockets to write in, were they different? Did they differ in characteristics that you're aware of?

MS. HOWARD: Yeah. So we spent a lot of time looking at what went into the docket. I would say they were a little bit different. One strategy that we had was to promote the docket before and after the meeting differently.

So prior to the meeting, we promoted it just as one other way people could participate and share their voice with the FDA. So you had, you know, attend in person, attend via webinar, comment to the docket. Once the meeting took place, we had a much better sense of, again, looking at our community, what we hear from our community that was shared and what wasn't shared.

And so, we specifically went out after the

meeting and said, you know, here are some of the things that we've heard from you, you know, over our history that didn't come up at the meeting. If you care about these things, write in.

And so, we did a little bit of targeted promotion of the docket post-meeting to ensure that those comments did make their way to you. But I think you saw more of kind of, as you said, those issues of the role -- the smaller populations and the particular symptoms that didn't come up because they're often, you know, more painful to discuss in a public setting.

MS. VAIDYA: Thank you. Yes?

DR. HAMMAD: Tarek Hammed, with EMD Serono. My question is for Theresa. I don’t mean to put you on the spot or anything. But I really liked your response when you said that you are looking for methodology, you're sure it's working, not really giving us any false hopes.

But I can see in CBER and CDRH specific initiatives to increase interim capacity of the reviewers to be able to review such methodology. Are there any specific plans within CDER to build up the

same kind of internal capacity?

DR. MULLIN: Yes, there are. One of the things that we're trying to do, it's sort of twofold. First, and I don't know if -- maybe you haven't been at the other meetings where I've said this, Tarek.

But we have -- literally for the size of CDER, I mean, our capacity right now in terms of specialty staff is not much bigger than it is in CBER or CDRH. So we have, you know, like three -- I would say three or four people who do this in the Office of Biostatistics and probably about a handful of people who are expert methodologists in Office of New Drugs, the COA team right now. They have project managers.

But, so we have very limited capacity which we need to build. These are the same people who are writing these guidances, working on the guidance documents and fielding everything that comes in, all the submissions.

So we need to obviously increase that capacity a bit. And we have plans to do that additional hiring, assuming we can find people. There's not enough people being trained in these areas in academia right now.

And the second thing is to try to get to some training for people. But given that these guidances have timeframes that are like now, we have to -- and some of these people, it's not their only day job is doing this work, that we're ordering things.

So it's not happening as fast as one would like if we had the capacity to go at everything at once. But yes, definitely it makes a whole lot of sense both to just have the experts have more experts and have people know these methods are important and how to use it, but then also have people know enough to know, oh, this is something we need to do here and I need to call some experts. I need to get some consults in here to help me with this as I do it.

So they know enough to know what they don't know. And also what they can tap into. And so, we're planning that over the next few years. But it's just not all -- I mean, we wish it would all happen a lot faster. But it just takes a little time.

DR. HAMMAD: Absolutely. But is the long-term vision to build up an internal consultancy or to have like some kind of review division or some -- is there

like any vision?

DR. MULLIN: Both. We're looking to in the Office of New Drugs to have one probably clinician expert in each of the divisions at least who kind of specializes in understanding and the use of these methods. Right now, an example -- I would say Paul Kluetz is a good example of somebody who does this for the oncology folks.

But there's a coupling of a person like that with the specialty sort of COA group within the new drugs and then bio stats is also building up its capabilities in this area as well. So we'll have a combination of people who are like within review divisions and also some people with greater expertise who can be working with them.

DR. HAMMAD: That's great to hear, because, as I said in my talk, without this from the agency point of view, I mean, this field will not go anywhere. So you are the starting point. I'm very happy to hear that. Thank you.

DR. MULLIN: No, I mean, just that's the other point about it. There's no point in building more

repositories if we don't get everybody to understand and start using these methods in the right way. So we have to do it all together.

MS. VAIDYA: Thanks, Tarek.

DR. CRAIG: So, Benjamin Craig, from the International Academy of Health Preference Research. I really would like to see an event like Leah held but for health preference research as in to actually bring all the methodologists together to talk about the diversity of methods.

I mean, we have a large community of individuals with diversity among us in terms of our different impressions for the collection and the measurement of these evidence and we have different interpretations. The methods, while they seem rigorous right now, it scares me to death.

I mean, all you need to have is one well-meaning firm to hire one well-meaning consultancy to motivate one well-meaning decision and then we realize later on, oh my gosh, we made a mistake because the methods weren't quite up to snuff. And when I hear among the academicians and the debates we're having

about how to do this, it's scary.

And so, we're so excited that you guys are doing this. But at the same time, we're really worried that this will be our death, that this will actually fall upon its face. We look at the PRO folks and it's like, oh, you guys are lucky now. You've already went through this process. But hopefully health preference research will get there also.

DR. MULLIN: All right. Thank you. We deal with life-and-death decisions all the time. I'm happy we're not dealing with that one.

MS. VAIDYA: Anymore questions from the audience? Okay, then. Well, with that, we'll wrap up this session. We had a great discussion and it is great to see that we've come so far in the past five years, thinking about PDUFA V. But there's a lot of work ahead of us, as we've heard from everyone here. So, a round of applause for our speakers.

(Applause.)

MS. VAIDYA: We will now be moving on to our break. We'll have a 15-minute break right now. It's almost -- let's say it's 2:55. So if we can reconvene

in 15 minutes at -- wait, yeah 3:10, sorry, 3:10, that'd be great. Thank you so much.

(Whereupon, the foregoing went off the record at 2:54 p.m., and went back on the record at 3:13 p.m.)

SESSION 3: SPECIAL TOPICS IN BENEFIT-RISK ASSESSMENT

DR. EGGERS: -- throughout the day really we've alluded to and touched upon, we're calling it the special topics in benefit-risk assessment and it's really just addressing some things that are important to address, especially as we move into future phases.

We have three presenters and then we have a panel discussion with a couple folks who will kick off the panel discussion for us. So our three presenters are Baruch Fischhoff, Richard Forshee and then Lisa Schwartz and Steven Woloshin, who will be addressing three more methodological presentations. So without further ado, I will let Baruch start.

ADVANCING DECISION SCIENCE METHODS FOR REGULATORY USE

DR. FISCHHOFF: Thank you. So I'm really pleased to be here. I had the privilege to be -- to chair EPA's -- FDA's risk communication advisory

committee for its first few years and then -- which I think gave me enough background into the complexities of the agency to have some value and having the privilege to work in some of the earlier stages of the benefit-risk framework.

And one of the things that I took away, and which I attribute to Bob Temple, is the idea that analysis ought to be an aid rather than a replacement to judgment. And if one thinks about this, one has -- there's judgment all the way through. You have judgment in the beliefs and eliciting from experts what they understand about the evidence and the residual uncertainties, from your non-experts, what they perceive the risks -- benefits and risk to be of the different products and how well they've understood what you've told them after you've communicated.

You have values in terms of the priorities, which problems should you be worrying about and in terms of the tradeoffs that you should be doing -- looking at. And if you think about the benefit-risk framework, it's all about judgments. That is, each of the cells has places for quantitative information to

the extent that it exists. But that quantitative information is always qualified by some kinds of -- by judgments about the quality of the evidence and about information that's not readily quantified.

So if you were going to submit judgments to a scientific journal, you would value the -- you would look at the quality of your judgments in terms of the standard psychometric properties. Are they reliable? Are they appropriately reliable across time, across judges, across methods? Sometimes they should be and sometimes they're not -- they shouldn't be.

You look at least at these three kinds of validity. Face validity, that should be socially acceptable. Is this an appropriate way to ask a question? Coherence, is there internal consistency across different ways of asking the question or different related questions? And then, is there what we call construct validity in psychology. Are there theoretically positive correlations between the judgments that people give you and other things that you know about their life circumstances and behavior?

If you have unsound judgments, if you ask

people questions that they can't answer, you can go wrong in three different ways. One is you can obscure value-laden assumptions in the judgments that you're presenting as representing people. Second, you can frustrate people who are trying to give you orderly responses, but your task isn't suited to the way that they customarily think. And third, you can misrepresent them by claiming to have captured their beliefs or values in ways that have not.

So here's one example of obscuring value-laden assumptions. For many years, I worked on stated preference methods in environmental elicitation. There's a process -- there's a procedure called contingent valuation. It was in one of Claude's boxes as CV.

If I was doing a contingent valuation study, I might show you two pictures of the Grand Canyon, one with some haze and one without. And I would -- I might ask you how much would you pay in additional gasoline taxes in order to have 80 days with haze rather than 120 days with haze. And those would be numbers that are required for cost-benefit analyses that require you

to monetize the environment for it to have any standing.

So one of the things that you find in contingent valuation studies is what are called protest responses. So here's this paper that I thought had a nice summary of protest responses. There are well-documented challenges to the implementation of contingent valuation, including strategic responses, anchoring or framing effects or refusal to engage with a request to state a willingness to pay value or accept/reject a given value, protesting.

This paper focuses on the specific issue of protesting. Respondents commonly refuse to state a WTP value or to indicate their acceptance of a given value in CV surveys. This may be because they place zero value on the commodity. Alternatively, respondents may object to the principle of placing a monetary value on the commodity or they may feel strongly that the responsibility for provision falls on another actor such as the government.

And this review -- this is a large industry doing these studies. This review had -- a remarkable

review of about five or six years ago, had I think 360 studies, enough that they could characterize what was the protest response rate in different kinds of studies.

So DC, if dichotomous choice format is used, and there's several of them, 43 percent of the responses are protest responses. If it's open-ended, then you get a different rate. So you would see, so somehow or another, they report numbers.

Remarkably, this study was -- the previous study was about how to impute values to people saying what they would have answered had they been willing to answer your question. So you get an answer from a CV study and this is in the background, how would you know if you didn't -- if you hadn't read the study.

We've had quite a bit of discussion about how to deal with heterogeneous health preferences. So my colleagues and I have a paper just coming out on medical decision-making looking at some of the ethical assumptions made in the analytical conventions for dealing with heterogeneous preferences, primarily in the cost-effectiveness analysis literature.

So if you've got to produce a number, you've got to make some assumptions. If you haven't shared the ethical underpinnings of those assumptions, then the consumers of your analyses don't know what you've done. This question of ethical things based -- ethical assumptions based -- is something that's troubled me for a long time. If you'd like to read more, I had this piece in Science a couple of years ago.

Second thing, you can frustrate orderly responses. You've got a question that people would like to answer. They have no objection to answer. But they can't translate themselves into your terms. So there was this lovely review of exclusion criteria in national health, state valuation studies.

This group came out about a year ago, managed to find about 75 studies in which there was enough detail on the bases in which noisy responses were excluded that they could characterize the criteria.

So the kind of criteria that might be used in preference studies to throw out -- to exclude data that are considered inappropriate, it would be if all health states were valued the same. That doesn't look right.

Fewer than -- more than x logical inconsistencies where x varies across studies. Incomplete or missing data. People who value being dead is worse than all or several health states and so on.

So if you're the consumer of the results that come out of a study like this and the study is presented as being representative of some particular population, it would be appropriate to ask whether they have excluded particular groups of the population, either by their demographics, say their literacy or their numeracy, or by view of their preferences, that they're trying to sell you something that the elicitation method doesn't allow you to do.

In this, here's a figure from this review that shows the percentage of people who are excluded with different elicitation procedures, SG is standard gamble for those familiar with this, TTO is time tradeoff method and VAS, visual analog scale.

So you can see some methods end up excluding more people than others. Is that because they are easier questions to answer because the researchers have better hands and being able to pose their questions in

ways that people find comprehensible or they're just more lenient in terms of the responses that they'll include?

Third possibility is you can misrepresent respondents. There's a figure from a paper long ago by Betsy Martin and Charles Martin who discovered there were studies asking people, representative sample of American women, asking then what was the probability that they were going to have a child in the next five years over on the right or in all future years on the left.

So they're the same answers. So had you -- so somehow or another, you're asking, you're giving a time period -- you as the researcher are giving a time period that is not registering for people. And if you reported either one -- one of the two or probably both misrepresent people if you assume -- the respondents, if you assume they're literally answering -- they're answering the literal question that you asked.

There's something else from our own work. This is a representative sample of American 15- and 16-year-olds in the national longitudinal study of youth

97 were asked kids a bunch of things that gave us very good probabilities on being in school, on all sorts of different things. We also asked them what was the probability you were going to die in the next year.

And most of us -- them gave us very low probabilities, as would be appropriate. But there was a blip at 50 percent. So people have found this. You can find this buried in many different studies, studies of the probability of getting sick from -- of getting lung cancer from smoking and other places.

It turns out that Americans, when they don’t know how to answer or don’t want to tell you will say 50/50 -- will say 50 in the sense of 50/50 rather than 50 percent. So if you took -- so they're not saying zero. But they're probably not saying 50 percent.

If you took those answers literally, didn't know the elicitation literature, folded them into your group mean or median, then you would have -- be guilty of some kind of essentially methodological malpractice and misrepresenting people by not recognizing the limits to your own methodology.

So if we want to ask people -- ask questions

that people can answer, the recommendations would be, first of all, consult the elicitation literature broadly. It takes -- one can copy questions that somebody else has used. That doesn't put you in a position to have gone through the apprenticeship needed to ask these questions.

Well, second, you need to involve respondents in the development of the questions, which we heard from many people over the -- particularly in the preceding panel. And you need to evaluate your research as critically and report its results candidly. You need to do this just as well with judgment studies as you do with -- as you do with medical studies.

So here's a source if people are interested in this for consulting literature. The consulting literature broadly with regard to eliciting beliefs. There's a really nice piece by Granger Morgan, one of our colleagues on expert elicitation, if you want to get judgments from experts about uncertainties in the data. This would be a good place to start.

Here's a place I like. It's my paper on how to elicit people's values. This is my parting shot. I

kind of gave up on the contingent valuation wars. But I tried to summarize what are the different methodological traditions, one of which is embraced by the contingent valuation people and the other of which is ignored. And both have something to say when you're trying to get people to think about unfamiliar topics.

Second thing is you have to involve respondents in the development. Knowing all the principles, knowing all the researchers, no substitute for talking to people. Again, as we heard in the previous session. So I don’t think you can do better than the Voice of the Patient initiative for listening to people, the other ones that responded to it.

I think that we -- the development process that I was part of and that the staff here has continued has -- this is -- you could think of the benefit-risk framework as a judgment elicitation process which deeply involved the FDA staff and some of its stakeholders and I think resulted in the robustness that was reported here as a reflection of the care of the work that people here did.

And when I think about -- I present this at a

lot of talks -- is that you can think about what are the basic design principles that are embedded in the benefit-risk framework reflect both analysis -- both analysis and behavioral research.

So it recognizes that scientific policy judgments are in all analyses so that people don’t confuse the two, neither the producers nor the consumers. It quantifies the quantifiable without ignoring other concerns. It highlights ethical and political tradeoffs rather than burying them in some metric where it would be very difficult to ferret out.

And then, it supports risk management by suggesting the place where you might be able to -- things you might do to make a product acceptable when it wasn't previously. Or you might be able to make an acceptable product even more attractive.

I ended up, this is a recent National Academy of Medicine report on pain management and the opioid epidemic. I was asked to be a reviewer of it and I was -- it's been out for about two months now. And they ended up advocating expanding the benefit-risk framework to include public health concerns.

So if you think about the opioid epidemic, you can think about what that might be. And that's sort of an interesting challenge. We're thinking about things that one might do. They had some legal scholars that argued, rightly or wrongly, that it was within FDA's mandate to be able to consider these things. Here might be an interesting direction to go.

So you've done your studies and you want to evaluate them critically, report them candidly. Here's the standard performance properties if they don't accompany a study that you get. Then you really as a consumer don't know how to think about it.

Some people have better hands than others. Some people will implicitly embody the values that FDA wants or its stakeholders want. Some of them won't. Some of them won't even be cognizant that their analytical conventions embody values.

So I thought I'd end with two things in this spirit. So one, here's one of our studies. So recently published. So in 2015, we -- so when Ebola sprung, FDA has a rapid response -- or rather NSF has a rapid response capability. By the time they got

activated after Ebola, we got funds with some colleagues who study posttraumatic stress to see what people thought about the epidemic. We asked representative sample of the public hard quantitative questions of the source that could be in principle ne validated by scientific judgments.

You will find a lot of people in my field, judgment and decision-making, who say that people are so innumerate that you can't give them numbers or listen to numbers. And sort of testing the limits of this, we asked people to estimate the basic reproductive number, R0, which we translated if someone gets Ebola in the U.S., how many people do you think will catch it from them directly.

So you might guess what kind of numbers a representative sample of Americans would give. And then, here's our -- here's the numbers that we gave. Most people, this was January 2015. Most of them thought it was zero or one, or one or two.

It might have been a rough estimate of a disease that's just gone on break but we didn't know how -- we didn't know for how long. Some people gave

us much higher numbers. And you could think -- so this was our disclosure. We showed how it correlated with the judgments of the probability of transmission in different situations. That was our effort to give people a feel -- consumers a feeling for whether or not you could trust these numbers.

And then finally, as several people have mentioned, one of the things that FDA has been trying to do is to figure out how to characterize uncertainty, which is in the left-hand column of the benefit-risk framework.

We had a workshop here in February and May of 2014. And Alex Davis and I had a proposal for how it is that you might characterize uncertainty in a systematic way that we thought might be analytically and behaviorally realistic.

And what we said, and so this is a testable hypothesis, which I put out as the sort of thing that FDA may want to look at, that most people understand confidence intervals in terms of what the variability of the data is. You can just read it out of the reports.

People at FDA are absolute experts in internal validity and external validity of studies. Sorry, I got misaligned on the transfer. And in the pedigree and how good the underlying science is.

If I had signatory authority and I wanted to make a decision, if you could report that in some systematic, succinct way, that might give me in effect a feeling for what the credible interval would be.

Nobody likes to give Bayesian credible intervals summarizing all of the uncertainty. But you could give people who are -- give people a systematic feeling for how good the evidence is, whether it's the signatory authority or somebody else. Okay. Thank you.

(Applause.)

DR. EGGERS: Thanks a lot, Baruch. Now, we'll have Richard Forshee.

POTENTIAL AREAS FOR QUANTITATIVE BENEFIT-RISK APPROACHES

DR. FORSHEE: Good afternoon, everyone. My name's Richard Forshee. I'm an associate director in the Center for Biologics Evaluation and Research in our

Office of Biostatistics and Epidemiology. And I lead a team called the analytics and benefit-risk assessment team. We actually do a lot of work on looking at quantitative benefit-risk assessments and I'll talk a little bit about that as I go forward.

I do want to pick up just on the last slide that Baruch had about credible intervals and just mention some of the work that we've been doing in that general area.

We have a program where we're trying to do what we call quantitative bias analysis, which is to try to take some of the other threats to the validity of a study that go beyond simply the sampling issues and use outside sources of data to get probability distributions about how large those biases might be and then quantify those in various ways. So that's not exactly what you were talking about doing, but just wanted to mention it's something that we've been thinking about.

Okay. So I want to start with a little bit of history. One of the really nice things about the White Oak campus here is that there are a variety of

historical posters that are spread throughout the campus. And I walk by this any time I'm going to the main cafeteria that we have. And these are also collected on Flickr. There's hundreds of historical FDA pictures there that you can look at.

The point that I want to make about this is that this was in 1964. And so, in 1964, people were already thinking about all of the many different sources of data and information that have to go into any FDA decision about whether to approve or not a given drug. So this is not something that's a new problem for FDA. This is something that we've been dealing with for at least 50-plus years.

This is also an old slide. This is from 1999. And I'm not asking people to read the whole slide. But this is talking about the system that we had in place for managing the risks of medical products.

And the points that I want people to take from this is even in this slide from the last century, 1999, we're still talking about the importance of thinking about benefit-risk assessment as a complex and iterative process that involves many participants. I'm

sure this is fitting with some of the themes that we've talked about during the rest of the meeting today. And what I would add to this is that, in my opinion, qualitative approaches are usually going to be sufficient.

But one of the points I want to make in the rest of my presentation is that I believe that quantitative approaches can improve the quality of the decision-making process in some cases.

The question is how do you figure out which of those cases are and how do you make sure that you're doing the quantitative approaches in a way that's really helping to add to and support the complex decision-making process that we engage in.

I want to talk a little bit about what we've been doing in the Center for Biologics Evaluation and Research in this area and the overarching point that I want to make is that for more than 10 years now, FDA CBER has been trying to build capacity within our organization for doing more quantitative benefit-risk assessment.

And as you heard from Telba's presentation

earlier, we're also working to build capacity in the patient preference area as well. One of the ways we've tried to build this capacity is by putting together a team that's dedicated to building out some of these new kinds of methods. We call it the analytics and benefit-risk assessment team. I see some of my team members are in the audience. We've got -- right now, we've got 10 people and we've got a couple of positions that we're trying to fill.

We don't only quantitative benefit-risk assessment. We also do some development of methods for post-market observational studies and we also do some health informatics work as well. But we do have a team in place to try and build out the capacities that we have in this area. And we have actually done a number of quantitative benefit-risk assessments.

Most of them have been in the area of blood safety and availability. But we do have experience both developing these, presenting them at advisory committees and scientific meetings and several of those have been published as well. Another thing that we're involved in is we're both trying to build capacity by

having internal training as well as engaging externally to try and build capacity more broadly for this kind of quantitative benefit-risk assessment.

Internally, I just want to mention that we have a series of three courses in CBER that we offer every year. We have a risk assessment course that focuses more on the technical side of putting together quantitative risk assessments and benefit-risk assessments.

We have a risk management course that looks at the more complicated question of how you put all of the information together, along with values, legal constraints and other things that might affect the decision. And we have a risk communication course that we offer as well. And our medical officers are our primary audience for these courses.

We've also done quite a bit of external work to try and build capacity in this area. This is one proceedings that we published from a workshop that we held on quantitative risk assessment for emerging infectious diseases in the blood supply.

And my colleague, John Scott, who's our acting

director of our Division of Biostatistics, participated in the recently published book on benefit-risk assessment methods and medical product development. So the point here is that we're trying to expand our capabilities to be ready for some of the needs that we anticipate in the near future.

Patrick and others have already talked a lot about this. This picture keeps coming up. It's a nice picture. Thank you, Pujita, for loaning the camera for that. I just want to mention that the key idea from this ICH expert working group was that we want the sponsors, when they're submitting their material, to provide a succinct, integrated and clearly explained benefit-risk assessment of the medicinal product for its intended use.

I think this is a really nice summary of what we were hoping to encourage with that guidance and it's a key part of what we wanted to do. Another thing that I want to highlight from the new ICH is that one of the things that we specifically say in that ICH guidance is that while a descriptive approach is generally going to be adequate, we also create the -- we also open the

door for more quantitative approaches.

And so, as part of that guidance, we specifically said that applicants may choose to use methods that quantitatively express the underlying judgments on uncertainties and the assessment and analyses that compare and/or weigh benefits and risks using the submitted evidence may be presented and we even pointed them to exactly where we'd want to see that in the guidance.

So up to this point, what I'm trying to say is that certainly in FDA CBER, we're trying to build capacity in this area. And there is certainly a possibility for more quantitative approaches to be considered, especially now that the ICH guidance has been out.

In the last few minutes of my presentation, I want to talk a little bit about some of the things that I think are important to consider when you're thinking about going to a more quantitative benefit-risk assessment approach.

As has been mentioned a number of times, it's very important to consider the modeling uncertainty and

variability when you're moving toward a more complex and formal benefit-risk assessment.

As was mentioned just in the last presentation, all of us are aware that all of the inputs in a model are going to have some uncertainty and variability and this can go well beyond simply the statistical variability that you would expect based on sample size, for example.

The distinction here between uncertainty and variability is that uncertainty is something that can theoretically be reduced if you get more and better data to help support the decision, whereas variability is considered to be an inherent property in the system that you're looking at.

So as we're -- if we're going to move towards more quantitative benefit-risk assessments, we have to make sure that we're using those models in such a way that they're actively conveying the uncertainty and the variability of the system that we're trying to model. And we're usually going to do this through some sort of computer simulation. Certainly in my team, we use a lot of probabilistic, quantitative computer simulations

in order to convey this notion of the uncertainty that we have.

In addition to being very clear and explicit about the uncertainty and variability that you have, it's important to do a lot of sensitivity analysis and validation of the models as well. In all of the benefit-risk assessment work that my team does, and it's a practice that I would recommend for others, you should make sure to include usually a large number of sensitivity analyses.

And some of the kinds of questions that you're going to want to ask, you're going to want to understand which of the inputs in the model have the biggest impact on the model results. And one of the things this will tell you is it can give you some guidance as to where to focus future research as well.

You also want to do sensitivity analysis to understand which of the assumptions for which you don’t have data, which of the assumptions are the ones that are most critical in the model. This helps everybody who will be using that model have a better understanding of how that model could go wrong.

And related to both of these, this can guide your future research agenda by telling you if you need to refine this more, where should you focus your future data-gathering. The other thing that I would mention in addition to sensitivity analysis is that, wherever possible, you're going to want to do some validation of the model.

And in particular, the best practices are going to be able to take the model that you've developed with a certain set of data and try and validate it against an external dataset to see if the results are going to still be valid when you move beyond the data that you originally used.

So I want to mention a few concluding thoughts regarding the value of specifically more quantitative benefit-risk assessment. One of the things that I have found incredibly useful about moving toward more formal benefit-risk assessments is that it really helps to provide a framework for discussion.

Early on in the process of a benefit-risk assessment, you have to get everyone involved around a table. People have to agree what the key inputs and

outputs of the model are going to be and how they relate to one another.

This exercise by itself is critically important to improving the understanding of the problem. And it also helps with a lot of the deliberation later on because you can point back to that model that's bene developed and link whatever concerns someone might be bringing up back to the specific point in the model and how it all fits together.

So simply the act of building a model I have found to be incredibly useful for some of the more complex decisions we've had to deal with.

The other thing that I find very useful about more quantitative benefit-risk assessment models is that it really helps you to integrate large amounts of data. And think back to the first slide that I put up on the presentation.

We have data coming from lots of different places and the data is of different quality, different types. And we need a way to try and put all of that together in making a decision and quantitative benefit-

risk assessments can help with that.

Another value of more quantitative approaches is that it helps to identify what the biggest sources of uncertainty are that still remain when you're trying to make your decision. And it helps to identify where some of the data gaps are, which, as I said earlier, can you help you target your future research.

One of the things that we use quantitative benefit-risk assessments for a lot in our blood safety area is to compare the different policy options that are available.

In the blood safety area, what we're always trying to balance is how much can we reduce the risk, for example, of an emerging infectious disease such as Zika virus. How much can we reduce the risk of these emerging infectious diseases and how many safe units are blood are we going to use as a result of testing? And quantitative benefit-risk assessment helps with that a lot.

I also believe that these quantitative methods, if it's done properly, can help to improve transparency in risk communication. But of course

there's always the risk that if it's too complex and you don’t spend enough time on the communication, you can lose people when you're discussing those issues.

As with any modeling exercise, if the data going in is not good, you're not going to be able to get a model that's believable and useful. So the risk assessment models have to -- are only going to be as good as the scientific theory and data on which they're built.

The other thing that we can run into is that if there's a lot of uncertainty, the best decision may still be unclear. And this last point, as it came up in some discussions before this, changing circumstances or new scientific discoveries can certainly require major updates to quantitative benefit-risk assessment models. But I would just add that this is also true with less quantitative approaches as well. So it's a problem for however we're going about making those decisions.

And the last thing I would like to mention is that no one believes that quantitative benefit-risk assessments are going to replace risk management and

the judgment that's necessary for making these very difficult decisions. So with that, thank you very much.

(Applause.)

DR. EGGERS: Thanks much. And now, we're going to have a talk focused on the role of benefit-risk framework and other -- and probably translated to similar things, the role of those as a communication tool to public stakeholders with -- and I'll let Steven introduce himself.

COMMUNICATING BENEFIT-RISK TO THE PUBLIC

DR. WOLOSHIN: Oh, it's a miracle. So we're going to divide this talk seamlessly. But in case you're trying to keep track, I'm Steven and that's Lisa over there. And we have -- we have two disclosures. First, we're married to each other and the second thing is we've been expert witnesses in testosterone litigation.

So there's a lot of confusion about the meaning of FDA approval. Nearly half of U.S. adults mistakenly believe that FDA only approves and only permits advertising of extremely effective drugs or

drugs without serious side effects. And most U.S. physicians mistakenly believe that approval means that the drug is as effective as others on the market for this condition, when of course drug approval only means that FDA believes benefits outweigh harms, not that the benefits are big or important or that the drug is very safe.

The FDA benefit-risk assessment helps allow prescribers and consumers to understand the real meaning of approval. It provides FDA's rationale for approving a new drug and how they weigh the benefits and the risk. And it's a unique source of independent analysis and interpretation not filtered or negotiated by industry, information that's otherwise hard to find.

So to give you an idea of how valuable this information is, let's take a look at a recently approved biologic drug for psoriasis called Siliq. Lisa and I were recently speaking to a large group of medical residents at a big academic medical center and we asked them when you hear about a new drug, how do you go about learning how well it works. How do you decide whether you're going to use it or not?

And I think clinicians out there won't be surprised by the answer. Most people said they would go UpToDate, this electronic textbook. And what UpToDate says about the drug is that it's highly effective, that FDA approved it to treat moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy and have failed to respond or lost response to other systemic therapies, that there's a REMS because of concerns regarding risk for suicidal ideation and completed suicides in treated patients and that there are some adverse effects, mild to moderate tinea infections and neutropenia.

So for the residents, the take-home message looking at this stuff was that the drug seems to work, you know, really well. But they had no idea how worried to be about the suicidality issue. They didn't know how to calibrate their uncertainty.

Now, some of the residents said that they would go to the medical literature. And here's -- this is the New England Journal article about the Phase III trials which was the basis for that UpToDate chapter. And what it said was that, again, that the drug is

effective and that -- sorry, that there are some mild or moderate side effects. And the conclusion was very strong. It said that the drug resulted in significant clinical improvement in patients with moderate to severe psoriasis.

But something was missing. And amazing, suicide is not mentioned in the abstract at all. In fact, the only -- suicide is only briefly mentioned in two clauses in the results. So there's no red flag here at all.

Now, I just want to turn to the FDA office director's benefit-risk summary and show you their take. The summary says the efficacy of Siliq is not in dispute. So there's no question that this drug works. However, the presence of a rare, fatal event observed in a controlled clinical trial setting is merely the tip of the iceberg. Once approved and used in a broader population, we can anticipate a higher occurrence.

Further, I am unaware of any product having been approved by the FDA with four completed suicides in a clinical development program. So the residents

thought, and we agreed, that this context really helped understand that this was a really important red flag, something that you can't ignore.

FDA's reasoning has great clinical value. The office director's thoughtful summary explained how FDA balanced benefits and risks in deciding to approve this drug.

I have considered the seriousness of the disease, the chronic nature of the disease, variability of response and duration of response to different treatments, patients' ability to access various approved treatments, the impact of the disease on patients and their families and the continued unmet medical need. Perhaps most importantly, I have considered the importance of patient autonomy. I believe that patients should have choice, but that choice should be informed.

So this document was really great because it made clear why FDA chose to approve the drug and why they chose to approve it with a variety of risk mitigation strategies including a boxed warning, a limited use for patients who failed other systemic

therapies and a REMS.

So we think that the benefit-risk summary assessment has really, really unique and important value. But of course there's ways to make it better. And we're going to go through a few.

The first one is pretty straightforward, to organize the narrative with visually distinct and named sections. So in other words, we've seen a lot of these slides with a lot of things. They're really big blocks of text and it would be a big help to go from this to this.

Structured headers not only make it easy to read, but it would also help make the narratives consistent across drugs. And there are a variety of possible headers that could be employed, for example, indication, benefit, risk, comparative efficacy, weighing benefit and risk, risk management and post-marketing requirements.

DR. SCHWARTZ: Seamless. Our next recommendation is about including structured tables with both the trial descriptions and efficacy and side effect data so people can understand the basis of

approval.

So for Siliq, there's a lot of information in the risk-benefit framework. This information we think is displayed inefficiently. Benefit appears over six pages. Risk appears over seven pages. Sometimes the data are quantified. Sometimes there's just p values.

And we think that structured tables and consistent data formats would make it easier for readers by avoiding long text which is bogged down with lots of numbers and that the text can really focus on the interpretation, which is really what's so incredibly valuable about the benefit-risk framework.

So this is what it might look like for benefit. So in this case, there were three trials. And I'm going to show you two here which were two identical, 12-week randomized trials that were done in adults aged 18 to 75 with stable moderate to severe plaque psoriasis.

In the trial, Siliq was compared to an active comparator, Stelara, and also to placebo. And in both trials, they had the same two primary outcomes, whether somebody had a major improvement in their psoriasis or

whether the doctor rated the psoriasis as minimal or none. And the secondary outcome was that there was no psoriasis. The physician rated the skin as completely clear.

Here is the data. And just to say that the two trials had incredibly consistent results and the drug clearly works. So the other thing that you could -- you know, of course, when you make tables like this, you have to decide what data you're going to present. In this case, the trials were completely consistent. So maybe you would just pick one illustrative trial.

Alternatively, since the trials had completely consistent results, maybe you want to pool the results. But the bottom line is regardless of which data is presented, the tables make it possible for readers to weigh the benefits and harms for themselves.

So for side effects, the table would present side effects in terms of their importance to ensure the appropriate emphasis. So for instance, you could start with a black box warning, either state what the black box warning is for or state that there isn't any black box warning. Then, serious side effects and then the

most common symptom side effects sorted by frequency. And here's what it might look like for Siliq. But the idea is just to illustrate how you could efficiently communicate the data.

We've done a body of research which the FDA's own research has replicated showing that patients can understand these kinds of data tables, which we've called drug facts box. And we believe if patients can understand them, that clinicians probably can. So we think they'd be a great idea to supplement the benefit-risk framework.

The other part of structured data tables is the benefit-risk framework includes current treatment options. And we think it would be great to include comparative efficacy data. We know that FDA does not generally do this.

But interestingly, for Siliq, in the medical review, the medical reviewer created a table which contrasted Siliq's benefits with other similar biologic drugs that are approved for psoriasis. And this table provides we think really useful context because your willingness to accept more side effects or more

uncertainty is likely to change depending on how much more benefit this treatment has compared to similar treatments. And in this case, its benefit, while it's highly effective, is in the ballpark of other biologics.

Our next suggestion is about summarizing the FDA review team's approval votes and the rationale. So for instance, in the primary review team, which was in the Division of Dermatology, the division director voted yes. And what you could include was a link to the reason and to the summary review so that people could understand the reasoning behind that vote.

And then, you can do the same thing for the clinical rest of the review team. And for example, if you wanted to understand why the medical reviewer voted no, you could click on the reason, which, if it were in a specific header, you could quote the risk outweighs the benefits provided by the biologic, the safety signal for suicidal ideation and behavior requires further data to mediate the risk in this high comorbid population.

The team leader voted yes to approve the drug

and here's what the team leader's rationale for that vote was. Siliq should be made available with labeling sufficient to describe and inform the risk, as well as a REMS with elements to ensure safe use to ensure that prescribers understand and acknowledge the risks and document the patients who use Siliq are fully consented regarding the benefits and potential risks, even the possibility of a fatal risk.

In addition, it would be great because sometimes FDA consults other divisions for their opinion. And in this case, psychiatry, the cardiac division, epidemiology and pharmacovigilance also voted and this would allow people to understand their votes and their reasoning behind their votes.

And we think routinely presenting the agreement or disagreement helps to highlight whether important uncertainties exist. So we think the framework is incredibly valuable and we think it should be disseminated more widely, of course with data tables, to prescribers and consumers. And we want to suggest that maybe you consider expanding and redesigning FDA drug trial snapshots for that purpose,

while of course creating a whole library of benefit-risk frameworks on their own would be valuable, drug trial snapshots is already a place where new drug approvals are being posted.

So this is a trial snapshot for Siliq and this website is created for consumers and it has a bunch of headers about what the drug is for and provides a narrative about what are the benefits of the drug.

At the bottom, if you click the more information actually, you can find data. But the data looks like this and the data is really intended for prescribers or maybe for researchers because there's a fair amount of statistical complexity here about data amputation and statistical methods.

But the idea is this is data from the review or the label in a structured format. And this might be a really great place to start off by introducing the risk-benefit framework by adding a header about why did FDA approve this drug and providing links to the risk-benefit framework or perhaps sort of a table of contents of the risk-benefit framework.

And we think it would be great if there were

actually two versions, one for consumers and one for prescribers. So rather than having a website that sort of communicates sort of to two audiences at the same time, to have communications that are directed at each audience distinctly.

So in conclusion, we think that FDA's benefit-risk assessments and review documents, which we've read for many years, are a gold mine. Certainly the benefit-risk assessment has made it much easier to read those documents. It's independent, informed, expert assessment of drug benefit and risk.

And it's an explicit discussion of how often difficult approval decisions are made in the face of sometimes really important uncertainty. And we think the dissemination efforts are really important to prescribers and to patients so that they can make wise decisions about drugs and we just think you guys are doing great work. So keep it up. Thanks.

(Applause.)

DR. EGGERS: Okay. I want to thank all of the presenters, Brooke, Rich and Steven and Lisa. And we have some additional people coming up for the panel

discussion. I'd like -- we met Clause earlier today. So I'm going to ask for Peter and Bennett to introduce themselves. I guess we'll start with Bennett, since you are situated. Introduce yourselves and provide some -- a few minutes of thoughts to kick off our panel discussion.

PANEL DISCUSSION AND Q&A

DR. LEVITAN: Okay. Hello. I'm Bennett Levitan. I'm in the epidemiology department of Janssen R&D, part of J&J. And I'm a member of a team that does benefit-risk assessment, patient preference studies and a bit of decision analysis.

Thank you very much for the opportunity to sit on the panel and share some thoughts. I thought the day has been fantastic. Really enjoyed hearing the talks. And you asked if I could put a couple of thoughts together. So if I focus on the three main themes, benefit-risk frameworks, incorporating the patient perspective and more quantitative benefit-risk techniques. So I'll give you a few thoughts.

The first, echoing some of the comments from Sara and Valerie, I find, and my team finds, benefit-

risk frameworks are incredibly helpful, even for people who are extremely experienced at benefit-risk, who do it -- we do it all the time. It's very helpful in structuring our thoughts, reminding us of things that we can sometimes forget, especially when I'm working with a team in real-time.

And it also makes very easy to communicate the rationale for a benefit-risk decision in a manner that becomes pretty consistent over time. In fact, we've begun including in a couple of our submissions the framework because -- FDA's framework because we find it a useful communication tool.

The ICH update did the clinical overview suggests a couple of tools that could help support it. And we actually do these things in addition to the framework. So we do a value tree exercise. So the idea of key benefits and key risks has to be defended.

If we're going to choose a small number of all the benefits and harms that we measure and say those are the ones that drive a benefit-risk assessment, we go through an exercise to identify those and describe those which we pick in a defensible manner.

We also do something very similar to what we just heard from Lisa and Steve. It's what Francesco called an effects table. It's basically a tabular summary of your key benefits and harms, with the two treatments, maybe a treatment difference and some ancillary information.

We find it's extremely helpful to have potentially a hundred pages of information all compressed into a table or two so that after you've gone through the background, you can rapidly interpret the table and build a benefit-risk argument off the therapy context, the medical need and that table.

We also find it's also important to bring the patient perspective into the benefit-risk framework and we've done that a number of times, though it's really still an open question how best to do that.

That brings me to the second topic of incorporating the patient perspective. It's a lot more than patient preference studies that we're talking about. Just to give you an idea, the questions that come up all the time are the ones we've heard today. Which methods? What methods can avoid bias? What

patients should we be using? Should we assess the preferences or the viewpoints or the perspective of patient who are risk, newly ill with the disease, chronically ill or those who have experienced various treatments? They'll all have a different perspective.

One of the things I'd like to strongly suggest we consider is just like sponsors speak with regulators over the course of years about designing a trial and the statistics for trial, they consider a collaborative discussion on how to bring the patient perspective into the drug development process, whose perspective and what methods might be appropriate.

Finally, on quantitative approaches to benefit-risk, so something that Tarek and Brett brought up I want to really emphasize. It's not an either/or thing. It's not qualitative or quantitative. Really every quantitative analysis is based on a qualitative underpinning. And if you jump into a quantitative approach too early, you'll probably miss very important things.

The question really is when is it worth the effort to do the additional time consuming and

resource-intensive quantitative assessment of benefit-risk. And sometimes you actually don't know that until the very end when you've gotten your data.

There's definitely a role. One of the other things I'd like to see happen in discussions between the sponsor and the FDA is actually outlining a benefit-risk approach.

The idea that Becky mentioned earlier about a toolkit I think is the way to go because there's tons of things that we use, not always all the time. And I think what's needed is some guidance for industry as a whole as to which methods from a toolkit or which tools would be most valuable, as well as some guidance as to how to implement particularly some of the more complex tools.

Finally, I agree with what we've heard behind the scenes, that there's a strong exploratory phase to the more quantitative approaches and the patient perspective aspects. I love preference studies. They're a lot of fun. They're very insightful. But I'm well aware of their limitations. I like what CDRH has been doing where they're sort of inviting companies

to collaborate and talk with them about preference studies.

Both parties know there are still issues. But they're working on it together and exploring how they could learn from these preference studies for the work they're doing. And that's what I hear Theresa talking about in somewhat of a different way, but on the CDER and CBER side. Anyway, thank you for an opportunity to share some of my thoughts.

DR. EGGERS: Thank you, Bennett. And now, so that we have a CDER and a medical officer decision-maker perspective, we've asked Peter to come up and if you could provide a few thoughts, reflections on what you've been hearing?

DR. STEIN: Sure, sure. I'd be happy to. I'm Peter Stein. I'm deputy director in the Office of New Drugs in CDER. And actually, listening throughout the day, I find that I'm about to say almost nothing that hasn't been said before by a number of people. In fact, some of the things probably will be about the fourth time it will be said. So perhaps you can take this as emphasis rather than unique innovative thought.

The first comment I'd make, and I think maybe reemphasize throughout the day, was the value of the framework as CDER and OND have gotten increasing experience with it. It clearly has been a tool both for helping with decisions and I think clearly -- and I think the last talk and prior talks also emphasized how useful it was as a communication tool to patients and physicians in helping with understanding FDA thinking in decisional -- in the decisional frameworks.

Now, I do think that very often -- and for many of the decisions that we make, the risk-benefit is relatively straightforward. The benefit may be very clear relative to a limited risk or the risk may be very clear relative to a limited benefit.

One hopes that's not often the case, but sometimes it is. And the decision doesn't necessarily require more than a qualitative framework in which to consider it. I think it still is helpful to put down clearly and articulate the benefits we understood, the risks that we perceived and how we weighed them. But just like in circumstances where the benefit is so clearly above the risk, it doesn't really require much

more than simply articulating it, documenting it and then moving forward with the decision.

I would say that one point to make perhaps is that when the qualitative framework was selected and there was discussions I know in years past about what framework to utilize, there was consideration of applying a quantitative rather than a qualitative framework.

And I think there was concerns raised about the challenges of trying to convert -- trying to translate benefits to sort of a numerical estimate and risks to a numerical estimate, put those in some sort of equation and come up with a number and have that imputed as the decision, which of course is not what quantitative benefit-risk is about.

But I think that expressed some of the concern and led to more comfort with the qualitative approaches. But I would say that in some sense that may be perhaps a mistaken understanding in the sense that when we do a qualitative framework, I would posit that we actually in fact are being quantitative in a way that doesn't necessarily state our quantitative

assessments.

We have to, in doing risk-benefit, think about what extent of benefit there is, which is really a weight, if you will. What's the quantum of benefit? And we also have to think about what extent of risk is, what's the quantum of risk. And we have to compare them.

And when we make an approval decision, even if we haven't put on the table our quantitative assessments, we in fact have to translate the endpoints that we saw in the clinical trial to some quantum of benefit and the risks and harms that we saw into some quantum of risk and make the calculation that those benefits outweighed the risks.

So I do think even when we consider the qualitative framework, in a sense we are hiding the quantitative process that we have to all go through because in many instances it's not a complex one. It perhaps doesn't require a lot of challenge in doing that.

I think that, as I think about the quantitative approaches -- and just to step back, when

I did a quick poll of a few people, Bob Temple was here earlier and a few other people that I asked, you know, how often are decisions do we think really challenging where the qualitative framework alone doesn't provide the tool necessary to make the decision.

When we face really complex decisions where there's benefit and risk and they appear to be, you know, not clearly differentiated and the decision is challenging or perhaps there's relatively limited benefit and maybe more limited risk, but where the tradeoff -- where the balance isn't entirely clear.

And I guess we'd probably estimate that something like 10 or 15 percent of the time, maybe less, maybe more, it's really a challenging decision. And many times the decision is not so challenging.

So where would the quantitative tool come in I think particularly in these more challenging decisions where we're really trying to understand, you know, what's the right decision here.

And I want to pick up on something Richard said because I actually think that the output of that tool is perhaps not as important as putting on --

putting on paper the inputs to the tool. I think what quantitative risk-benefit, at least from my perspective, lets us do and perhaps makes us do is bring the decision-makers together to make explicit what their assumptions are.

What do they really think this would likely translate into if this was to be -- if the drug was to be approved? What would the benefits look like? How would we quantitate them? How impactful would they be?

What are the harms? What are the risks? How would we translate the clinical trial data to a benefit and to risks in the population that would be treated with this? What specific assumptions did the individual decision-makers make when they -- when they decided for or against the approval decision?

And by putting those on paper, putting them on the table, as it were, and comparing, those kinds of assumptions can be challenged. And I think it's that process of engaging in a discussion about what assessments one individual made versus another individual made versus another individual made, I think that's where the process can be so valuable. I'm not

downplaying the output of the process.

But I think it's really in the testing of the input and in people's expressing their range of uncertainty and looking at those ranges in the sensitivity analysis that can be done that we really have greater insight into the process. I think the challenges of course are trying to figure out how we convert the endpoints from clinical trials into extensive benefit. Endpoints can be sometimes directly translatable. If it's overall survival, that's fairly straightforward.

On the other hand, how do we convert, for example, a drug that lowers LDL to a quantum of clinical benefit? But of course, as I said before, I think we have to do that.

First, we have to translate it into some form that suggests what clinical benefit we think that provides in the study population and make another step in translating it into the benefit we think it will provide in the treated population if the drug was to be approved.

And similarly for harm, how do we translate

adverse events into specific harms in the study population and then translate that further into the population that would be treated?

So I think all of these processes that are engaged with the quantitative risk-benefit can be very valuable. And I hope in the years to come, we gain more experience in CDER as CBER has been I think ahead of the curve in really thinking about this and I think CDER needs to continue to think about how we can utilize that, these type of processes.

And there have been some inroads to that. We've made some efforts in our oncology group and in other groups looking at quantitative risk-benefit frameworks. I'm not sure we're at the stage where we're thinking that's how decisions will be made. But I think it will give us substantial insight to it.

So I guess the other comment that I would make is that I do think quantitative frameworks also allow a very nice tie-in to patient input because I think they help us with making the weighting and the scaling that's necessary in the quantitative approach.

And so, I think as we get more and more

experience with patient-focused drug development, with patient input into drug development decisions, I think there'll be a natural input into the quantitative frameworks and helping us with the weightings that are necessary to go into those calculations. So I'll stop there and --

DR. EGGERS: Thank you very much, Peter. I'll open it up if there are any questions. Oh, yeah? Yes? So as people are -- Clause, do you have any comments that you'd like to add based on from your talk this morning to this afternoon now?

DR. BOLTE: I can't help to think of a Swiss Army knife. You may as well think that Clause must have had an extended narcoleptic fit at some point today after his travel over and not sleeping very well. No, I've been very vigilant all the time.

What I mean by this Swiss Army knife approach, it's a nice souvenir, the Swiss Army knife from our country. It's a multipurpose tool. But typically, the more components you have, the less useful, the less functional it is. So trying to translate this into the benefit-risk framework, I would caution that we -- at

least at this stage, while we are developing in many different directions and trying to include different factors and weights and trying to quantify them as well, to limit -- to limit the framework to key functionalities and purposes, as I outlined earlier.

So without going into a monologue right now because I had this opportunity this morning, I would caution again to limit at this point in time the use of a probably multipurpose tool to just some key functions we discussed, namely facilitating the decision-making process, documenting it as well.

And I'm not so sure even about the third component, communicating it. If at all, only internally, not yet externally because it depends very much on the audience, the way you communicate it, as we heard from many different presenters.

And then, the final thought is for those of you who had the benefit to also attend business school, you come across a concept that is widely used there. And I was wondering all the time when I was listening today, to what extent could we probably use the balanced scorecard methodology here at all.

The balanced scorecard methodology is very well-established in a generic way. It helps with performance management. It can help to outline a strategic roadmap. It can be used in scientific as well as sales marketing and HR functionalities and purposes.

Key is that you have different, very well-defined components which cannot offset each other. So benefit-risk, benefit includes patient preferences and patient-reported outcomes and all that.

Benefit-risk, uncertainties and again, in a provocative way, this is just my opinion. I have to qualify that. It's not my agency's -- cost as well as the fourth dimension in such a balanced scorecard is perhaps something we should consider at some point.

DR. EGGERS: Okay. Thank you, Clause. Are there any questions?

MR. EMMETT: Hi. Andrew Emmett, with Pfizer. Thank you for the excellent presentations and panels. I have a question for our FDA colleagues and others. I think one thing we've heard throughout the course of the day is an interest under PDUFA VI and looking ahead

to really adopting a lifecycle approach to structured benefit-risk and patient-focused drug development and really leverage these tools and strategies throughout the continuum of drug development, starting early on in the development.

And we're starting to see a lot of experimentation along those lines. We've been hearing the companies have been submitting structured benefit-risk frameworks with background packages for meetings, with NDA/BLAs. We're seeing a lot more interest in patient preference studies.

Based on the learnings that we've had so far, from the FDA perspective, can you share any best practices that you've seen for that type of FDA sponsor engagement and communication in the premarket setting, at PDUFA milestone meetings?

And what would you say should be sponsors' expectations for the level of FDA engagement around a structured benefit-risk framework or patient-focused drug development data if that's submitted in a premarket setting. Thank you.

DR. EGGERS: Well, I'll turn to Peter to see

if you have any experiential regarding the interactions and what makes them useful.

DR. STEIN: So a couple of comments on that. I wouldn't say -- and I can't say that I have huge experience and have taken a poll of how many packages have included structured benefit-risk at various stages. But we clearly have seen sponsors that have taken the opportunity to put in a structured benefit-risk framework. And obviously, we're going to look at our own.

I think just like the value that we see in it in terms of framing our considerations in a structured fashion, the ones I've seen from sponsors I think help do the same thing. And I think that's some of the earlier presentations and the new ICH recommendations really I think highlight the importance of such a structured format.

So I think it helps the discussion to articulate the assumptions, articulate the context for the decision more clearly, articulate the benefits, the risks and the risk-benefit assessment in a way that I think enhances the discussion.

I would also add that there are clearly -- you know, from the premarket perspective, this is very helpful. But this is also part of how we must be thinking about the lifecycle as we go forward.

So as issues come up, new safety findings, I think the same framework helps. We know more about the drug's benefit.

As the lifecycle continues and as we see new potential risks, new defined risks, I think it helps us put it into the same framework of what we know about the benefits of the drug, the risks of the drug, the value of the drug over time. Are there new drugs that provide equal or greater benefit? What's the unmet need years into the drug's lifecycle?

So I think continuing to utilize the framework is valuable and I think companies that bring a structured and thoughtful approach help us in thinking about it as well. We certainly review what companies provide and I think that provides a more -- I think a more detailed and thoughtful discussion when you engage with us.

So I think it's helpful. I can't tell you

what percentage of companies put it into that formal framework. But I think where it's presented that way, I think there's real value in that.

DR. EGGERS: So, go ahead, Rich.

DR. FORSHEE: So I'll share just a few thoughts, one set of thoughts on the premarket side and one set of thoughts on the post-market side. I think the main message I would like to give on the premarket side is come talk to us early.

And I think in particular, if you're planning on doing anything that is more cutting edge, such as something that's going to potentially have quantitative benefit-risk approaches included or that's going to be doing some sophisticated patient preference, please talk to us very early on in the process. I think that that will provide the best dialogue between a sponsor and the FDA.

Regarding the post-market piece of this, particularly on the biologics side, and at the moment I'm thinking more about vaccines in particular, because we have such a low threshold for risk when we're talking about vaccines because they're so widely used

and oftentimes they're given to prevent a possible illness as opposed to a treatment of a problem that people already have, we're concerned about very low risks that might be out there.

And so, we put a lot of emphasis on the post-market -- post-market side. And this is -- the emphasis has become even stronger since the Food and Drug Amendment Acts that require the establishment of more active surveillance which has led us to be using more health claims data to try and assess potentially very, very low but serious risks that might be associated with vaccines.

I think that integrating the new data that comes up post-market into something like a structured benefit-risk assessment, I think we're still learning the best ways to do this.

But I think that that's going to be something that's very important and I think that when we consider how to integrate the sort of real-world evidence that is developed after a product is on the market and we think about how to integrate that data, it's oftentimes going to come from observational data, which has its

own special issues with interpretation, how to integrate that with the data that's come from the premarket side is something that I think still requires some additional thought. But I think it's an important area that we're going to have to confront.

DR. EGGERS: This is a topic that -- this topic of the dialogue between sponsors and FDA is a topic that twill come up in PDUFA VI. It was of great interest there.

I just -- I don’t have the experience working with the sponsor. But what came up as being important there, hearkening on some things that have been talked about today, was the importance of coming early to discuss the therapeutic context, particularly as early in the development programs because benefit-risk is a consideration early on and having a shared understanding of that therapeutic context early in development can help set stage for decisions and considerations moving forward.

So we'll be looking in that as part of -- as part of PDUFA VI about that therapeutic context. If there are no questions, we are -- oh, go ahead. Come

on up.

MS. DICKINSON: Actually, I think my question has been partly answered already. Sheila Dickenson, Novartis. I had a question about benefit-risk in the post-marketing setting, which I think we've been touching on a little bit.

I'm curious are the FDA using the grid that we've been discussing today in the context of post-marketing assessments and do you have examples on your website I could go and look at where you've been doing this? I would very much like to see what you've been doing.

DR. EGGERS: So I can take this. The answer to your second question is there probably are no examples out in the public sphere regarding the post-market decisions.

But they have been part of conversations in those particularly tough examples exactly to what Peter was describing where you're not sure where a new safety signal emerges and you're not sure where it fits in the armamentarium. And you have to now think what does benefit mean and how can you now measure benefit.

So is it utilization? Is it other things? We have now some other indicators of benefit in the setting, new evidence to come in. It does -- discussions about uncertainty are as great when you talk in the post-market setting because of the variable data sources as they are when you're talking in the premarket setting where there's just limited evidence. So is --

DR. LEVITAN: Yeah. Sheila, one place to look for examples might be the periodic benefit-risk evaluation reports, or PBRERs. Now that they have a structured approach similar to what's in ICH's clinical overview update. In those probably rare cases where there's a radical change in the data and a company can't say its things are the same, you'll probably find a more detailed assessment -- benefit-risk assessment post-approval.

DR. EGGERS: Okay. Anyone else? Baruch, yes?

DR. FISCHHOFF: I'd like to pick up the question of preference elicitation because I've been sort of reflecting on this all day. And I mean, I think the kind of process that we heard -- you know, if

we had a process where we had Telba, you know, understanding the agency perspective, somebody like -- I'm taking the previous panel -- Brett, who's familiar with the full size of the suite of alternative perspectives, has seen lots of different preferences, can interpret, somebody like Leah who's able to bring in the heterogeneity of patient preferences, I can see that being a very important discovery process that, in a way, would have kind of a hologram of the complexity of anything else.

Just like, you know, if you've listened to one of the Voice of the Patient things, you know, listen to the whole webcast online, you know, you realize, wow, every bit of this world if equally complicated. So I think that there's great -- and where does that benefit come from?

The benefit, people know the science. People who know preference elicitation and people who've taken the care to make certain that people have fully under -- you know, have met the communication standard that Steve and Lisa were talking about so that people who are participants in their -- in this are actually

telling you what their -- you know, their answer -- you've given them a question that you can answer.

And yet, what I've seen in areas that have looked at this -- and so, I think that that's an analytical -- behaviorally informed, analytical perspective can give you a lot.

And, but I think that the emphasis on quantification leads you into a very dark place and it leads you into the same I think scandalous situation you have with contingent valuation research or with kind of preference elicitation that's done for cost-effectiveness analysis or discrete choice in a lot of other people where people have displays that are incomprehensible, that haven't been developed to a -- you know, that don’t actually include the information that people need, where there's no manipulation checks to tell -- to check that there's actually been comprehension, that the analytics are opaque, even to reviewers of their -- of their papers, that an industry of contractors builds up around it and they establish their own conventions about we're going to throw out all the protest responses or we're going to impute

values to people who refuse to answer our questions or we're going to use this exclusion criteria or that exclusion criteria.

If you pooled all the exclusion criteria, you would have no respondents in most of those -- in most of those studies because they've asked people questions that they can't answer. And if they did think -- if they thought they could answer, it's probably because they haven't understood the question because the displays are so poorly evaluated.

So I think that -- you know, I think maybe it's worthwhile using quantitative for the risk side and analytical for the benefit -- for the -- quantitative for sort of the scientific, estimating the cost and benefit and analytical for the preference side.

You can tell if your risk or benefit estimates turn out to be wrong because you'll have some evidence in the future. If you've chosen to misrepresent -- you know, if you've chosen to misrepresent people's values, ignore heterogeneity in population, who's to know?

DR. LEVITAN: You bring -- Baruch brings up a

very good point and there's actually evidence that something like this could potentially happen. After CDRH released their draft guidance on patient preference studies, suddenly there were more organizations that described themselves as being capable of doing patient preference studies.

Now, we always work with academic or boutique consulting groups that are academic in nature. But we have the funds and time to be able to afford that. But not everyone can. So I think your point is well-taken.

And it stresses all the more need to have some type of -- I don't want to use the word guidance. That's maybe the wrong term. But best practice document. ISFOR has the beginning of it. Other organizations are beginning to put it together. IMI, the Innovative Medicines Initiative is working on it.

Some documents say if you meet these standards, or the International Academy of Healthcare Preference Research, IAHPR, Ben Craig, an organization like that that puts out this set of requirements and then you could say we followed these requirements will lessen some of the concerns.

DR. FORSHEE: So I do want to mention a couple of comments have led me to make this comment. With the quantitative benefit-risk assessments that we've done in CBER to date, we are stopping before we're doing the weighting and valuation component.

So we will go so far as to estimate, for example, the number of transfusion transmitted cases of Zika virus that our model would predict and we would go so far as to say but it's going to lead to this many units of blood that would otherwise have been available not being available because of false positives from testing, for example.

And so, we will go as far as to estimate the likely distributions of each of the benefits and risks that were identified in the early parts of the exercise. But then, that's usually presented to the review teams and to the advisory committees to allow a more qualitative expert judgment about figuring out what that balance looks like.

This isn't to say we would never go to that next step of exploring what the tradeoffs are. But we haven't yet. So that's where we've been comfortable

going to the point of estimating the likely distributions of the key benefit and risk endpoints that were identified and then using more traditional expert judgments to make final decisions about how to balances those.

DR. EGGERS: Well, with that, as the timekeeper, I'm going to have to end the session. Look forward to further discussions. You can be relieved of your posts. Look forward to future discussions. And I think Graham is going to come up for open public comments.

OPEN PUBLIC COMMENT

MR. THOMPSON: All righty. We are almost at the end of our meeting. I'd like to thank everyone who came in person and the almost -- there are over 400 people who attended via webcast. It's great to have you all here.

So this is the open public comment session of our meeting. We have seven people signed up for OPC. I'll go through your names in order in a few minutes. Please keep in mind that this is an opportunity for you to present your comment to us. But we're not going to

be responding to comments individually.

They will be transcribed and they will be part of the public record. If you don't get an opportunity to speak or you have more comments than you have time for, please feel free to submit them to our public docket.

All comments submitted to the docket will be considered the same as anything that was submitted here. The docket will be open until November 18th and you can find a link on our website.

We'd like this to be a transparent process. So we encourage you to note any financial interests you may have that are related to your comment. If you don't have any, you can feel free to say that. If you prefer not to provide this information, that's also fine. You can still provide your comments.

As I mentioned, we have seven people. And to keep this moving quickly, I'll give all the names now and please line up when the previous person has finished. First, we have Caila Brander, then James Valentine, Angela Lundberg, Jon Furman, Kristen Hsu, Jack Mitchell and Benjamin Craig.

We have about two minutes per person. So I won't have a timer. But please respect -- oh yeah, there's a mic in the middle. You can just line up there, using the free mic, yeah. And make sure to hold the mic close because people on the webcast, it can be hard to hear. Yeah, that's perfect.

MS. BRANDER: Great.

MR. THOMPSON: yeah, so you can start us off.

MS. BRANDER: Okay. Hi. I'm Caila Brander. I'm the policy coordinator at the National Women's Health Network, which is a nonprofit advocacy organization that works to bring the voices of women consumers to policy and regulatory tables. By choice, we do not accept financial support from drug or device manufacturers. We submitted lengthier comments to the docket. But we just want to raise up three key points.

The first is that we don’t believe that the current overreliance on the post-market research and review is sufficient to determine if drugs are safe for a diverse population. First of all, the FDA's adverse event reporting system only captures a fraction of the actual number of adverse events that occur.

Additionally, drug companies do not fulfil post-market research requirements in a timely manner, if at all. Overall, the number of post-market studies with delays doubled between 2009 and 2011.

Flibanserin is a recent example of a drug mentioned earlier, a female sexual dysfunction drug, that was approved two years ago despite serious safety concerns when the drug was mixed with alcohol. Therefore, the FDA required three follow-up post-market clinical trials to determine if indeed the mixture with alcohol was a serious safety risk.

But the three clinical trials, one of which was supposed to be completed in December of 2016, are still listed on the FDA website as pending, meaning that they have not begun.

The safety of women and people of color should not be dependent on the incomplete reporting systems or an industry which can choose to delay or ignore the FDA's post-market requirements.

Secondly, to ensure that a drug is safe, we need to have great inclusion of women and people of color in clinical trials in the premarket review stage.

And third of all, we encourage the FDA's effort to incorporate patient perspectives into the drug approval process.

But we encourage there to be transparency about the financial support that patients are receiving that bring them to the table and encourage there to be transparency for drug reviewers to know when pharmaceutical companies have funded patient testimony at public meetings.

In closing, we call on the FDA to make sure that the drug approval process is safer for women and people of color by addressing these concerns. Thank you so much for the opportunity to speak today.

MR. THOMPSON: Thank you, Caila. And next, we have James Valentine.

MR. VALENTINE: Thank you, Graham. Good afternoon. My name is James Valentine and I'm an associate at Hyman, Phelps & McNamara. While I've worked with eight of the nine patient communities that will have hosted externally led PFDD meetings through the end of this month, I'm here today providing comments on behalf of just one of those clients, the

Myotonic Dystrophy Foundation.

On September 15, 2016, the foundation held the first ever externally led PFDD meeting under FDA's new letter of intent process, which brought together over 200 community members. As FDA is probably aware from the PFDD meetings it's hosted, the PFDD meeting took many months to plan and required a considerable resource investment by the foundation to pull off a meeting of this magnitude.

MDF was happy to do so, knowing this meeting would help to establish the therapeutic context for myotonic dystrophy. According to PDUFA V, this was the intent, as part of FDA's structured benefit-risk framework, to have the PFDD meetings inform the first two rows of the framework. Drafts of these two rows are even included in the appendix of every voice of the patient report.

This leads me to what I was asked to request of you today. Given that FDA has passed the torch to patient communities to host these externally led PFDD meetings, the foundation would like to ask that FDA commit to using these Voice of Patient reports to help

FDA reviewers establish the therapeutic context in product approval decisions.

Such a commitment would include stating how FDA will distribute these materials to relevant FDA review staff. This would also include telling us, the involved and affected patient communities, how reviewers are being directed to use these materials. For example, when filling in the structured benefit-risk framework for a particular product, as a starting point, should the first two rows be prepopulated with the draft provided in the appendix in the Voice of the Patient report?

In addition, we hope that for each new drug approval, the agency will commit to tell us how PFDD-related materials, including the Voice of the Patient report and the draft benefit-risk framework, are used in each individual drug review, something that would be consistent with its requirement under the 21st Century Cures patient experience data provision.

This will allow patient communities to assess to what degree their efforts are making a difference in drug development and review. I should note this is not

a onetime determination for each patient community. For example, earlier this month, MDF hosted a follow-up session at its annual meeting to do a deeper dive in CNS-related symptoms to supplement the information generated at its initial PFDD meeting.

In closing, thank you again for the wonderful opportunity to host the first externally led PFDD meeting and to share our thoughts about the use of PFDD-generated information in benefit-risk decisions. We hope we can be a resource to you as you consider these issues in the future. Thank you.

MR. THOMPSON: Thank you, James. Next, we have Angela Lundberg.

MS. LUNDBERG: Hi. My name is Angela Lundberg and I traveled from Minneapolis, Minnesota at my own expense to share my perspective as a patient with you today. Thank you for giving me the opportunity to do this.

I have been harmed by antidepressant medication and I was not warned of the risks before taking it. In 2015 and 2016, I was prescribed SNRI antidepressants. I was not depressed or anxious when I

was first prescribed these drugs. However, the first SNRI made me feel anxious. So my doctor recommended that I switch to a different SNRI, Effexor. And that's what I did.

After about a month of switching to Effexor, I was suddenly hit with severe anxiety, agitation, panic, restlessness, insomnia and feeling like I was jumping out of my skin. I was also -- oh, I had extreme obsessive thoughts and fears racing through my head constantly. I was severely depressed for the first time in my life and sobbing uncontrollably for no reason. I also felt as though my head wasn't attached to my body, like I was having an out-of-body experience.

Looking back, I think I was experiencing something called akathisia. It's a known side effect of antidepressant drugs. I also had suicidal thoughts for the first time in my life. And for the first time in my life, I went to the psychiatric ER because what I was experiencing was so unbearable. Luckily, I was able to find a psychiatrist quickly to help me safely stop taking the drug.

Months of my life were stolen by these drugs. While I had the adverse reactions, I couldn't work. I couldn't drive. I couldn't leave the house. I couldn't even be upright for several weeks. The only thing -- the only reason I was able to hang on and not hurt or kill myself was I kept telling myself it's not you, it's the drugs. It's not you. It's not you. Hang on.

Even after tapering off of Effexor, it took a long time to feel like my normal self again. This was a terrifying experience and the worst thing that has never happened in my life. If I had known that this could happen, I never would have taken these drugs.

I know now patients that are desperate for treatments and are willing to take a risk, or they think they are. But it isn't until your life is turned upside-down by a terrible adverse reaction to a drug that you realize that even a small chance of a risk can happen to you.

MR. THOMPSON: Angela, can you provide some concluding thoughts?

MS. LUNDBERG: Sure. I just want to say

please keep in mind that patients deserve safeguards. We need to be able to trust the FDA to make sure the benefits outweigh the risks for the drugs that the FDA approves and that patients know exactly what these risks are. I almost lost my life because of a drug and I don't want anyone else to suffer that way. Thank you.

MR. THOMPSON: Thank you, Angela. Now, we have Jon Furman.

MR. FURMAN: Hello, everybody. Jon Furman again. Don't have any conflicts of interest. It looks like I'm about to talk about what it looks like when things go wrong, when things go badly. Specifically, what can quinolone antibiotics teach us about risk-benefit assessment?

My experience with this class of drugs, I was first given this -- one of these drugs in 1999 and quickly developed neuropathy, chronic fatigue and bizarre central nervous system issues, including pretty much what you just heard from the previous speaker.

The doctors, my PCP, specialists couldn't diagnose what was happening. They had no idea what was

going on, couldn’t tell me anything. Subsequently, I was given more quinolones, five times over the next 13 years. Each time, my conditions worsened. And I personally didn't put it all together until 2012.

Unfortunately, some things have gotten better and some of the symptoms are permanent. So I've had to learn how to deal with them. I've talked to -- since 2012, I've talked to hundreds of people personally that this has happened to with these same drugs. Usually their doctors didn't catch it either. Some of these people later on died from their condition. Often suicide was what they chose to be the final answer there.

So we have a situation with an entire class of drugs and you've got to ask how many people have been affected by this and didn't even know what hit them. I'm thankful that the FDA has update warning labels on all quinolones in the past couple of years to something that's close to appropriate. It looks a whole lot better than it did in the past. Some of the information is there.

But these drugs were on the market for 20-plus

years before that happened. When the FDA recently updated the warning label, they also created a term, FQAD, which stands for fluoroquinolone-associated disability, which indicates both disability and a long-term nature, if not permanency of the effects of these drugs.

So a couple of thoughts on this. The FDA, when it came to quinolones, did not do a good job premarket or post-market on risk analysis. These drugs became very commonly used drugs. And as they became commonly used, they became first-line antibiotics when they were really never intended to be used that way. They were supposed to originally only be used when other drugs failed.

MR. THOMPSON: Jon, can you give us some final thoughts?

MR. FURMAN: Well, sure. Glad to do that. The situation with quinolones indicates to me a catastrophic disaster essentially of risk-benefit analysis. It's come to my attention that when the FDA indicates a drug is safe, and I know there's some complexities in how that happens, that that's generally

believed. Risks, on the other hand, are often ignored by prescribers.

So it is very important that the FDA get risk assessment right as quickly as possible and as completely as possible. And you know, a final thought here. You know, I remember there was a slide earlier about creating a moonshot-type framework for risk-benefit analysis. And you know, I'd like to advise that that's admirable. But we want to avoid equally a Titanic-type situation. So please proceed carefully. Thank you.

MR. THOMPSON: Thank you, Jon. Next, we have Kristen Hsu.

MS. HSU: Hi. My name --

MR. THOMPSON: You can hold it. That's fine.

MS. HSU: My name is Kristen Hsu and I'm here on behalf of the Amyloidosis Research Consortium. The ARC is a patient-led organization founded in 2015 with the vision to make material and significant contribution to the curability of amyloidosis.

Amyloidosis is a group of rare, misfolded protein diseases that are progressive in nature and

fatal. There are currently no FDA-approved treatments for any type of amyloidosis. But the landscape is changing and this is a really exciting time. There are a number of companies with products in late-stage development and additional products underway.

However, with the risks of the difficult environment that come with rare diseases, these treatments cross multiple divisions. There is generally a lack of understanding of the natural history of the disease and an unclear benefit-risk framework with few clinical endpoints and considerable uncertainties. The value proposition is a concern for a number of companies developing products.

To help with this, ARC organized an externally led patient-focused drug development meeting in November of 2015 and we quickly submitted a Voice of the Patient report shortly thereafter. These efforts, we believe, are critical to understanding the disease and the needs of the patients.

The concern though is there's not yet a clear directive or path on how these become ongoing tools that will be embedded in the complex and detailed

review processes. The PFDD meetings, for example, are immensely resource-intensive for a group like ours and we hope that they have an ongoing impact beyond the members of the FDA who we were grateful were able to attend.

Similarly, with the Voice of the Patient report, understanding how and where that document fits in with the review process and whether there are opportunities to ensure that they don't become outdated as the landscape evolves and that they can be updated and used as part of the review process and also that there be an online repository for any externally submitted documents like ours.

We think this is a critically important program and we applaud the FDA for the care with which it's been implemented. We hope there will be additional opportunities for groups like ours to engage further and ensure that these efforts have longevity and impact within the benefit-risk framework.

MR. THOMPSON: Thank you, Kristen. Next, we have Jack Mitchell.

MR. MITCHELL: Thank you for the opportunity

to speak today. I'm Jack Mitchell, director of health policy for the National Center for Health Research. NCHR provides objective research information and promotes public health and legislative policies on behalf of patients and consumers. We accept no pharmaceutical or medical device industry funding. So I have no conflicts of interest to report.

NCHR would like to commend FDA for holding this day-long panel on the progress of benefit-risk analysis, which is ultimately the foundation of all the agency's regulatory decisions. We've heard today from a variety of experts, both inside and outside the agency, about FDA's efforts over the past eight years, which have produced some very positive outcomes for drug reviewers, industry stakeholders and patients alike.

However, we are here today to ask for even more attention to be directed to the patient perspective in this critical benefit-risk decision-making. I'm not a clinician. But as a former FDA and HHS official and as a senior Senate committee investigator overseeing public health issues, as well

as with my current role at NCHR, I've heard from a significant number of patients from different perspectives over 25 years.

It's truly disturbing how often patients who have been harmed by a drug or medical product have felt a sense of betrayal because they believed, fairly or not, that they had counted on FDA to ensure that medical products are safe and effective and that they had been fully informed of the risks involved. Unfortunately, safety information is far from fully known when many drugs and medical devices are approved.

As we know, patients don’t often fully understand these risks, if at all. While those who follow FDA know differently, many patients assume that when an FDA advisory committee recommends an approval and FDA agrees and signs off, the medical product is safe without reservation or condition. Often, of course, that is not the whole picture.

Approvals and safety ramifications can be hotly contested and disputed among different knowledgeable experts who have equally good intentions. Most patients -- and this is a medical device, not a

drug issue -- but most patients know very little, if anything, about the 510(k) substantial equivalence program which governs most medical device approvals.

Most patients have no idea that sophisticated surgical implantable devices are approved with very little clinical evidence or human trials, nor do they know that five year ago, the Institute of Medicine, now part of the National Academy of Sciences, recommended in a detailed report that the entire 510(k) process be scrapped as it was unable to established safety and effectiveness. FDA turned down that recommendation, with minor changes to 510(k), which is still the governing -- the main governing medical device approval system.

FDA must also always remember its critical role as a voice for patients and to ensure that clinical trials are large and diverse enough to evaluate risks on a premarket basis wherever possible. We also ask that FDA do a better job in enforcing the completion of required post-market studies, which too often are frequently agreed to, but not initiated, let alone finished.

The near-term elevation of the patient engagement can be a watershed event and an opportunity to amplify the voice of patients both within the agency and publicly. Patients, after all, are the primary underlying reason you are doing benefit-risk analysis in the first place. I thank you for your time and attention.

MR. THOMPSON: Thank you, Jack. And our last speaker will be Benjamin Craig. It looks like Benjamin has left. Going once, going twice? All right. We'll now move to some closing remarks from Theresa Mullin.

CLOSING REMARKS

DR. MULLIN: Well, it's been a long day. So I could just say thank you and let it go with that. But I guess I would like to try to give you a brief summary, a quick summary of what we've been hearing today. First of all, I do want to thank you for coming to this meeting, especially those of you who have come from far away to share your perspectives with us today and for those of you on the phone.

And we've just heard a lot and learned a lot in this meeting. And I'll just try to not do justice

to it, but try to cover some of what I think are the highlights based on my notes.

And the day began with Rich Moscicki going over -- you know, kind of setting the stage here for us that this is -- our benefit-risk assessment is really a part of our public health function. We regulate drugs, devices and biologics, at least on the medical products side. We don't regulate the practice of medicine.

So what we can do is try to determine whether products are safe and effective for their intended use. And I think what this framework is supposed to be doing is helping us. And it is helping us communicate better that benefit and risk.

We have heard from speakers today that there are ways to make that even more effective and accessible as a source of information to prescribers. And we heard from Dr. Hammad earlier today about the importance -- we're working way upstream of what some people are thinking of, which is the point of care. And so, you know, we need to work -- continue to work on making this information even better presented.

We heard from Mary Thanh Hai about how we've

been looking at this framework to see how well is it working for those purposes of organizing our thought with a lot of -- you know, it's millions of pages actually of information that often go into these assessments. How does it help us to weigh all of that information and try to communicate and distill a decision from it?

We heard from Valerie Overton. She works at ERG, that her evaluation, and including all of those interviews and all of those applications show that it is overall positive. It is being pretty effective in terms of how it's communicating the information.

And then, we heard about the ICH experience and how the information has helped there. Now we have a fairly standardized structure for sponsors, drug sponsors to use to submit that information to support this kind of approach to assessment.

At the EMA, they're taking an even further structured approach and they're trying to figure out now how to even go after the different types of uncertainty that are involved in our decision-making and to try to deal with those in a very productive

manner.

Swissmedic told us about -- Clause was telling us how they practically approach the benefit-risk assessment in our post-trust society and the challenges that are presented by that.

In addition to Tarek confirming that the structured benefit-risk approach was, I think, as he put it, a no-brainer in terms of how useful it was, he did raise a variety of other methodological, philosophical and practical concerns that I think would keep us busy for perhaps the next 10 years and well-employed in that work.

Becky Noel told us we needed to keep pushing the benefit-risk framework to be further used and integrated into the approaches that we take at the agency as well as what's being done by industry. And how do we make sure there's good connection between all of these efforts that could be siloed if we're not careful?

And then, we heard from another colleague in the Center for Biologics, Jeff Roberts, telling us about how he's been using the framework for vaccine

decision-making, which has a very sort of different approach to benefit-risk acceptability. And the framework seems pretty robust for the internal regulatory decision-making for that purpose as well.

And then, we had an afternoon session where we did talk more about the patient-focused drug development and the patient-centered efforts that the various centers are employing, which we consider to be pretty complimentary, very much a work in progress.

We would agree that nothing is happening as quickly as we would like it to. But there is so much to be done and we want to do it right. So it's going to be a little frustrating in terms of how long it takes us to get good tools in place that we can use, we can use correctly and reliably and transparently and we do move things forward.

As Brett Hauber put it, there are a lot of tools in the toolbox. But we need to understand how they work and where they're appropriate and how they might work best.

Leah McCormick gave us more information about the Psoriasis Foundation's experience and how far

they've been trying to go to help look at that heterogeneity across a population because that's very important in understanding what the views and what's most important to a population.

And then, Alicyn Campbell talked more about the use of the benefit-risk framework in the context of oncology and the importance of that holistic approach, not only looking at benefits, but also making sure you integrate into that burdens or risks. And she raised the question about what kind of patient-focused information is really relevant to the patients. And is it time to start thinking about a patient-oriented label and presented a presentation of that information.

And then, in our last panel, Baruch Fischhoff gave us an overview of key methodological considerations and the pitfalls in a lot of these judgment tools and approaches and what we need to be trying to keep in mind as we go forward to evaluate critically and report candidly, which I like very much.

Rich Forshee talked about benefit-risk being complex and iterative and it involves a lot of participants. And that's still true at FDA. It's been

true all along and maybe getting more complex. We don't need to use quantitative methods for all decisions. But there may be a subset where it really is helpful to explore uncertainties and do sensitivity analyses around our decisions, not just for premarket review but for other public health decisions that regulators have to make as well.

And then, Steve Woloshin and Lisa Schwartz seamlessly -- amazingly seamlessly, actually -- made a presentation showing us how they think this information is very valuable.

But they had some ideas for how we can make it better and how we can make it more accessible and maybe make it more available so that the primary care doctor, as well as the specialist can have access to the kind of risk information that FDA puts into its reviews. So that can continue to make its way into the points of care so that that's well-understood and maybe made more accessible to patients.

And then, we heard from Bennett telling us about how we might better -- they use the information to better organize their thoughts and distill

information within their companies. And they're looking forward to how we're going to be integrating this into our guidance in a few years.

And Pete talked about the value of benefit-risk as a communication tool. Not all decisions probably require that I think is the view you generally hear from us here, but that maybe 10 to 15 percent of decisions really do warrant that extra work to try to work up and put all the assumptions on the table and that effort to get all the assumptions out there and maybe extrapolate and look at benefit-risk out in the indicated population is worth our doing. And to have the tools to do it.

And finally, I'll just say Clause then warned us about not to make the benefit-risk framework into a Swiss Army knife that had too many features and functions and just to really focus on a few key features that are the ones you're going to use all the time, structuring decisions, thinking about that, maybe looking at a balanced scorecard methodology to try to bring information together in kind of a simple structure.

And then finally, I think Baruch ended with concern about the potential for abuse of these methods. And I'll just end with telling you that when we were talking about these commitments, the patient-focused commitments and other PDUFA VI commitments to the energy and commerce committee staff, you know, maybe months ago it seems at this point, but it was for the purpose of this reauthorization.

We got questions from the congressional staff about these methods and weren't we concerned that it could be used to manipulate patients' perspectives and that inappropriately and that we would -- the method would be used inappropriately. Companies would do things that weren't appropriate.

And all we could do was reassure them that regulators are the most skeptical people that at least I've never met. They hardly believe anything you tell them. And they are definitely going to be very skeptical of things that are submitted.

And I think that they're going to worry about model opacity and they're going to worry about too much clever use of -- they're going to be very concerned.

And so, that's why we're taking the time to make sure that what we're doing is the right way to do it and that the reviewers all know it.

So this capacity-building idea and getting the information out within the agency is we think critical to move this forward because we're not going to accept anything that doesn't look right and that we can't open up and look inside of and make sure it works properly so that we can assure patients -- we're doing the right thing for patients.

So on that note, I'll let you all go home and thanks very much again for coming here today.

(Applause.)

(Whereupon, the foregoing adjourned at 5:10 p.m.)

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CERTIFICATE OF NOTARY PUBLIC

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

MICHAEL FARKAS

Notary Public in and for the

Commonwealth of Virginia

CERTIFICATE OF TRANSCRIBER

I, BENJAMIN GRAHAM, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.

September 27, 2017

DATE BENJAMIN GRAHAM

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