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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PUBLIC MEETING ON BENEFIT-RISK FRAMEWORK IMPLEMENTATION

Monday, September 18, 2017

FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, MD 20993

Reported by: Michael Farkas,
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A P P E A R A N C E S

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

2 WELCOME

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

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

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

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

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

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

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

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

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

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

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

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

21 OPENING REMARKS

22 DR. MOSCICKI: Thank you, and I want to

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

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

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

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

1 its intended use.

2 Now, the meaning of effectiveness is in fact
3 specified by statute and I'll read this for you:

4 "Evidence consisting of adequate, well-controlled
5 investigations on the basis of which it could fairly
6 and responsibly be concluded that a drug will have the
7 effect it purports or is represented to have under the
8 conditions of use prescribed, recommended or suggested
9 in the labeling."

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

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

1 review process.

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

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

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

22 So all of that comes into benefit-risk

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

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

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

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

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

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

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

1 benefit and tolerance of risk.

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

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

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

17 (Applause.)

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

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

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

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

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

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

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

1 benefits outweigh its risks to the population.

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

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

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

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

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

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

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

22 So you're looking at the shell of the

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

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

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

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

1 the population by looking at the severity across
2 demographics.

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

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

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

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

1 strategy to manage the risks.

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

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

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

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

1 We published a plan in February of 2013. In May of
2 2013, CBER, the Center for Biologics, integrated the
3 benefit-risk framework into the review templates for
4 the original BLAs and BLA efficacy supplements.

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

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

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

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

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

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

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

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

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

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

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

22 Examples could be structured techniques to

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

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

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

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

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

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

9 (Applause.)

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

13 REGULATORY CASE STUDY

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

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

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

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

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

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

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

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

17 I also chose this one because it was an
18 extremely challenging regulatory decision. While the
19 drug itself was very effective or was effective at
20 lowering hemoglobin A1c, which is an established
21 measure of glycemic control for diabetes, that benefit
22 was counterbalanced by some safety concerns.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So the kind of data that come out of these

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

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

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

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

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

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

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

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

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

1 the public.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And what you also saw in this application

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

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

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

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

22 With respect to the quantitative, you already

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

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

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

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

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

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

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

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

1 scale.

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

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

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

18 (Applause.)

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

1 ASSESSING THE IMPLEMENTATION OF FDA'S BENEFIT-RISK
2 FRAMEWORK

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

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

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

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

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

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

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

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

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

1 applications.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So I think Sara mentioned that the agency is

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

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

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

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

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

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

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

22 And in other cases, the level of detail was

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

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

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

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

1 development meetings were just then happening.

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

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

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

20 MS. OVERTON: Yes.

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

22 Thanks.

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

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

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

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

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

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

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

18 (Applause.)

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

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

3 INTERNATIONAL COUNCIL FOR HARMONIZATION

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

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

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

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

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

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

17 So here is the M4E R1 that was recently
18 replaced. It's basically three-quarters of a page, and
19 with credit to Francesco Pignatti, from EMA, he did a
20 word cloud of the previous version of benefit in the
21 §2.5.6 and you see that there and you see which words,
22 particular word shows up most prominently. I'll come

1 back to this later in my presentation.

2 So here's the representation on our expert
3 working group at ICH. We began meeting in the fall of
4 2014, I think it was, and then finished in the early
5 summer of 2016, so pretty broad representation across
6 regulators, industry and other health authorities.

7 So when we first began meeting in the fall of
8 2014, we pretty quickly reached consensus on general
9 principles for what a revised guideline should look
10 like.

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

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

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

7 We felt that the new guidelines should not
8 specify methods for the benefit-risk assessment nor
9 methods for how a regulator should think about the
10 benefit-risk assessment to kind of maintain that
11 autonomy on behalf of the regulator and recognizing
12 that other ICH guidelines speak about benefits and
13 risks, we did have a principle and a focus that the new
14 §2.5.6 should be consistent with those other documents,
15 which was a little bit of a challenge.

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

1 of new information.

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

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

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

22 Consistent with other sections in the revised

1 2.5.6, we asked that any limitations or uncertainties
2 in these areas should be discussed if they're known.
3 And information about disease severity and
4 subpopulations, that should be considered and, to the
5 extent that it's known, communicated to the regulator
6 because that's certainly something that we think about.

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

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

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

1 §2.5.6.2 and 3, it's more than just listing out the key
2 benefits and key risks. It's really about discussing
3 why you think they're key and pertinent to the benefit-
4 risk assessment.

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

8 Did I go too fast? Okay. Moving on to
9 §2.5.6.4 and the benefit-risk assessment, as I said
10 before, there's no prescribed approach for the benefit-
11 risk assessment that we put in the guideline. But I
12 think I tend to think about it in terms of we kind of
13 had a permissive approach into the revision of the
14 §2.5.6 rather than a proscriptive approach.

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

1 own here. There's no keyboard.

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

7 And if there are additional analyses done by
8 the applicant that maybe perhaps are of a more
9 quantitative nature or a visual display, that those
10 analyses can be submitted in an appendix to 2.5.6. I
11 think that's 2.5.6.5. But you know, how you analyze
12 that information and draw conclusions from it, that
13 should show up in the benefit-risk assessment in
14 2.5.6.4.

15 And about patient perspectives, there was a
16 lot of discussion in the working group about the
17 inclusion of patient perspectives and any information
18 or analysis that a company does to glean this
19 information to help frame and inform the benefit-risk
20 assessment, that that information may be included in
21 §2.5.6 as well.

22 So this can include descriptive information on

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

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

10 So while we didn't go into these ICH
11 conversations expecting to create a more balanced
12 document in terms of benefits and risks, that wound up
13 happening. So risk seemed to be a focus of revision
14 one, at least in terms of what the guidance that is
15 provided there. And now, it's more of a benefit-risk
16 2.5.6, and I think that's a good thing.

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

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

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

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

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

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

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

2 Some folks on the group were worried about the
3 §2.5.6 becoming very extensive because elsewhere in the
4 clinical overview, the ICH guideline, I think there's a
5 rule of thumb that the whole clinical overview should
6 be like 30 pages. And you know, even before we revised
7 2.5.6, we were seeing clinical overviews well over 30
8 pages.

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

15 So I think so far so good on this. And those
16 who do use the new guideline, there is still variation.
17 There must be discussions that go on in companies about
18 creating additional substructure even within the
19 revised 2.5.6 structure that we did. So while we have
20 2.5.6.1 or 2.5.6.2, I was seeing 2.5.6.1.1.1. So for
21 some, there was a fair bit of detail.

22 And this is my pictorial acknowledgement

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

5 (Applause.)

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

7 MR. FREY: Okay.

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

13 (Whereupon, the foregoing went off the record
14 at 10:22 a.m. and went back on the record at
15 10:38 a.m.)

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

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

5 DR. PIGNATTI: Yes.

6 MR. THOMPSON: Okay.

7 DR. PIGNATTI: Hello, Graham.

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

11 INTERNATIONAL REGULATORY AGENCIES

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

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

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

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

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

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

22 What has changed? Next slide, please. Well,

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

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

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

22 Next slide, please. What has changed also was

1 in the primary pharmaceutical legislation, initially
2 applications were to be reviewed if efficacy was
3 lacking because only 10 years later in 1975, when the
4 concept of benefit-risk was more or less introduced but
5 only in the preamble to the regulation, it is only in
6 2004 that we have this term benefit-risk really
7 prominent in pharmaceutical legislation.

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

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

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

22 Next slide, please. And we translated the

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

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

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

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

1 framework to deal with those.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

1 interest we have to consider.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 and were no data for certain age groups as well.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 (Applause.)

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

19 PHARMACEUTICAL INDUSTRY

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

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

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

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

1 quality of the evidence, it plays a role here.

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

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

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

1 This was Pujita's camera.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And that's where actually I have an issue with

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 One of the ways that this additional
15 elaboration comes about is through a Q&A document.
16 §2.5.6 did not get a Q&A document because the expert
17 working group consensus was that industry and
18 regulators would benefit from living with the update
19 for a short interval to better identify the types of
20 questions and pain points that companies were
21 experiencing. And there's been no change in that
22 position since the workgroup concluded that summer.

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

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

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

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

1 capacity-building, what do we need to do to go further?

2 Well, there are three things. The first is that we

3 need to progress the FDA framework. There are ways

4 that we can do this. We've made an excellent start.

5 And we should celebrate the achievements that have come

6 from working together. But there are ways that we can

7 go further.

8 So how do we advance the baseline? Well, we

9 might consider the use of data summarization and

10 visualizations that are supportive of the decision. We

11 could consider a methods toolkit or a methods catalog,

12 again, similar to what came out of MDIC, standards for

13 methods applications. So if we do have folks who want

14 to use more quantitative approaches to benefit-risk

15 assessment, again, how should they be doing that? What

16 does good look like?

17 Understanding how we can achieve alignment on

18 the assessment of outcome importance and then adaption

19 and application to post-marketing assessments.

20 The second large area that I think we might

21 have an opportunity for capacity-building is in his

22 topic of patient perspective methods. So we certainly

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

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

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

1 assessment.

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

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

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

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

7 (Applause.)

8 PANEL DISCUSSION AND Q&A

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 MR. THOMPSON: Dr. Temple?

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

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

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

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

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

8 DR. TEMPLE: Yeah.

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

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

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

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

1 response.

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

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

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

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

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

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

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

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

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

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

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

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

12 DR. HAMMAD: Sure.

13 DR. TEMPLE: You just know that they do.

14 DR. HAMMAD: Sure.

15 DR. TEMPLE: So one of the things that we've
16 been urging since our guidance on §14 was put out in
17 2006 is showing the cumulative distribution of
18 responses or showing bar graphs showing what the range
19 of response is.

20 DR. HAMMAD: Yeah.

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

22 --

1 DR. HAMMAD: Absolutely.

2 DR. TEMPLE: For flibanserin, it did.

3 DR. HAMMAD: Yeah.

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

8 DR. HAMMAD: Yeah.

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

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

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

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

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

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

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

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

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

15 DR. HAMMAD: Yeah.

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

19 DR. HAMMAD: Yeah. Exactly.

20 DR. TEMPLE: Right.

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

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

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

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

17 MR. THOMPSON: Bennett, you have a question?

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

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

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

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

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

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

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

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

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

1 benefit-risk framework was pretty good.

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

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

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

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

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

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

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

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

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

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

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

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

11 DR. MULLIN: (Off mic.)

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

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

15 DR. LEVITAN: One to two a.m.

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

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

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

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

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

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

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

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

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

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

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

1 situation? Thank you. Oh, Jon Furman.

2 MR. THOMPSON: Thank you.

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

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

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

1 you can identify?

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

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

13 (Applause.)

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

16 (Whereupon, the foregoing went off the record
17 at 12:07 p.m., and went back on the record at
18 1:00 p.m.)

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

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

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

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

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

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

1 FDA EXPERIENCES AND PERSPECTIVES

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

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

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

1 approach.

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

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

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

1 terms of this and applying statutory standards.

2 So here, we have this benefit-risk framework.

3 And just to orient you, you saw that this morning. I'm
4 going to talk about the yellow highlighted area here.

5 That's the place where we started with this patient-
6 focused drug development initiative, the idea that
7 patients' information could help inform that
8 therapeutic context that you heard about earlier today.

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

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

1 way.

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

9 So we started this initiative, as I said, in
10 2012 based on the observation that patients were
11 uniquely positioned to inform our benefit-risk
12 decision. They're the ones that are going to take the
13 drug after it's been approved. They're the ones who
14 will experience any benefit or harm that will come from
15 it. And we didn't have a systematic way to do that at
16 the time.

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

1 particular timeframe and that also is another
2 constraint.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 We've also identified patient groups who have

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 (Applause.)

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

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

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

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

1 factors for benefit-risk determinations.

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

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

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

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

1 regulatory decision-making.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 One obesity device called Maestro was approved
7 based on some information derived from the decision aid
8 tool, not only but some of that information. That
9 study helped to develop the patient preference
10 information guidance document that was released in
11 2016. It's subscribed by Center for Devices and Center
12 for Biologics.

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

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

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

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

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

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

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

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

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

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

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

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

10 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 investigation.

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

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

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

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

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

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

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

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

1 preference information.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 (Applause.)

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

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

13 STAKEHOLDERS' PERSPECTIVES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 It started with going to patients, and not

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 those different groups that I had shown upfront.

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

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

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

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

22 But there are precedents for doing this and

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

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

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

17 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Ultimately, this open dialogue is what has our

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

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

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

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

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

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

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

22 As I said, I think that patient advocacy

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And finally, that patient and patient

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

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

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

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

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

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

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

14 I want to just close with a quote from one of
15 the public comments that was submitted to the docket
16 for the 2016 psoriasis patient drug development
17 meeting.

18 The NPF was pleased to support more than a
19 hundred patients registering to participate in person
20 in that meeting and more than double that online. And
21 as part of our outreach to our community, we encouraged
22 those folks who could not be there on March 17th to

1 share their perspectives with the public docket.

2 And this was a comment, part of a comment
3 offered to the docket by a woman who I don't know. She
4 didn't have a lot of advocacy experience with the
5 foundation, if any that I'm aware of.

6 But I thought it was very interesting that as
7 part of her comment she specifically called out that
8 desire as a patient to engage with regulators as well
9 as with industry and offer her perspectives. Thank
10 you.

11 (Applause.)

12 MS. VAIDYA: Thank you, Leah. And next, we
13 have Alicyn Campbell.

14 MS. CAMPBELL: Sorry. It was a bit of a long
15 walk from over there. Hi. Let me make sure I do this
16 correctly. Hi. So for those of you I haven't met, I'm
17 Alicyn Campbell and I'm the global head of patient-
18 centered outcomes research for oncology at Genentech,
19 which is a member of the Roche Group.

20 So I'll be talking a lot today from the
21 oncology perspective and also just I'm not a preference
22 person, although I was part of the -- he gave me a

1 really nice setup with that Rituxan preference example.
2 We didn't conspire beforehand.

3 But I'm definitely a social scientist and I've
4 been in outcomes research for almost 11 years now. And
5 I'm going to be talking about patient-reported outcomes
6 and clinical outcomes assessments and how those can
7 help with the FDA benefit-risk framework. And my
8 disclaimer is my thoughts are my own and they're not
9 those of Genentech or of Roche.

10 So whenever I talk to folks about the patient
11 voice, I always like to talk or start with a scan like
12 this because I think when we talk about benefit or
13 treatment benefit, we tend to look at objective
14 measures. And so, for those of you who aren't oncology
15 people, and I'll forgive you -- just kidding -- this is
16 a scan showing progression-free survival.

17 And so, you can clearly tell that the
18 patient's having benefit and the tumor's shrinking.
19 But if you think about the FDA definition of clinical
20 benefit, which is impacting how a patient feels,
21 functions or survives, I would argue what this scan is
22 telling us about how this patient feels or functions or

1 their symptom burden. And so, when we talk about
2 efficacy or benefit, we tend to use examples like this.

3 On the flipside, when we think about safety or
4 risk, this is a common toxicity criteria for adverse
5 event table that's commonly used in oncology. And you
6 can see it has a long list of adverse events, from
7 highest to lowest frequencies across the two treatment
8 arms.

9 And so, for this session, when we talk about
10 benefit-risk, I'd argue in the last two examples I've
11 shown you, we don't see the patient voice. It's really
12 absent. And I think we know that although adverse
13 event tables are great for characterizing the risk
14 associated with laboratory values, it's been well-
15 documented by Ethan Bosch, Amy Abernathy and others in
16 the patient-reported outcome community that it
17 definitely tends to underrepresent or undercut the
18 patients' impact.

19 So we've talked a lot today about how it would
20 be great to have systematic inclusion of the patient
21 perspective. In particular, I really liked Tarek's
22 slide where he had a patient with all the different

1 semantic word clouds for the ways we can talk about the
2 patient voice. And so, I would posit we already have
3 some pretty good quantitative methods we can use to
4 better understand the patient impact that I think would
5 be helpful for risk-benefit assessment.

6 So if we start on the right -- and I just want
7 to make -- yeah, I knew that was going to happen when I
8 tried to use the pointer. Now I've been fired. Sorry.
9 I didn't have the pointer training here. I'll just --
10 I will not use the pointer.

11 If you start on the right, these are the types
12 of measures we can use to systematically and
13 quantitatively assess the patient experience of
14 treatment and also of disease.

15 And so, first is the patient-reported outcome.
16 And so, that comes from a patient without
17 interpretation from anyone else. I think these are
18 particular important in oncology when looking at
19 adverse events because oftentimes patients are
20 concerned with telling their provider about a symptom
21 for fear of losing the medication.

22 And so, the confidential patient-reported

1 outcomes often give us a fuller picture of a cancer
2 patient's experience with their disease. We also have
3 clinician-reported outcomes. And so, these are
4 measurements based on a report that comes from a well-
5 trained health professional after observation.

6 These are much more common in areas like
7 neuroscience, additionally sometimes in pediatric areas
8 where patients aren't able to self-report, observer-
9 reporter outcomes, this could be for a caregiver for a
10 patient with Alzheimer's disease or autism. And then
11 finally, performance tests. This could be a six-minute
12 walk test.

13 It's essentially a test that requires patient
14 cooperation to complete. And a lot of the digital
15 health and mHealth applications we're starting to see
16 could fall into this area.

17 And on the left, you can see the broad array
18 of concepts these can measure. You can measure signs.
19 You can measure symptoms, interference with activities
20 of daily living, functioning and behaviors. So when we
21 think about how do we document systematically the
22 patient experience into risk-benefit, I think we have

1 some good tools by systematically including this
2 evidence.

3 So when I think about the framework -- and
4 remember, I'm a social scientist. I'm not as much of a
5 risk-benefit framework person -- I think we tend to
6 talk about them as separate. And that's something that
7 always kind of stymies me.

8 You know, with the second word cloud someone
9 showed earlier today, benefit and risk were there. And
10 to me, it's really the same. To me, it's hard to
11 really tease those out as mutually exclusive concepts.
12 It's not always an either/or for the patient,
13 especially depending on the type of disease it is.

14 And so, in oncology, the benefit-risk could
15 really shift depending on your curability expectation.
16 So if I have a hematologic malignancy and I know that I
17 might have to undergo a variety of treatments that
18 might have side effects for a finite period of time for
19 a very high chance of cure, my benefit-risk tolerance
20 is extremely different than someone with a metastatic
21 solid tumor who doesn't have a very positive prognosis
22 and might only have a few months.

1 And so, I think as we look forward to what do
2 we need include in the benefit-risk framework, I think
3 just something more formal and quantitative for
4 evaluation of patient-relevant evidence would be
5 helpful because we're systematically generating this
6 data now. But we're not always sure how it's being
7 included for decision-making.

8 Something I'd also like to suggest today is
9 considering including an overall assessment such as a
10 patient's willingness to continue treatment as part of
11 benefit-risk.

12 You know, these are things we could routinely
13 incorporate into real-world care or clinical trials in
14 a simple way to really understand, you know, at the
15 end, is it worth it because, you know, we've been
16 talking about a lot of really sophisticated statistical
17 and classical health economic methods. But sometimes
18 when I talk to patients, what they say to me is at the
19 end is it worth it for me. And so, it's something to
20 keep in mind.

21 I'd also like to reference two of the patient-
22 focused drug development meetings. I had the honor of

1 attending the breast cancer meeting in particular and
2 this is very similar to what we heard from patients.
3 You know, early breast cancer patients were much more
4 interested in the impacts and the tolerability of a
5 treatment because they didn't have disease symptoms and
6 were looking at a cure rate.

7 And so, I do think there's a lot of
8 opportunity there to understand the continuum of risk-
9 benefit. And maybe in the future it will end up being
10 a disease-specific or therapeutic area-specific
11 framework.

12 And this slide should be familiar to folks.
13 But I thought it was an important one to include today
14 because when we talk about operationalizing patient-
15 focused drug development, which I think, you know, I'd
16 really like to congratulate the agency.

17 As an outcomes researcher for over 11 years,
18 the way folks talk about the patient perspective now
19 than before patient-focused drug development four years
20 ago is huge. The patient's really at the center now
21 and I really think the awareness that this initiative
22 raised helped.

1 I do think we're doing a great job on the data
2 gathering and patient-reported outcomes. But the piece
3 that's still a question is on the right. The
4 quantifying benefit-risks. And I think until we have
5 further information about how exactly that's done, as
6 sponsors and researchers, we're not going to be sure
7 how to be generating the right data for decision-
8 making.

9 And so, I think as we look forward to the
10 PDUFA VI commitment, further information on exactly the
11 type of patient-relevant data and what might be most
12 useful for decision-making I think will be really
13 helpful.

14 I also think, to reference the really
15 wonderful presentation before me, I think we need to
16 talk to patients about this because they might have a
17 really different benefit-risk than we think. And I
18 think their input's essential in the review and
19 approval process and even in the risk-benefit process.

20 And so, considering how we better obtain data
21 to include their voice, not just about their experience
22 but from a preference perspective, as both my prior

1 presentees shared, I think is important.

2 So you know, this is something I think about a
3 lot, is, is it time for a separate patient label. And
4 I thought this might be a good place to bring it up
5 because all the data we've been talking about is pretty
6 descriptive, right?

7 It's descriptive. It's analytic. It's large.
8 We kind of have a space problem. And so, to kind of
9 illustrate that, I thought I'd show you a couple
10 examples of some patient-relevant evidence because I
11 just like to show data.

12 So here's an example of the patient-reported
13 version of the common toxicity criteria for adverse
14 events. I realize that's a really long acronym. And
15 this is really the patients' experience of side
16 effects. And this is just a dataset that
17 hypothetically showed bar charts, because we know
18 patients like bar charts.

19 They don't like hazard ratios. Those aren't
20 intuitive. And it just shows bar charts that talk
21 about frequency and percent. And this is just for one
22 symptom. So if we had 20 symptoms and you're thinking

1 about the size of a U.S. PI, you can imagine we'd run
2 out of space pretty quickly.

3 This is some data that Dr. Amylou Dueck, from
4 the Mayo Clinic, who is also a developer of the PRO-
5 CTCAE recently published and here it shows the patient-
6 reported experience of tolerability next to the CTC
7 adverse event item, which I also liked.

8 But as you can see, this is just the maximum
9 score. And we've already pretty much filled up a slide
10 with three symptoms. And if you reflect back to the
11 second slide I showed, you know, sometimes we might
12 have 20 to 30 symptoms.

13 And then, here's an example of the patient
14 preference data from the Rommel paper that was
15 referenced and these were also presented at the
16 advisory committee of patients' preference for
17 preferring subcutaneous to IV administration.

18 And again, it's at two different time points.
19 It's done in a bar chart. It has descriptive
20 information. It's a patient friendly way of presenting
21 data.

22 But as you can see, systematic inclusion of

1 the patient voice in the large amount of information we
2 have creates a vast amount of data. And really, you
3 need to present it at the item concept level because if
4 I'm a patient who really cares about those side effects
5 of interest, we do need to get into that level of
6 detail.

7 And so, you know, the expectation I often here
8 is that patients could download the manuscript. Well,
9 there's a cost associated with downloading a
10 manuscript. There's health literacy and understanding
11 how to search PubMed. And also just the way we present
12 data.

13 I really like hazard ratios too. But when we
14 talk to patients, they tend to tell us it's not
15 intuitive to them. And so, really thinking about
16 actively finding out how patients like to see
17 information and we've been doing work in that area and
18 the types of descriptive data I showed you previously
19 is really what they prefer.

20 And so, it's just something to think about
21 because we do need to have a better way as we collect
22 more patient-focused data, as we will continue to from

1 a policy perspective, to communicate this to patients
2 in a way they understand and not expect them, when they
3 have a lot going on in their lives and a short amount
4 of time to choose your treatment, whether it's after
5 cancer or for psoriasis, to have the health literacy
6 ability to really find and interpret a fairly academic
7 manuscript.

8 And so, I think also with 21st Century Cures,
9 we're only going to be seeing more information. And
10 so, the data I showed you at the end on rituximab was
11 actually included in the tradename Hycela label in a
12 verbal descriptive format rather than in a bar chart
13 format.

14 But it's just something to think about as we
15 continue to collect this data. I think there needs to
16 be careful consideration not only about how it's
17 incorporated into the framework but also how we're
18 communicating it to patients because, in the end,
19 they're also making an individual risk-benefit
20 assessment about the best treatment choice for
21 themselves and their family.

22 So in summary, you know, from my perspective,

1 I think patient-focused drug development was hugely
2 successful at demonstrating the value of the patient
3 perspective for drug developers and drug reviews. It
4 was a real privilege to be part of some of those
5 meetings.

6 I think it's important for future frameworks
7 to really think about the fact that benefit-risk might
8 be -- there's some overlap. A more specific framework
9 would be very helpful for sponsors to ensure that we're
10 generating the patient-relevant evidence you need for
11 decisions.

12 And I think as we look forward, I know Dr.
13 Mullin referenced the four PDUFA VI patient-centricity
14 guidances. I think it'll be really interesting to see
15 what synergies are there between advancing this work
16 and that work in tandem and as well as the expanded use
17 of patient preference methods such as, you know, time
18 tradeoff, standard gamble, patient preference studies,
19 again, a variety of the health economic elicitation
20 methods that were referenced I think will be really key
21 to success.

22 But in closing, I think it's a really exciting

1 time for patients because I think they're really at the
2 forefront and I think we're really close to being able
3 to have really important information communicated to
4 them in a way that they can understand to make better
5 decisions. Thank you.

6 (Applause.)

7 PANEL DISCUSSION AND Q&A

8 MS. VAIDYA: Thank you, Brett, Leah and
9 Alicyn. So that wraps up our presentations for this
10 session and now I'll open it up to the audience to
11 please come to the mic if you have any questions for
12 our panelists today. Don't be shy.

13 Okay. So as you get your thoughts together, I
14 will ask a -- I will ask a question to our panelists.
15 So we've talked a lot about, you know, looking back at
16 the past five years, what we've done so far.

17 Looking ahead though, you all briefly touched
18 upon this, but what are the greatest opportunities you
19 see in incorporating patient experiences into drug
20 development and decision-making for the next two to
21 three years or so? And I'll open it up to the panel.
22 Anyone can take this question. Theresa?

1 DR. MULLIN: Well, I don't want to leave that
2 question hanging, I guess. I felt before this meeting
3 that we already had a lot of work ahead of us and I
4 feel like people have been very generous with their
5 ideas and opportunities and have come up with even more
6 ideas.

7 I think that, you know, to the point Alicyn
8 was just making, I mean -- and thank you to everyone
9 for their very thoughtful comments too. I mean, I
10 think if anything, it just really has kind of created -
11 - I mean it -- more things that we need to be thinking
12 about.

13 The first opportunity I guess out of the box
14 for us, well, it's a couple-fold. But in terms of
15 externally facing, I mean, we are hard at work trying
16 to take -- yes, there is a lot of established
17 information out there. But we're trying to really turn
18 it into usable, applicable material to indeed start
19 with what I think Brett said is the first question of
20 what matters.

21 I mean, what matters to people? We do really
22 want to make sure we don't skip that one because we're

1 not -- we learned a lot. One thing we learned in those
2 meetings is that we didn't go in there necessarily --
3 sometimes we sort of had an idea and other times we
4 really learned a lot about what was most important to
5 patients.

6 So we can't assume we already know that or
7 that we have the full range of the cross-section of
8 that opinion.

9 So we're really going to have our first public
10 meeting related -- it's a workshop related to that
11 first guidance which is going to cover quite a bit,
12 including -- Tarek, we're trying to cover terminology
13 and see what we can do to wrestle down terminology and
14 also that first set of questions about the early
15 qualitative research to try to hone in better on what's
16 most important in terms of the burden of the disease
17 and the burden of treatment, which I think is a bit of
18 what Alicyn was getting to.

19 We're calling it burden of treatment but we're
20 saying that you've got to always consider both in order
21 to see if it's really tolerable to use a treatment
22 that's been developed. So that's our first

1 opportunity. And I think the other -- so the internal
2 piece which is very challenging I think for us is that
3 this is really a different way of working and it does
4 require -- some people have mentioned a culture, I
5 think.

6 And for a large organization of scientists and
7 people who want to do the right thing and be very
8 careful and be consistent, we want our regulatory
9 decisions to be consistent.

10 We say that decisions are like our case law
11 and we need to be consistent with past decisions. We
12 have to look at the precedent for any of our decisions.
13 We're really looking at I just would say something like
14 trying to turn the ocean liner because we have -- we
15 need to be consistent with the past. And yet, we're
16 trying to get people to adopt new ways of working and
17 being innovative and doing all these things that really
18 maybe feel a little bit at odds with being consistent
19 with the past.

20 So I think that will be a big challenge for us
21 internally to do it well. And again, I'll go to
22 Brett's point about being sure that when we put all of

1 these methods in front of people, that we don't sink
2 this by having somebody start using the wrong methods
3 at the wrong time and then this gets a bad taste --
4 people get a bad taste from it and then you don't want
5 to do it anymore. So we're really conscious of trying
6 to have people appropriately use new methods and so
7 that we're building on successes and trying to minimize
8 how much we're learning from mistakes.

9 MS. VAIDYA: Thank you, Theresa. Yes, Brett?

10 MR. HAUBER: I think there's a lot that can be
11 done in the short-term. But I guess the way that I
12 view it, there's lots of areas where work can be done.
13 I think from my perspective, my personal perspective
14 alone, the more I learn about PFDD and the FDA
15 initiatives, I just have so much more respect for the
16 people who have to steer that very large ocean liner in
17 a different direction.

18 And I think that's a long-term proposition and
19 would rely on the experts with the institutional
20 knowledge to tell us how best to do that. But I think
21 we also have other opportunities within early phase
22 drug development, in real-world data and maybe a narrow

1 window to incorporate patient perspectives in products
2 that are already in phase three. And I think all of
3 those things need work.

4 And a number of -- I've been doing this a
5 little longer than 11 years. That doesn't make me
6 smarter. It just makes me older. So but I remember a
7 time when everyone was really risk-averse. And I think
8 that's changing now. And I think there are
9 opportunities for people to explore some of these
10 tougher questions at all of those phases.

11 And I think there's been a sea change not only
12 within FDA but also within industry and in academia to
13 say, hey, let's look at ways to do this. So I think
14 there are lots of opportunities across the spectrum.
15 Some of them are going to bear fruit pretty quickly and
16 others are just going to take time.

17 So I think the short-term perspective might
18 not be the right perspective. Maybe that's my point.
19 I think it's a long road and we all need to work to go
20 along that road.

21 MS. VAIDYA: Great. Thank you. Anyone else?
22 Okay. Yes, go ahead, Telba?

1 DR. IRONY: Just something to add, I think.
2 Added opportunities that we have and maybe things that
3 we can do within the FDA is more like educating our
4 reviewers.

5 It's very important to educate them and
6 explain what can be done, what cannot be done, why is
7 it useful, when is it important and building capacity
8 within the FDA to be able to, you know, review the
9 studies, learn how to use them and see the utility of
10 them within the regulatory process.

11 And finally, you mentioned about the labeling
12 and communicating the risks, the benefits and making
13 sure that the patients, the people that are going to
14 use the treatments understand the risks, understand the
15 benefits and perhaps will have shared decision-making
16 tools with their own physicians to be able to make
17 decisions, particularly when it's a close call, when
18 the decisions are very difficult because the benefits
19 might not -- might be perhaps not total.

20 You know, maybe only a subgroup of patients
21 would experience the benefit. There will be risks.
22 But there is an unmet medical need. So how do you make

1 these kind of decisions? How do you communicate the
2 uncertainty? Sometimes the benefit -- there was a
3 discussion this morning. A subgroup of patients might
4 experience the benefit but not all of them. We don't
5 know who these patients are.

6 So the benefit is not a total benefit. It's
7 the benefit of having a chance of having the benefit.
8 So how do you communicate that to a patient? Meaning
9 they will incur risks for a chance of experience the
10 benefit. This is a very hard concept to communicate.
11 So we probably have to together understand how to do it
12 and learn how to do it.

13 MS. VAIDYA: Great point. Thank you, Telba.
14 Could you take --

15 UNIDENTIFIED AUDIENCE MEMBER: So I should
16 start off by saying that I spent the entire session
17 formulating my question, which was answered in your
18 last slide. So I'm going to reformulate my question
19 because I think this is of maybe more interest to me.

20 So there's people -- there's politics out here
21 in this city as well as regulation. And I'm sure
22 you're aware of the people who say, you know, FDA

1 should not be so much worried about whether something
2 works. But if it's safe, you should give people a
3 chance.

4 So having worked at FDA many years ago, I'm
5 inherently skeptical to that notion. But as I heard
6 talk today about subsets and how some subpopulations
7 have effect that may not be reflected in the
8 population, I think, well, maybe that makes some more
9 sense to me.

10 So I guess my question is do you see this as a
11 potential opening to use these patient preferences and
12 PRO and quality of life and all of that? I mean, I'd
13 like to think of a day when, you know, an indication
14 could be driven by some of these -- maybe not driven,
15 but at least much more highly supported than just based
16 on your population needs. Is there a chance?

17 And it also goes back to that slide I saw at
18 the beginning about how to predict your future by
19 making it. I don't know how to make this. So you guys
20 have to help me to understand. Okay?

21 DR. MULLIN: Well, I'll just say I think one
22 of the reasons we're going to spend a bunch of time on

1 these guidances to make sure that we have rigorous
2 enough methods so that we are not concerned about
3 people's desperate patients being manipulated and, you
4 know, willing to try anything and so on.

5 I think that the work Telba described, for
6 example, is at the disease level. It's not about a
7 particular product. I think that this work will be
8 better supported if we don't get into the potential
9 conflicts that would almost be inevitable if a product
10 sponsor were doing it at the product level.

11 But if you can work at the disease level and
12 the people with that disease and the tradeoffs they
13 would be willing to make, kind of absent a particular -
14 - maybe you're taking the characteristics, the
15 operating performance characteristics you would expect
16 might be typical in that class.

17 But you know, you're not getting in there.
18 And all of the time we're spending on trying to make
19 sure that we give rigorous enough methodology to go
20 from what people report in a very open, qualitative
21 way, but a very compelling way to something that
22 actually can be reliably measured and consistently

1 measured and thus used in clinical trials. We're very
2 concerned about the same things.

3 So we want to develop these methods, not make
4 the perfect the enemy of the good and so that it's --
5 we think that they're reliable. Our reviewers will
6 consider them to be reliable methods that have been
7 used and so we can go forward and feel pretty confident
8 about the quality of the evidence. And that's exactly
9 where we want to be.

10 MS. VAIDYA: Thank you, Theresa. Yeah, Sara?

11 DR. EGGERS: Yeah. I have a question for
12 Leah. Sara Eggers, from FDA. I'm part of the team
13 that does the patient-focused drug development
14 meetings. And before the question, a thank-you to your
15 group and others because when we are preparing for our
16 PFDD meetings, we rely heavily on the outreach and the
17 capacity that patient groups have to do that.

18 Maybe my colleagues have seen your rubric,
19 your stratification rubric. I hadn't seen it. Did you
20 do that -- so you -- if I understand correctly, you
21 stratified and said there are particular
22 characteristics of patients and was it that you wanted

1 to make sure that you had reached out so that they knew
2 about our meeting? Can you explain a little bit more
3 about that and what you did with it?

4 MS. HOWARD: Sure. Sure. Yeah. So I'm happy
5 to. So, you know, over the course of the NPF's
6 history, we've spent a lot of time talking to our
7 community and, you know, to the conversation here.

8 What we've heard is different things from
9 different subsets of our community about what they're
10 looking for when it comes to treatment, what risk
11 they're willing to tolerate, what their expectations
12 and hopes are. And so, one of the things that we
13 really wanted to do to assist you with hearing about
14 all those same things that we had heard about was
15 ensure that we had identified kind of the various
16 subpopulations of our community.

17 So we know, for example, that folks that live
18 in rural areas face different access challenges than
19 those in urban areas. Folks that work have different
20 demands on their time than people who are at home. And
21 so, that limits or not their ability to pursue
22 different treatments and kind of on down the line. And

1 so, one of the things that we did was sat down and
2 said, okay, across our community, who are those
3 different populations that have different needs and
4 different expectations. A pregnant woman is going to
5 have different options than, you know, a health male in
6 the middle of their life.

7 So what we did was literally wrote out kind of
8 who all those different voices were and then spent time
9 reaching out to those different subsets of our
10 community. We did that through our own networks. My
11 colleagues that are on the ground across the country
12 talked to different people in these different
13 populations and encouraged them to participate in the
14 meeting in whatever capacity they were available.

15 We also did that through different other
16 organizations. So for example, the dermatologists that
17 serve pediatrics have their own group. So we
18 specifically contacted those folks and said, you know,
19 here's this opportunity for you or your patients to
20 share their perspectives. And then, you know, we used
21 social media and kind of other outreach opportunities
22 to remind those folks that this opportunity existed for

1 them to come and share their perspectives.

2 You know, I think ultimately, as you saw at
3 the meeting, we had a lot of different voices, which
4 was our main goal. And we didn't want, you know, a
5 hundred patients with severe disease who were all
6 looking for, you know, the next something.

7 We really did want the agency to be able to
8 hear from people with mild disease who were just trying
9 to address, you know, this particular symptom, you
10 know, on down the line. And so, being able to
11 acknowledge that our community isn't always after the
12 same thing was really important for us and we wanted to
13 use that grid to do it.

14 DR. EGGERS: Well, that's commendable because
15 it is -- when we have a public meeting here in White
16 Oak, we know -- we know that that means the docket is
17 very important because not everyone can come to White
18 Oak to be at the meeting.

19 MS. HOWARD: Right.

20 DR. EGGERS: So thank you for that.

21 MS. HOWARD: Sure.

22 DR. EGGERS: My final question is then you

1 also encouraged people to submit to the docket. And
2 I'm going to assume it's the people that are harder to
3 reach. I mean, if you -- if the same factors make it
4 difficult for you to access one treatment, it probably
5 makes it difficult for you to access FDA to give your
6 voice.

7 Did you find in your outreach to people on the
8 dockets to write in, were they different? Did they
9 differ in characteristics that you're aware of?

10 MS. HOWARD: Yeah. So we spent a lot of time
11 looking at what went into the docket. I would say they
12 were a little bit different. One strategy that we had
13 was to promote the docket before and after the meeting
14 differently.

15 So prior to the meeting, we promoted it just
16 as one other way people could participate and share
17 their voice with the FDA. So you had, you know, attend
18 in person, attend via webinar, comment to the docket.
19 Once the meeting took place, we had a much better sense
20 of, again, looking at our community, what we hear from
21 our community that was shared and what wasn't shared.

22 And so, we specifically went out after the

1 meeting and said, you know, here are some of the things
2 that we've heard from you, you know, over our history
3 that didn't come up at the meeting. If you care about
4 these things, write in.

5 And so, we did a little bit of targeted
6 promotion of the docket post-meeting to ensure that
7 those comments did make their way to you. But I think
8 you saw more of kind of, as you said, those issues of
9 the role -- the smaller populations and the particular
10 symptoms that didn't come up because they're often, you
11 know, more painful to discuss in a public setting.

12 MS. VAIDYA: Thank you. Yes?

13 DR. HAMMAD: Tarek Hamed, with EMD Serono.
14 My question is for Theresa. I don't mean to put you on
15 the spot or anything. But I really liked your response
16 when you said that you are looking for methodology,
17 you're sure it's working, not really giving us any
18 false hopes.

19 But I can see in CBER and CDRH specific
20 initiatives to increase interim capacity of the
21 reviewers to be able to review such methodology. Are
22 there any specific plans within CDER to build up the

1 same kind of internal capacity?

2 DR. MULLIN: Yes, there are. One of the
3 things that we're trying to do, it's sort of twofold.
4 First, and I don't know if -- maybe you haven't been at
5 the other meetings where I've said this, Tarek.

6 But we have -- literally for the size of CDER,
7 I mean, our capacity right now in terms of specialty
8 staff is not much bigger than it is in CBER or CDRH.
9 So we have, you know, like three -- I would say three
10 or four people who do this in the Office of
11 Biostatistics and probably about a handful of people
12 who are expert methodologists in Office of New Drugs,
13 the COA team right now. They have project managers.

14 But, so we have very limited capacity which we
15 need to build. These are the same people who are
16 writing these guidances, working on the guidance
17 documents and fielding everything that comes in, all
18 the submissions.

19 So we need to obviously increase that capacity
20 a bit. And we have plans to do that additional hiring,
21 assuming we can find people. There's not enough people
22 being trained in these areas in academia right now.

1 And the second thing is to try to get to some training
2 for people. But given that these guidances have
3 timeframes that are like now, we have to -- and some of
4 these people, it's not their only day job is doing this
5 work, that we're ordering things.

6 So it's not happening as fast as one would
7 like if we had the capacity to go at everything at
8 once. But yes, definitely it makes a whole lot of
9 sense both to just have the experts have more experts
10 and have people know these methods are important and
11 how to use it, but then also have people know enough to
12 know, oh, this is something we need to do here and I
13 need to call some experts. I need to get some consults
14 in here to help me with this as I do it.

15 So they know enough to know what they don't
16 know. And also what they can tap into. And so, we're
17 planning that over the next few years. But it's just
18 not all -- I mean, we wish it would all happen a lot
19 faster. But it just takes a little time.

20 DR. HAMMAD: Absolutely. But is the long-term
21 vision to build up an internal consultancy or to have
22 like some kind of review division or some -- is there

1 like any vision?

2 DR. MULLIN: Both. We're looking to in the
3 Office of New Drugs to have one probably clinician
4 expert in each of the divisions at least who kind of
5 specializes in understanding and the use of these
6 methods. Right now, an example -- I would say Paul
7 Kluetz is a good example of somebody who does this for
8 the oncology folks.

9 But there's a coupling of a person like that
10 with the specialty sort of COA group within the new
11 drugs and then bio stats is also building up its
12 capabilities in this area as well. So we'll have a
13 combination of people who are like within review
14 divisions and also some people with greater expertise
15 who can be working with them.

16 DR. HAMMAD: That's great to hear, because, as
17 I said in my talk, without this from the agency point
18 of view, I mean, this field will not go anywhere. So
19 you are the starting point. I'm very happy to hear
20 that. Thank you.

21 DR. MULLIN: No, I mean, just that's the other
22 point about it. There's no point in building more

1 repositories if we don't get everybody to understand
2 and start using these methods in the right way. So we
3 have to do it all together.

4 MS. VAIDYA: Thanks, Tarek.

5 DR. CRAIG: So, Benjamin Craig, from the
6 International Academy of Health Preference Research. I
7 really would like to see an event like Leah held but
8 for health preference research as in to actually bring
9 all the methodologists together to talk about the
10 diversity of methods.

11 I mean, we have a large community of
12 individuals with diversity among us in terms of our
13 different impressions for the collection and the
14 measurement of these evidence and we have different
15 interpretations. The methods, while they seem rigorous
16 right now, it scares me to death.

17 I mean, all you need to have is one well-
18 meaning firm to hire one well-meaning consultancy to
19 motivate one well-meaning decision and then we realize
20 later on, oh my gosh, we made a mistake because the
21 methods weren't quite up to snuff. And when I hear
22 among the academicians and the debates we're having

1 about how to do this, it's scary.

2 And so, we're so excited that you guys are
3 doing this. But at the same time, we're really worried
4 that this will be our death, that this will actually
5 fall upon its face. We look at the PRO folks and it's
6 like, oh, you guys are lucky now. You've already went
7 through this process. But hopefully health preference
8 research will get there also.

9 DR. MULLIN: All right. Thank you. We deal
10 with life-and-death decisions all the time. I'm happy
11 we're not dealing with that one.

12 MS. VAIDYA: Anymore questions from the
13 audience? Okay, then. Well, with that, we'll wrap up
14 this session. We had a great discussion and it is
15 great to see that we've come so far in the past five
16 years, thinking about PDUFA V. But there's a lot of
17 work ahead of us, as we've heard from everyone here.
18 So, a round of applause for our speakers.

19 (Applause.)

20 MS. VAIDYA: We will now be moving on to our
21 break. We'll have a 15-minute break right now. It's
22 almost -- let's say it's 2:55. So if we can reconvene

1 in 15 minutes at -- wait, yeah 3:10, sorry, 3:10,
2 that'd be great. Thank you so much.

3 (Whereupon, the foregoing went off the record
4 at 2:54 p.m., and went back on the record at
5 3:13 p.m.)

6 SESSION 3: SPECIAL TOPICS IN BENEFIT-RISK ASSESSMENT

7 DR. EGGERS: -- throughout the day really
8 we've alluded to and touched upon, we're calling it the
9 special topics in benefit-risk assessment and it's
10 really just addressing some things that are important
11 to address, especially as we move into future phases.

12 We have three presenters and then we have a
13 panel discussion with a couple folks who will kick off
14 the panel discussion for us. So our three presenters
15 are Baruch Fischhoff, Richard Forshee and then Lisa
16 Schwartz and Steven Woloshin, who will be addressing
17 three more methodological presentations. So without
18 further ado, I will let Baruch start.

19 ADVANCING DECISION SCIENCE METHODS FOR REGULATORY USE

20 DR. FISCHHOFF: Thank you. So I'm really
21 pleased to be here. I had the privilege to be -- to
22 chair EPA's -- FDA's risk communication advisory

1 committee for its first few years and then -- which I
2 think gave me enough background into the complexities
3 of the agency to have some value and having the
4 privilege to work in some of the earlier stages of the
5 benefit-risk framework.

6 And one of the things that I took away, and
7 which I attribute to Bob Temple, is the idea that
8 analysis ought to be an aid rather than a replacement
9 to judgment. And if one thinks about this, one has --
10 there's judgment all the way through. You have
11 judgment in the beliefs and eliciting from experts what
12 they understand about the evidence and the residual
13 uncertainties, from your non-experts, what they
14 perceive the risks -- benefits and risk to be of the
15 different products and how well they've understood what
16 you've told them after you've communicated.

17 You have values in terms of the priorities,
18 which problems should you be worrying about and in
19 terms of the tradeoffs that you should be doing --
20 looking at. And if you think about the benefit-risk
21 framework, it's all about judgments. That is, each of
22 the cells has places for quantitative information to

1 the extent that it exists. But that quantitative
2 information is always qualified by some kinds of -- by
3 judgments about the quality of the evidence and about
4 information that's not readily quantified.

5 So if you were going to submit judgments to a
6 scientific journal, you would value the -- you would
7 look at the quality of your judgments in terms of the
8 standard psychometric properties. Are they reliable?
9 Are they appropriately reliable across time, across
10 judges, across methods? Sometimes they should be and
11 sometimes they're not -- they shouldn't be.

12 You look at least at these three kinds of
13 validity. Face validity, that should be socially
14 acceptable. Is this an appropriate way to ask a
15 question? Coherence, is there internal consistency
16 across different ways of asking the question or
17 different related questions? And then, is there what
18 we call construct validity in psychology. Are there
19 theoretically positive correlations between the
20 judgments that people give you and other things that
21 you know about their life circumstances and behavior?

22 If you have unsound judgments, if you ask

1 people questions that they can't answer, you can go
2 wrong in three different ways. One is you can obscure
3 value-laden assumptions in the judgments that you're
4 presenting as representing people. Second, you can
5 frustrate people who are trying to give you orderly
6 responses, but your task isn't suited to the way that
7 they customarily think. And third, you can
8 misrepresent them by claiming to have captured their
9 beliefs or values in ways that have not.

10 So here's one example of obscuring value-laden
11 assumptions. For many years, I worked on stated
12 preference methods in environmental elicitation.
13 There's a process -- there's a procedure called
14 contingent valuation. It was in one of Claude's boxes
15 as CV.

16 If I was doing a contingent valuation study, I
17 might show you two pictures of the Grand Canyon, one
18 with some haze and one without. And I would -- I might
19 ask you how much would you pay in additional gasoline
20 taxes in order to have 80 days with haze rather than
21 120 days with haze. And those would be numbers that
22 are required for cost-benefit analyses that require you

1 to monetize the environment for it to have any
2 standing.

3 So one of the things that you find in
4 contingent valuation studies is what are called protest
5 responses. So here's this paper that I thought had a
6 nice summary of protest responses. There are well-
7 documented challenges to the implementation of
8 contingent valuation, including strategic responses,
9 anchoring or framing effects or refusal to engage with
10 a request to state a willingness to pay value or
11 accept/reject a given value, protesting.

12 This paper focuses on the specific issue of
13 protesting. Respondents commonly refuse to state a WTP
14 value or to indicate their acceptance of a given value
15 in CV surveys. This may be because they place zero
16 value on the commodity. Alternatively, respondents may
17 object to the principle of placing a monetary value on
18 the commodity or they may feel strongly that the
19 responsibility for provision falls on another actor
20 such as the government.

21 And this review -- this is a large industry
22 doing these studies. This review had -- a remarkable

1 review of about five or six years ago, had I think 360
2 studies, enough that they could characterize what was
3 the protest response rate in different kinds of
4 studies.

5 So DC, if dichotomous choice format is used,
6 and there's several of them, 43 percent of the
7 responses are protest responses. If it's open-ended,
8 then you get a different rate. So you would see, so
9 somehow or another, they report numbers.

10 Remarkably, this study was -- the previous
11 study was about how to impute values to people saying
12 what they would have answered had they been willing to
13 answer your question. So you get an answer from a CV
14 study and this is in the background, how would you know
15 if you didn't -- if you hadn't read the study.

16 We've had quite a bit of discussion about how
17 to deal with heterogeneous health preferences. So my
18 colleagues and I have a paper just coming out on
19 medical decision-making looking at some of the ethical
20 assumptions made in the analytical conventions for
21 dealing with heterogeneous preferences, primarily in
22 the cost-effectiveness analysis literature.

1 So if you've got to produce a number, you've
2 got to make some assumptions. If you haven't shared
3 the ethical underpinnings of those assumptions, then
4 the consumers of your analyses don't know what you've
5 done. This question of ethical things based -- ethical
6 assumptions based -- is something that's troubled me
7 for a long time. If you'd like to read more, I had
8 this piece in Science a couple of years ago.

9 Second thing, you can frustrate orderly
10 responses. You've got a question that people would
11 like to answer. They have no objection to answer. But
12 they can't translate themselves into your terms. So
13 there was this lovely review of exclusion criteria in
14 national health, state valuation studies.

15 This group came out about a year ago, managed
16 to find about 75 studies in which there was enough
17 detail on the bases in which noisy responses were
18 excluded that they could characterize the criteria.

19 So the kind of criteria that might be used in
20 preference studies to throw out -- to exclude data that
21 are considered inappropriate, it would be if all health
22 states were valued the same. That doesn't look right.

1 Fewer than -- more than x logical inconsistencies where
2 x varies across studies. Incomplete or missing data.
3 People who value being dead is worse than all or
4 several health states and so on.

5 So if you're the consumer of the results that
6 come out of a study like this and the study is
7 presented as being representative of some particular
8 population, it would be appropriate to ask whether they
9 have excluded particular groups of the population,
10 either by their demographics, say their literacy or
11 their numeracy, or by view of their preferences, that
12 they're trying to sell you something that the
13 elicitation method doesn't allow you to do.

14 In this, here's a figure from this review that
15 shows the percentage of people who are excluded with
16 different elicitation procedures, SG is standard gamble
17 for those familiar with this, TTO is time tradeoff
18 method and VAS, visual analog scale.

19 So you can see some methods end up excluding
20 more people than others. Is that because they are
21 easier questions to answer because the researchers have
22 better hands and being able to pose their questions in

1 ways that people find comprehensible or they're just
2 more lenient in terms of the responses that they'll
3 include?

4 Third possibility is you can misrepresent
5 respondents. There's a figure from a paper long ago by
6 Betsy Martin and Charles Martin who discovered there
7 were studies asking people, representative sample of
8 American women, asking them what was the probability
9 that they were going to have a child in the next five
10 years over on the right or in all future years on the
11 left.

12 So they're the same answers. So had you -- so
13 somehow or another, you're asking, you're giving a time
14 period -- you as the researcher are giving a time
15 period that is not registering for people. And if you
16 reported either one -- one of the two or probably both
17 misrepresent people if you assume -- the respondents,
18 if you assume they're literally answering -- they're
19 answering the literal question that you asked.

20 There's something else from our own work.
21 This is a representative sample of American 15- and 16-
22 year-olds in the national longitudinal study of youth

1 97 were asked kids a bunch of things that gave us very
2 good probabilities on being in school, on all sorts of
3 different things. We also asked them what was the
4 probability you were going to die in the next year.

5 And most of us -- them gave us very low
6 probabilities, as would be appropriate. But there was
7 a blip at 50 percent. So people have found this. You
8 can find this buried in many different studies, studies
9 of the probability of getting sick from -- of getting
10 lung cancer from smoking and other places.

11 It turns out that Americans, when they don't
12 know how to answer or don't want to tell you will say
13 50/50 -- will say 50 in the sense of 50/50 rather than
14 50 percent. So if you took -- so they're not saying
15 zero. But they're probably not saying 50 percent.

16 If you took those answers literally, didn't
17 know the elicitation literature, folded them into your
18 group mean or median, then you would have -- be guilty
19 of some kind of essentially methodological malpractice
20 and misrepresenting people by not recognizing the
21 limits to your own methodology.

22 So if we want to ask people -- ask questions

1 that people can answer, the recommendations would be,
2 first of all, consult the elicitation literature
3 broadly. It takes -- one can copy questions that
4 somebody else has used. That doesn't put you in a
5 position to have gone through the apprenticeship needed
6 to ask these questions.

7 Well, second, you need to involve respondents
8 in the development of the questions, which we heard
9 from many people over the -- particularly in the
10 preceding panel. And you need to evaluate your
11 research as critically and report its results candidly.
12 You need to do this just as well with judgment studies
13 as you do with -- as you do with medical studies.

14 So here's a source if people are interested in
15 this for consulting literature. The consulting
16 literature broadly with regard to eliciting beliefs.
17 There's a really nice piece by Granger Morgan, one of
18 our colleagues on expert elicitation, if you want to
19 get judgments from experts about uncertainties in the
20 data. This would be a good place to start.

21 Here's a place I like. It's my paper on how
22 to elicit people's values. This is my parting shot. I

1 kind of gave up on the contingent valuation wars. But
2 I tried to summarize what are the different
3 methodological traditions, one of which is embraced by
4 the contingent valuation people and the other of which
5 is ignored. And both have something to say when you're
6 trying to get people to think about unfamiliar topics.

7 Second thing is you have to involve
8 respondents in the development. Knowing all the
9 principles, knowing all the researchers, no substitute
10 for talking to people. Again, as we heard in the
11 previous session. So I don't think you can do better
12 than the Voice of the Patient initiative for listening
13 to people, the other ones that responded to it.

14 I think that we -- the development process
15 that I was part of and that the staff here has
16 continued has -- this is -- you could think of the
17 benefit-risk framework as a judgment elicitation
18 process which deeply involved the FDA staff and some of
19 its stakeholders and I think resulted in the robustness
20 that was reported here as a reflection of the care of
21 the work that people here did.

22 And when I think about -- I present this at a

1 lot of talks -- is that you can think about what are
2 the basic design principles that are embedded in the
3 benefit-risk framework reflect both analysis -- both
4 analysis and behavioral research.

5 So it recognizes that scientific policy
6 judgments are in all analyses so that people don't
7 confuse the two, neither the producers nor the
8 consumers. It quantifies the quantifiable without
9 ignoring other concerns. It highlights ethical and
10 political tradeoffs rather than burying them in some
11 metric where it would be very difficult to ferret out.

12 And then, it supports risk management by
13 suggesting the place where you might be able to --
14 things you might do to make a product acceptable when
15 it wasn't previously. Or you might be able to make an
16 acceptable product even more attractive.

17 I ended up, this is a recent National Academy
18 of Medicine report on pain management and the opioid
19 epidemic. I was asked to be a reviewer of it and I was
20 -- it's been out for about two months now. And they
21 ended up advocating expanding the benefit-risk
22 framework to include public health concerns.

1 So if you think about the opioid epidemic, you
2 can think about what that might be. And that's sort of
3 an interesting challenge. We're thinking about things
4 that one might do. They had some legal scholars that
5 argued, rightly or wrongly, that it was within FDA's
6 mandate to be able to consider these things. Here
7 might be an interesting direction to go.

8 So you've done your studies and you want to
9 evaluate them critically, report them candidly. Here's
10 the standard performance properties if they don't
11 accompany a study that you get. Then you really as a
12 consumer don't know how to think about it.

13 Some people have better hands than others.
14 Some people will implicitly embody the values that FDA
15 wants or its stakeholders want. Some of them won't.
16 Some of them won't even be cognizant that their
17 analytical conventions embody values.

18 So I thought I'd end with two things in this
19 spirit. So one, here's one of our studies. So
20 recently published. So in 2015, we -- so when Ebola
21 sprung, FDA has a rapid response -- or rather NSF has a
22 rapid response capability. By the time they got

1 activated after Ebola, we got funds with some
2 colleagues who study posttraumatic stress to see what
3 people thought about the epidemic. We asked
4 representative sample of the public hard quantitative
5 questions of the source that could be in principle ne
6 validated by scientific judgments.

7 You will find a lot of people in my field,
8 judgment and decision-making, who say that people are
9 so innumerate that you can't give them numbers or
10 listen to numbers. And sort of testing the limits of
11 this, we asked people to estimate the basic
12 reproductive number, R_0 , which we translated if someone
13 gets Ebola in the U.S., how many people do you think
14 will catch it from them directly.

15 So you might guess what kind of numbers a
16 representative sample of Americans would give. And
17 then, here's our -- here's the numbers that we gave.
18 Most people, this was January 2015. Most of them
19 thought it was zero or one, or one or two.

20 It might have been a rough estimate of a
21 disease that's just gone on break but we didn't know
22 how -- we didn't know for how long. Some people gave

1 us much higher numbers. And you could think -- so this
2 was our disclosure. We showed how it correlated with
3 the judgments of the probability of transmission in
4 different situations. That was our effort to give
5 people a feel -- consumers a feeling for whether or not
6 you could trust these numbers.

7 And then finally, as several people have
8 mentioned, one of the things that FDA has been trying
9 to do is to figure out how to characterize uncertainty,
10 which is in the left-hand column of the benefit-risk
11 framework.

12 We had a workshop here in February and May of
13 2014. And Alex Davis and I had a proposal for how it
14 is that you might characterize uncertainty in a
15 systematic way that we thought might be analytically
16 and behaviorally realistic.

17 And what we said, and so this is a testable
18 hypothesis, which I put out as the sort of thing that
19 FDA may want to look at, that most people understand
20 confidence intervals in terms of what the variability
21 of the data is. You can just read it out of the
22 reports.

1 People at FDA are absolute experts in internal
2 validity and external validity of studies. Sorry, I
3 got misaligned on the transfer. And in the pedigree
4 and how good the underlying science is.

5 If I had signatory authority and I wanted to
6 make a decision, if you could report that in some
7 systematic, succinct way, that might give me in effect
8 a feeling for what the credible interval would be.

9 Nobody likes to give Bayesian credible
10 intervals summarizing all of the uncertainty. But you
11 could give people who are -- give people a systematic
12 feeling for how good the evidence is, whether it's the
13 signatory authority or somebody else. Okay. Thank
14 you.

15 (Appause.)

16 DR. EGGERS: Thanks a lot, Baruch. Now, we'll
17 have Richard Forshee.

18 POTENTIAL AREAS FOR QUANTITATIVE BENEFIT-RISK
19 APPROACHES

20 DR. FORSHEE: Good afternoon, everyone. My
21 name's Richard Forshee. I'm an associate director in
22 the Center for Biologics Evaluation and Research in our

1 Office of Biostatistics and Epidemiology. And I lead a
2 team called the analytics and benefit-risk assessment
3 team. We actually do a lot of work on looking at
4 quantitative benefit-risk assessments and I'll talk a
5 little bit about that as I go forward.

6 I do want to pick up just on the last slide
7 that Baruch had about credible intervals and just
8 mention some of the work that we've been doing in that
9 general area.

10 We have a program where we're trying to do
11 what we call quantitative bias analysis, which is to
12 try to take some of the other threats to the validity
13 of a study that go beyond simply the sampling issues
14 and use outside sources of data to get probability
15 distributions about how large those biases might be and
16 then quantify those in various ways. So that's not
17 exactly what you were talking about doing, but just
18 wanted to mention it's something that we've been
19 thinking about.

20 Okay. So I want to start with a little bit of
21 history. One of the really nice things about the White
22 Oak campus here is that there are a variety of

1 historical posters that are spread throughout the
2 campus. And I walk by this any time I'm going to the
3 main cafeteria that we have. And these are also
4 collected on Flickr. There's hundreds of historical
5 FDA pictures there that you can look at.

6 The point that I want to make about this is
7 that this was in 1964. And so, in 1964, people were
8 already thinking about all of the many different
9 sources of data and information that have to go into
10 any FDA decision about whether to approve or not a
11 given drug. So this is not something that's a new
12 problem for FDA. This is something that we've been
13 dealing with for at least 50-plus years.

14 This is also an old slide. This is from 1999.
15 And I'm not asking people to read the whole slide. But
16 this is talking about the system that we had in place
17 for managing the risks of medical products.

18 And the points that I want people to take from
19 this is even in this slide from the last century, 1999,
20 we're still talking about the importance of thinking
21 about benefit-risk assessment as a complex and
22 iterative process that involves many participants. I'm

1 sure this is fitting with some of the themes that we've
2 talked about during the rest of the meeting today. And
3 what I would add to this is that, in my opinion,
4 qualitative approaches are usually going to be
5 sufficient.

6 But one of the points I want to make in the
7 rest of my presentation is that I believe that
8 quantitative approaches can improve the quality of the
9 decision-making process in some cases.

10 The question is how do you figure out which of
11 those cases are and how do you make sure that you're
12 doing the quantitative approaches in a way that's
13 really helping to add to and support the complex
14 decision-making process that we engage in.

15 I want to talk a little bit about what we've
16 been doing in the Center for Biologics Evaluation and
17 Research in this area and the overarching point that I
18 want to make is that for more than 10 years now, FDA
19 CBER has been trying to build capacity within our
20 organization for doing more quantitative benefit-risk
21 assessment.

22 And as you heard from Telba's presentation

1 earlier, we're also working to build capacity in the
2 patient preference area as well. One of the ways we've
3 tried to build this capacity is by putting together a
4 team that's dedicated to building out some of these new
5 kinds of methods. We call it the analytics and
6 benefit-risk assessment team. I see some of my team
7 members are in the audience. We've got -- right now,
8 we've got 10 people and we've got a couple of positions
9 that we're trying to fill.

10 We don't only quantitative benefit-risk
11 assessment. We also do some development of methods for
12 post-market observational studies and we also do some
13 health informatics work as well. But we do have a team
14 in place to try and build out the capacities that we
15 have in this area. And we have actually done a number
16 of quantitative benefit-risk assessments.

17 Most of them have been in the area of blood
18 safety and availability. But we do have experience
19 both developing these, presenting them at advisory
20 committees and scientific meetings and several of those
21 have been published as well. Another thing that we're
22 involved in is we're both trying to build capacity by

1 having internal training as well as engaging externally
2 to try and build capacity more broadly for this kind of
3 quantitative benefit-risk assessment.

4 Internally, I just want to mention that we
5 have a series of three courses in CBER that we offer
6 every year. We have a risk assessment course that
7 focuses more on the technical side of putting together
8 quantitative risk assessments and benefit-risk
9 assessments.

10 We have a risk management course that looks at
11 the more complicated question of how you put all of the
12 information together, along with values, legal
13 constraints and other things that might affect the
14 decision. And we have a risk communication course that
15 we offer as well. And our medical officers are our
16 primary audience for these courses.

17 We've also done quite a bit of external work
18 to try and build capacity in this area. This is one
19 proceedings that we published from a workshop that we
20 held on quantitative risk assessment for emerging
21 infectious diseases in the blood supply.

22 And my colleague, John Scott, who's our acting

1 director of our Division of Biostatistics, participated
2 in the recently published book on benefit-risk
3 assessment methods and medical product development. So
4 the point here is that we're trying to expand our
5 capabilities to be ready for some of the needs that we
6 anticipate in the near future.

7 Patrick and others have already talked a lot
8 about this. This picture keeps coming up. It's a nice
9 picture. Thank you, Pujita, for loaning the camera for
10 that. I just want to mention that the key idea from
11 this ICH expert working group was that we want the
12 sponsors, when they're submitting their material, to
13 provide a succinct, integrated and clearly explained
14 benefit-risk assessment of the medicinal product for
15 its intended use.

16 I think this is a really nice summary of what
17 we were hoping to encourage with that guidance and it's
18 a key part of what we wanted to do. Another thing that
19 I want to highlight from the new ICH is that one of the
20 things that we specifically say in that ICH guidance is
21 that while a descriptive approach is generally going to
22 be adequate, we also create the -- we also open the

1 door for more quantitative approaches.

2 And so, as part of that guidance, we
3 specifically said that applicants may choose to use
4 methods that quantitatively express the underlying
5 judgments on uncertainties and the assessment and
6 analyses that compare and/or weigh benefits and risks
7 using the submitted evidence may be presented and we
8 even pointed them to exactly where we'd want to see
9 that in the guidance.

10 So up to this point, what I'm trying to say is
11 that certainly in FDA CBER, we're trying to build
12 capacity in this area. And there is certainly a
13 possibility for more quantitative approaches to be
14 considered, especially now that the ICH guidance has
15 been out.

16 In the last few minutes of my presentation, I
17 want to talk a little bit about some of the things that
18 I think are important to consider when you're thinking
19 about going to a more quantitative benefit-risk
20 assessment approach.

21 As has been mentioned a number of times, it's
22 very important to consider the modeling uncertainty and

1 variability when you're moving toward a more complex
2 and formal benefit-risk assessment.

3 As was mentioned just in the last
4 presentation, all of us are aware that all of the
5 inputs in a model are going to have some uncertainty
6 and variability and this can go well beyond simply the
7 statistical variability that you would expect based on
8 sample size, for example.

9 The distinction here between uncertainty and
10 variability is that uncertainty is something that can
11 theoretically be reduced if you get more and better
12 data to help support the decision, whereas variability
13 is considered to be an inherent property in the system
14 that you're looking at.

15 So as we're -- if we're going to move towards
16 more quantitative benefit-risk assessments, we have to
17 make sure that we're using those models in such a way
18 that they're actively conveying the uncertainty and the
19 variability of the system that we're trying to model.
20 And we're usually going to do this through some sort of
21 computer simulation. Certainly in my team, we use a
22 lot of probabilistic, quantitative computer simulations

1 in order to convey this notion of the uncertainty that
2 we have.

3 In addition to being very clear and explicit
4 about the uncertainty and variability that you have,
5 it's important to do a lot of sensitivity analysis and
6 validation of the models as well. In all of the
7 benefit-risk assessment work that my team does, and
8 it's a practice that I would recommend for others, you
9 should make sure to include usually a large number of
10 sensitivity analyses.

11 And some of the kinds of questions that you're
12 going to want to ask, you're going to want to
13 understand which of the inputs in the model have the
14 biggest impact on the model results. And one of the
15 things this will tell you is it can give you some
16 guidance as to where to focus future research as well.

17 You also want to do sensitivity analysis to
18 understand which of the assumptions for which you don't
19 have data, which of the assumptions are the ones that
20 are most critical in the model. This helps everybody
21 who will be using that model have a better
22 understanding of how that model could go wrong.

1 And related to both of these, this can guide
2 your future research agenda by telling you if you need
3 to refine this more, where should you focus your future
4 data-gathering. The other thing that I would mention
5 in addition to sensitivity analysis is that, wherever
6 possible, you're going to want to do some validation of
7 the model.

8 And in particular, the best practices are
9 going to be able to take the model that you've
10 developed with a certain set of data and try and
11 validate it against an external dataset to see if the
12 results are going to still be valid when you move
13 beyond the data that you originally used.

14 So I want to mention a few concluding thoughts
15 regarding the value of specifically more quantitative
16 benefit-risk assessment. One of the things that I have
17 found incredibly useful about moving toward more formal
18 benefit-risk assessments is that it really helps to
19 provide a framework for discussion.

20 Early on in the process of a benefit-risk
21 assessment, you have to get everyone involved around a
22 table. People have to agree what the key inputs and

1 outputs of the model are going to be and how they
2 relate to one another.

3 This exercise by itself is critically
4 important to improving the understanding of the
5 problem. And it also helps with a lot of the
6 deliberation later on because you can point back to
7 that model that's been developed and link whatever
8 concerns someone might be bringing up back to the
9 specific point in the model and how it all fits
10 together.

11 So simply the act of building a model I have
12 found to be incredibly useful for some of the more
13 complex decisions we've had to deal with.

14 The other thing that I find very useful about
15 more quantitative benefit-risk assessment models is
16 that it really helps you to integrate large amounts of
17 data. And think back to the first slide that I put up
18 on the presentation.

19 We have data coming from lots of different
20 places and the data is of different quality, different
21 types. And we need a way to try and put all of that
22 together in making a decision and quantitative benefit-

1 risk assessments can help with that.

2 Another value of more quantitative approaches
3 is that it helps to identify what the biggest sources
4 of uncertainty are that still remain when you're trying
5 to make your decision. And it helps to identify where
6 some of the data gaps are, which, as I said earlier,
7 can you help you target your future research.

8 One of the things that we use quantitative
9 benefit-risk assessments for a lot in our blood safety
10 area is to compare the different policy options that
11 are available.

12 In the blood safety area, what we're always
13 trying to balance is how much can we reduce the risk,
14 for example, of an emerging infectious disease such as
15 Zika virus. How much can we reduce the risk of these
16 emerging infectious diseases and how many safe units
17 are blood are we going to use as a result of testing?
18 And quantitative benefit-risk assessment helps with
19 that a lot.

20 I also believe that these quantitative
21 methods, if it's done properly, can help to improve
22 transparency in risk communication. But of course

1 there's always the risk that if it's too complex and
2 you don't spend enough time on the communication, you
3 can lose people when you're discussing those issues.

4 As with any modeling exercise, if the data
5 going in is not good, you're not going to be able to
6 get a model that's believable and useful. So the risk
7 assessment models have to -- are only going to be as
8 good as the scientific theory and data on which they're
9 built.

10 The other thing that we can run into is that
11 if there's a lot of uncertainty, the best decision may
12 still be unclear. And this last point, as it came up
13 in some discussions before this, changing circumstances
14 or new scientific discoveries can certainly require
15 major updates to quantitative benefit-risk assessment
16 models. But I would just add that this is also true
17 with less quantitative approaches as well. So it's a
18 problem for however we're going about making those
19 decisions.

20 And the last thing I would like to mention is
21 that no one believes that quantitative benefit-risk
22 assessments are going to replace risk management and

1 the judgment that's necessary for making these very
2 difficult decisions. So with that, thank you very
3 much.

4 (Applause.)

5 DR. EGGERS: Thanks much. And now, we're
6 going to have a talk focused on the role of benefit-
7 risk framework and other -- and probably translated to
8 similar things, the role of those as a communication
9 tool to public stakeholders with -- and I'll let Steven
10 introduce himself.

11 COMMUNICATING BENEFIT-RISK TO THE PUBLIC

12 DR. WOLOSHIN: Oh, it's a miracle. So we're
13 going to divide this talk seamlessly. But in case
14 you're trying to keep track, I'm Steven and that's Lisa
15 over there. And we have -- we have two disclosures.
16 First, we're married to each other and the second thing
17 is we've been expert witnesses in testosterone
18 litigation.

19 So there's a lot of confusion about the
20 meaning of FDA approval. Nearly half of U.S. adults
21 mistakenly believe that FDA only approves and only
22 permits advertising of extremely effective drugs or

1 drugs without serious side effects. And most U.S.
2 physicians mistakenly believe that approval means that
3 the drug is as effective as others on the market for
4 this condition, when of course drug approval only means
5 that FDA believes benefits outweigh harms, not that the
6 benefits are big or important or that the drug is very
7 safe.

8 The FDA benefit-risk assessment helps allow
9 prescribers and consumers to understand the real
10 meaning of approval. It provides FDA's rationale for
11 approving a new drug and how they weigh the benefits
12 and the risk. And it's a unique source of independent
13 analysis and interpretation not filtered or negotiated
14 by industry, information that's otherwise hard to find.

15 So to give you an idea of how valuable this
16 information is, let's take a look at a recently
17 approved biologic drug for psoriasis called Siliq.
18 Lisa and I were recently speaking to a large group of
19 medical residents at a big academic medical center and
20 we asked them when you hear about a new drug, how do
21 you go about learning how well it works. How do you
22 decide whether you're going to use it or not?

1 And I think clinicians out there won't be
2 surprised by the answer. Most people said they would
3 go UpToDate, this electronic textbook. And what
4 UpToDate says about the drug is that it's highly
5 effective, that FDA approved it to treat moderate to
6 severe plaque psoriasis in adults who are candidates
7 for systemic therapy or phototherapy and have failed to
8 respond or lost response to other systemic therapies,
9 that there's a REMS because of concerns regarding risk
10 for suicidal ideation and completed suicides in treated
11 patients and that there are some adverse effects, mild
12 to moderate tinea infections and neutropenia.

13 So for the residents, the take-home message
14 looking at this stuff was that the drug seems to work,
15 you know, really well. But they had no idea how
16 worried to be about the suicidality issue. They didn't
17 know how to calibrate their uncertainty.

18 Now, some of the residents said that they
19 would go to the medical literature. And here's -- this
20 is the New England Journal article about the Phase III
21 trials which was the basis for that UpToDate chapter.
22 And what it said was that, again, that the drug is

1 effective and that -- sorry, that there are some mild
2 or moderate side effects. And the conclusion was very
3 strong. It said that the drug resulted in significant
4 clinical improvement in patients with moderate to
5 severe psoriasis.

6 But something was missing. And amazing,
7 suicide is not mentioned in the abstract at all. In
8 fact, the only -- suicide is only briefly mentioned in
9 two clauses in the results. So there's no red flag
10 here at all.

11 Now, I just want to turn to the FDA office
12 director's benefit-risk summary and show you their
13 take. The summary says the efficacy of Siliq is not in
14 dispute. So there's no question that this drug works.
15 However, the presence of a rare, fatal event observed
16 in a controlled clinical trial setting is merely the
17 tip of the iceberg. Once approved and used in a
18 broader population, we can anticipate a higher
19 occurrence.

20 Further, I am unaware of any product having
21 been approved by the FDA with four completed suicides
22 in a clinical development program. So the residents

1 thought, and we agreed, that this context really helped
2 understand that this was a really important red flag,
3 something that you can't ignore.

4 FDA's reasoning has great clinical value. The
5 office director's thoughtful summary explained how FDA
6 balanced benefits and risks in deciding to approve this
7 drug.

8 I have considered the seriousness of the
9 disease, the chronic nature of the disease, variability
10 of response and duration of response to different
11 treatments, patients' ability to access various
12 approved treatments, the impact of the disease on
13 patients and their families and the continued unmet
14 medical need. Perhaps most importantly, I have
15 considered the importance of patient autonomy. I
16 believe that patients should have choice, but that
17 choice should be informed.

18 So this document was really great because it
19 made clear why FDA chose to approve the drug and why
20 they chose to approve it with a variety of risk
21 mitigation strategies including a boxed warning, a
22 limited use for patients who failed other systemic

1 therapies and a REMS.

2 So we think that the benefit-risk summary
3 assessment has really, really unique and important
4 value. But of course there's ways to make it better.
5 And we're going to go through a few.

6 The first one is pretty straightforward, to
7 organize the narrative with visually distinct and named
8 sections. So in other words, we've seen a lot of these
9 slides with a lot of things. They're really big blocks
10 of text and it would be a big help to go from this to
11 this.

12 Structured headers not only make it easy to
13 read, but it would also help make the narratives
14 consistent across drugs. And there are a variety of
15 possible headers that could be employed, for example,
16 indication, benefit, risk, comparative efficacy,
17 weighing benefit and risk, risk management and post-
18 marketing requirements.

19 DR. SCHWARTZ: Seamless. Our next
20 recommendation is about including structured tables
21 with both the trial descriptions and efficacy and side
22 effect data so people can understand the basis of

1 approval.

2 So for Siliq, there's a lot of information in
3 the risk-benefit framework. This information we think
4 is displayed inefficiently. Benefit appears over six
5 pages. Risk appears over seven pages. Sometimes the
6 data are quantified. Sometimes there's just p values.

7 And we think that structured tables and
8 consistent data formats would make it easier for
9 readers by avoiding long text which is bogged down with
10 lots of numbers and that the text can really focus on
11 the interpretation, which is really what's so
12 incredibly valuable about the benefit-risk framework.

13 So this is what it might look like for
14 benefit. So in this case, there were three trials.
15 And I'm going to show you two here which were two
16 identical, 12-week randomized trials that were done in
17 adults aged 18 to 75 with stable moderate to severe
18 plaque psoriasis.

19 In the trial, Siliq was compared to an active
20 comparator, Stelara, and also to placebo. And in both
21 trials, they had the same two primary outcomes, whether
22 somebody had a major improvement in their psoriasis or

1 whether the doctor rated the psoriasis as minimal or
2 none. And the secondary outcome was that there was no
3 psoriasis. The physician rated the skin as completely
4 clear.

5 Here is the data. And just to say that the
6 two trials had incredibly consistent results and the
7 drug clearly works. So the other thing that you could
8 -- you know, of course, when you make tables like this,
9 you have to decide what data you're going to present.
10 In this case, the trials were completely consistent.
11 So maybe you would just pick one illustrative trial.

12 Alternatively, since the trials had completely
13 consistent results, maybe you want to pool the results.
14 But the bottom line is regardless of which data is
15 presented, the tables make it possible for readers to
16 weigh the benefits and harms for themselves.

17 So for side effects, the table would present
18 side effects in terms of their importance to ensure the
19 appropriate emphasis. So for instance, you could start
20 with a black box warning, either state what the black
21 box warning is for or state that there isn't any black
22 box warning. Then, serious side effects and then the

1 most common symptom side effects sorted by frequency.

2 And here's what it might look like for Siliq. But the
3 idea is just to illustrate how you could efficiently
4 communicate the data.

5 We've done a body of research which the FDA's
6 own research has replicated showing that patients can
7 understand these kinds of data tables, which we've
8 called drug facts box. And we believe if patients can
9 understand them, that clinicians probably can. So we
10 think they'd be a great idea to supplement the benefit-
11 risk framework.

12 The other part of structured data tables is
13 the benefit-risk framework includes current treatment
14 options. And we think it would be great to include
15 comparative efficacy data. We know that FDA does not
16 generally do this.

17 But interestingly, for Siliq, in the medical
18 review, the medical reviewer created a table which
19 contrasted Siliq's benefits with other similar biologic
20 drugs that are approved for psoriasis. And this table
21 provides we think really useful context because your
22 willingness to accept more side effects or more

1 uncertainty is likely to change depending on how much
2 more benefit this treatment has compared to similar
3 treatments. And in this case, its benefit, while it's
4 highly effective, is in the ballpark of other
5 biologics.

6 Our next suggestion is about summarizing the
7 FDA review team's approval votes and the rationale. So
8 for instance, in the primary review team, which was in
9 the Division of Dermatology, the division director
10 voted yes. And what you could include was a link to
11 the reason and to the summary review so that people
12 could understand the reasoning behind that vote.

13 And then, you can do the same thing for the
14 clinical rest of the review team. And for example, if
15 you wanted to understand why the medical reviewer voted
16 no, you could click on the reason, which, if it were in
17 a specific header, you could quote the risk outweighs
18 the benefits provided by the biologic, the safety
19 signal for suicidal ideation and behavior requires
20 further data to mediate the risk in this high comorbid
21 population.

22 The team leader voted yes to approve the drug

1 and here's what the team leader's rationale for that
2 vote was. Siliq should be made available with labeling
3 sufficient to describe and inform the risk, as well as
4 a REMS with elements to ensure safe use to ensure that
5 prescribers understand and acknowledge the risks and
6 document the patients who use Siliq are fully consented
7 regarding the benefits and potential risks, even the
8 possibility of a fatal risk.

9 In addition, it would be great because
10 sometimes FDA consults other divisions for their
11 opinion. And in this case, psychiatry, the cardiac
12 division, epidemiology and pharmacovigilance also voted
13 and this would allow people to understand their votes
14 and their reasoning behind their votes.

15 And we think routinely presenting the
16 agreement or disagreement helps to highlight whether
17 important uncertainties exist. So we think the
18 framework is incredibly valuable and we think it should
19 be disseminated more widely, of course with data
20 tables, to prescribers and consumers. And we want to
21 suggest that maybe you consider expanding and
22 redesigning FDA drug trial snapshots for that purpose,

1 while of course creating a whole library of benefit-
2 risk frameworks on their own would be valuable, drug
3 trial snapshots is already a place where new drug
4 approvals are being posted.

5 So this is a trial snapshot for Siliq and this
6 website is created for consumers and it has a bunch of
7 headers about what the drug is for and provides a
8 narrative about what are the benefits of the drug.

9 At the bottom, if you click the more
10 information actually, you can find data. But the data
11 looks like this and the data is really intended for
12 prescribers or maybe for researchers because there's a
13 fair amount of statistical complexity here about data
14 amputation and statistical methods.

15 But the idea is this is data from the review
16 or the label in a structured format. And this might be
17 a really great place to start off by introducing the
18 risk-benefit framework by adding a header about why did
19 FDA approve this drug and providing links to the risk-
20 benefit framework or perhaps sort of a table of
21 contents of the risk-benefit framework.

22 And we think it would be great if there were

1 actually two versions, one for consumers and one for
2 prescribers. So rather than having a website that sort
3 of communicates sort of to two audiences at the same
4 time, to have communications that are directed at each
5 audience distinctly.

6 So in conclusion, we think that FDA's benefit-
7 risk assessments and review documents, which we've read
8 for many years, are a gold mine. Certainly the
9 benefit-risk assessment has made it much easier to read
10 those documents. It's independent, informed, expert
11 assessment of drug benefit and risk.

12 And it's an explicit discussion of how often
13 difficult approval decisions are made in the face of
14 sometimes really important uncertainty. And we think
15 the dissemination efforts are really important to
16 prescribers and to patients so that they can make wise
17 decisions about drugs and we just think you guys are
18 doing great work. So keep it up. Thanks.

19 (Applause.)

20 DR. EGGERS: Okay. I want to thank all of the
21 presenters, Brooke, Rich and Steven and Lisa. And we
22 have some additional people coming up for the panel

1 discussion. I'd like -- we met Clause earlier today.
2 So I'm going to ask for Peter and Bennett to introduce
3 themselves. I guess we'll start with Bennett, since
4 you are situated. Introduce yourselves and provide
5 some -- a few minutes of thoughts to kick off our panel
6 discussion.

7 PANEL DISCUSSION AND Q&A

8 DR. LEVITAN: Okay. Hello. I'm Bennett
9 Levitan. I'm in the epidemiology department of Janssen
10 R&D, part of J&J. And I'm a member of a team that does
11 benefit-risk assessment, patient preference studies and
12 a bit of decision analysis.

13 Thank you very much for the opportunity to sit
14 on the panel and share some thoughts. I thought the
15 day has been fantastic. Really enjoyed hearing the
16 talks. And you asked if I could put a couple of
17 thoughts together. So if I focus on the three main
18 themes, benefit-risk frameworks, incorporating the
19 patient perspective and more quantitative benefit-risk
20 techniques. So I'll give you a few thoughts.

21 The first, echoing some of the comments from
22 Sara and Valerie, I find, and my team finds, benefit-

1 risk frameworks are incredibly helpful, even for people
2 who are extremely experienced at benefit-risk, who do
3 it -- we do it all the time. It's very helpful in
4 structuring our thoughts, reminding us of things that
5 we can sometimes forget, especially when I'm working
6 with a team in real-time.

7 And it also makes very easy to communicate the
8 rationale for a benefit-risk decision in a manner that
9 becomes pretty consistent over time. In fact, we've
10 begun including in a couple of our submissions the
11 framework because -- FDA's framework because we find it
12 a useful communication tool.

13 The ICH update did the clinical overview
14 suggests a couple of tools that could help support it.
15 And we actually do these things in addition to the
16 framework. So we do a value tree exercise. So the
17 idea of key benefits and key risks has to be defended.

18 If we're going to choose a small number of all
19 the benefits and harms that we measure and say those
20 are the ones that drive a benefit-risk assessment, we
21 go through an exercise to identify those and describe
22 those which we pick in a defensible manner.

1 We also do something very similar to what we
2 just heard from Lisa and Steve. It's what Francesco
3 called an effects table. It's basically a tabular
4 summary of your key benefits and harms, with the two
5 treatments, maybe a treatment difference and some
6 ancillary information.

7 We find it's extremely helpful to have
8 potentially a hundred pages of information all
9 compressed into a table or two so that after you've
10 gone through the background, you can rapidly interpret
11 the table and build a benefit-risk argument off the
12 therapy context, the medical need and that table.

13 We also find it's also important to bring the
14 patient perspective into the benefit-risk framework and
15 we've done that a number of times, though it's really
16 still an open question how best to do that.

17 That brings me to the second topic of
18 incorporating the patient perspective. It's a lot more
19 than patient preference studies that we're talking
20 about. Just to give you an idea, the questions that
21 come up all the time are the ones we've heard today.
22 Which methods? What methods can avoid bias? What

1 patients should we be using? Should we assess the
2 preferences or the viewpoints or the perspective of
3 patient who are risk, newly ill with the disease,
4 chronically ill or those who have experienced various
5 treatments? They'll all have a different perspective.

6 One of the things I'd like to strongly suggest
7 we consider is just like sponsors speak with regulators
8 over the course of years about designing a trial and
9 the statistics for trial, they consider a collaborative
10 discussion on how to bring the patient perspective into
11 the drug development process, whose perspective and
12 what methods might be appropriate.

13 Finally, on quantitative approaches to
14 benefit-risk, so something that Tarek and Brett brought
15 up I want to really emphasize. It's not an either/or
16 thing. It's not qualitative or quantitative. Really
17 every quantitative analysis is based on a qualitative
18 underpinning. And if you jump into a quantitative
19 approach too early, you'll probably miss very important
20 things.

21 The question really is when is it worth the
22 effort to do the additional time consuming and

1 resource-intensive quantitative assessment of benefit-
2 risk. And sometimes you actually don't know that until
3 the very end when you've gotten your data.

4 There's definitely a role. One of the other
5 things I'd like to see happen in discussions between
6 the sponsor and the FDA is actually outlining a
7 benefit-risk approach.

8 The idea that Becky mentioned earlier about a
9 toolkit I think is the way to go because there's tons
10 of things that we use, not always all the time. And I
11 think what's needed is some guidance for industry as a
12 whole as to which methods from a toolkit or which tools
13 would be most valuable, as well as some guidance as to
14 how to implement particularly some of the more complex
15 tools.

16 Finally, I agree with what we've heard behind
17 the scenes, that there's a strong exploratory phase to
18 the more quantitative approaches and the patient
19 perspective aspects. I love preference studies.
20 They're a lot of fun. They're very insightful. But
21 I'm well aware of their limitations. I like what CDRH
22 has been doing where they're sort of inviting companies

1 to collaborate and talk with them about preference
2 studies.

3 Both parties know there are still issues. But
4 they're working on it together and exploring how they
5 could learn from these preference studies for the work
6 they're doing. And that's what I hear Theresa talking
7 about in somewhat of a different way, but on the CDER
8 and CBER side. Anyway, thank you for an opportunity to
9 share some of my thoughts.

10 DR. EGGERS: Thank you, Bennett. And now, so
11 that we have a CDER and a medical officer decision-
12 maker perspective, we've asked Peter to come up and if
13 you could provide a few thoughts, reflections on what
14 you've been hearing?

15 DR. STEIN: Sure, sure. I'd be happy to. I'm
16 Peter Stein. I'm deputy director in the Office of New
17 Drugs in CDER. And actually, listening throughout the
18 day, I find that I'm about to say almost nothing that
19 hasn't been said before by a number of people. In
20 fact, some of the things probably will be about the
21 fourth time it will be said. So perhaps you can take
22 this as emphasis rather than unique innovative thought.

1 The first comment I'd make, and I think maybe
2 reemphasize throughout the day, was the value of the
3 framework as CDER and OND have gotten increasing
4 experience with it. It clearly has been a tool both
5 for helping with decisions and I think clearly -- and I
6 think the last talk and prior talks also emphasized how
7 useful it was as a communication tool to patients and
8 physicians in helping with understanding FDA thinking
9 in decisional -- in the decisional frameworks.

10 Now, I do think that very often -- and for
11 many of the decisions that we make, the risk-benefit is
12 relatively straightforward. The benefit may be very
13 clear relative to a limited risk or the risk may be
14 very clear relative to a limited benefit.

15 One hopes that's not often the case, but
16 sometimes it is. And the decision doesn't necessarily
17 require more than a qualitative framework in which to
18 consider it. I think it still is helpful to put down
19 clearly and articulate the benefits we understood, the
20 risks that we perceived and how we weighed them. But
21 just like in circumstances where the benefit is so
22 clearly above the risk, it doesn't really require much

1 more than simply articulating it, documenting it and
2 then moving forward with the decision.

3 I would say that one point to make perhaps is
4 that when the qualitative framework was selected and
5 there was discussions I know in years past about what
6 framework to utilize, there was consideration of
7 applying a quantitative rather than a qualitative
8 framework.

9 And I think there was concerns raised about
10 the challenges of trying to convert -- trying to
11 translate benefits to sort of a numerical estimate and
12 risks to a numerical estimate, put those in some sort
13 of equation and come up with a number and have that
14 imputed as the decision, which of course is not what
15 quantitative benefit-risk is about.

16 But I think that expressed some of the concern
17 and led to more comfort with the qualitative
18 approaches. But I would say that in some sense that
19 may be perhaps a mistaken understanding in the sense
20 that when we do a qualitative framework, I would posit
21 that we actually in fact are being quantitative in a
22 way that doesn't necessarily state our quantitative

1 assessments.

2 We have to, in doing risk-benefit, think about
3 what extent of benefit there is, which is really a
4 weight, if you will. What's the quantum of benefit?
5 And we also have to think about what extent of risk is,
6 what's the quantum of risk. And we have to compare
7 them.

8 And when we make an approval decision, even if
9 we haven't put on the table our quantitative
10 assessments, we in fact have to translate the endpoints
11 that we saw in the clinical trial to some quantum of
12 benefit and the risks and harms that we saw into some
13 quantum of risk and make the calculation that those
14 benefits outweighed the risks.

15 So I do think even when we consider the
16 qualitative framework, in a sense we are hiding the
17 quantitative process that we have to all go through
18 because in many instances it's not a complex one. It
19 perhaps doesn't require a lot of challenge in doing
20 that.

21 I think that, as I think about the
22 quantitative approaches -- and just to step back, when

1 I did a quick poll of a few people, Bob Temple was here
2 earlier and a few other people that I asked, you know,
3 how often are decisions do we think really challenging
4 where the qualitative framework alone doesn't provide
5 the tool necessary to make the decision.

6 When we face really complex decisions where
7 there's benefit and risk and they appear to be, you
8 know, not clearly differentiated and the decision is
9 challenging or perhaps there's relatively limited
10 benefit and maybe more limited risk, but where the
11 tradeoff -- where the balance isn't entirely clear.

12 And I guess we'd probably estimate that
13 something like 10 or 15 percent of the time, maybe
14 less, maybe more, it's really a challenging decision.
15 And many times the decision is not so challenging.

16 So where would the quantitative tool come in I
17 think particularly in these more challenging decisions
18 where we're really trying to understand, you know,
19 what's the right decision here.

20 And I want to pick up on something Richard
21 said because I actually think that the output of that
22 tool is perhaps not as important as putting on --

1 putting on paper the inputs to the tool. I think what
2 quantitative risk-benefit, at least from my
3 perspective, lets us do and perhaps makes us do is
4 bring the decision-makers together to make explicit
5 what their assumptions are.

6 What do they really think this would likely
7 translate into if this was to be -- if the drug was to
8 be approved? What would the benefits look like? How
9 would we quantitate them? How impactful would they be?

10 What are the harms? What are the risks? How
11 would we translate the clinical trial data to a benefit
12 and to risks in the population that would be treated
13 with this? What specific assumptions did the
14 individual decision-makers make when they -- when they
15 decided for or against the approval decision?

16 And by putting those on paper, putting them on
17 the table, as it were, and comparing, those kinds of
18 assumptions can be challenged. And I think it's that
19 process of engaging in a discussion about what
20 assessments one individual made versus another
21 individual made versus another individual made, I think
22 that's where the process can be so valuable. I'm not

1 downplaying the output of the process.

2 But I think it's really in the testing of the
3 input and in people's expressing their range of
4 uncertainty and looking at those ranges in the
5 sensitivity analysis that can be done that we really
6 have greater insight into the process. I think the
7 challenges of course are trying to figure out how we
8 convert the endpoints from clinical trials into
9 extensive benefit. Endpoints can be sometimes directly
10 translatable. If it's overall survival, that's fairly
11 straightforward.

12 On the other hand, how do we convert, for
13 example, a drug that lowers LDL to a quantum of
14 clinical benefit? But of course, as I said before, I
15 think we have to do that.

16 First, we have to translate it into some form
17 that suggests what clinical benefit we think that
18 provides in the study population and make another step
19 in translating it into the benefit we think it will
20 provide in the treated population if the drug was to be
21 approved.

22 And similarly for harm, how do we translate

1 adverse events into specific harms in the study
2 population and then translate that further into the
3 population that would be treated?

4 So I think all of these processes that are
5 engaged with the quantitative risk-benefit can be very
6 valuable. And I hope in the years to come, we gain
7 more experience in CDER as CBER has been I think ahead
8 of the curve in really thinking about this and I think
9 CDER needs to continue to think about how we can
10 utilize that, these type of processes.

11 And there have been some inroads to that.
12 We've made some efforts in our oncology group and in
13 other groups looking at quantitative risk-benefit
14 frameworks. I'm not sure we're at the stage where
15 we're thinking that's how decisions will be made. But
16 I think it will give us substantial insight to it.

17 So I guess the other comment that I would make
18 is that I do think quantitative frameworks also allow a
19 very nice tie-in to patient input because I think they
20 help us with making the weighting and the scaling
21 that's necessary in the quantitative approach.

22 And so, I think as we get more and more

1 experience with patient-focused drug development, with
2 patient input into drug development decisions, I think
3 there'll be a natural input into the quantitative
4 frameworks and helping us with the weightings that are
5 necessary to go into those calculations. So I'll stop
6 there and --

7 DR. EGGERS: Thank you very much, Peter. I'll
8 open it up if there are any questions. Oh, yeah? Yes?
9 So as people are -- Clause, do you have any comments
10 that you'd like to add based on from your talk this
11 morning to this afternoon now?

12 DR. BOLTE: I can't help to think of a Swiss
13 Army knife. You may as well think that Clause must
14 have had an extended narcoleptic fit at some point
15 today after his travel over and not sleeping very well.
16 No, I've been very vigilant all the time.

17 What I mean by this Swiss Army knife approach,
18 it's a nice souvenir, the Swiss Army knife from our
19 country. It's a multipurpose tool. But typically, the
20 more components you have, the less useful, the less
21 functional it is. So trying to translate this into the
22 benefit-risk framework, I would caution that we -- at

1 least at this stage, while we are developing in many
2 different directions and trying to include different
3 factors and weights and trying to quantify them as
4 well, to limit -- to limit the framework to key
5 functionalities and purposes, as I outlined earlier.

6 So without going into a monologue right now
7 because I had this opportunity this morning, I would
8 caution again to limit at this point in time the use of
9 a probably multipurpose tool to just some key functions
10 we discussed, namely facilitating the decision-making
11 process, documenting it as well.

12 And I'm not so sure even about the third
13 component, communicating it. If at all, only
14 internally, not yet externally because it depends very
15 much on the audience, the way you communicate it, as we
16 heard from many different presenters.

17 And then, the final thought is for those of
18 you who had the benefit to also attend business school,
19 you come across a concept that is widely used there.
20 And I was wondering all the time when I was listening
21 today, to what extent could we probably use the
22 balanced scorecard methodology here at all.

1 The balanced scorecard methodology is very
2 well-established in a generic way. It helps with
3 performance management. It can help to outline a
4 strategic roadmap. It can be used in scientific as
5 well as sales marketing and HR functionalities and
6 purposes.

7 Key is that you have different, very well-
8 defined components which cannot offset each other. So
9 benefit-risk, benefit includes patient preferences and
10 patient-reported outcomes and all that.

11 Benefit-risk, uncertainties and again, in a
12 provocative way, this is just my opinion. I have to
13 qualify that. It's not my agency's -- cost as well as
14 the fourth dimension in such a balanced scorecard is
15 perhaps something we should consider at some point.

16 DR. EGGERS: Okay. Thank you, Clause. Are
17 there any questions?

18 MR. EMMETT: Hi. Andrew Emmett, with Pfizer.
19 Thank you for the excellent presentations and panels.
20 I have a question for our FDA colleagues and others. I
21 think one thing we've heard throughout the course of
22 the day is an interest under PDUFA VI and looking ahead

1 to really adopting a lifecycle approach to structured
2 benefit-risk and patient-focused drug development and
3 really leverage these tools and strategies throughout
4 the continuum of drug development, starting early on in
5 the development.

6 And we're starting to see a lot of
7 experimentation along those lines. We've been hearing
8 the companies have been submitting structured benefit-
9 risk frameworks with background packages for meetings,
10 with NDA/BLAs. We're seeing a lot more interest in
11 patient preference studies.

12 Based on the learnings that we've had so far,
13 from the FDA perspective, can you share any best
14 practices that you've seen for that type of FDA sponsor
15 engagement and communication in the premarket setting,
16 at PDUFA milestone meetings?

17 And what would you say should be sponsors'
18 expectations for the level of FDA engagement around a
19 structured benefit-risk framework or patient-focused
20 drug development data if that's submitted in a
21 premarket setting. Thank you.

22 DR. EGGERS: Well, I'll turn to Peter to see

1 if you have any experiential regarding the interactions
2 and what makes them useful.

3 DR. STEIN: So a couple of comments on that.
4 I wouldn't say -- and I can't say that I have huge
5 experience and have taken a poll of how many packages
6 have included structured benefit-risk at various
7 stages. But we clearly have seen sponsors that have
8 taken the opportunity to put in a structured benefit-
9 risk framework. And obviously, we're going to look at
10 our own.

11 I think just like the value that we see in it
12 in terms of framing our considerations in a structured
13 fashion, the ones I've seen from sponsors I think help
14 do the same thing. And I think that's some of the
15 earlier presentations and the new ICH recommendations
16 really I think highlight the importance of such a
17 structured format.

18 So I think it helps the discussion to
19 articulate the assumptions, articulate the context for
20 the decision more clearly, articulate the benefits, the
21 risks and the risk-benefit assessment in a way that I
22 think enhances the discussion.

1 I would also add that there are clearly -- you
2 know, from the premarket perspective, this is very
3 helpful. But this is also part of how we must be
4 thinking about the lifecycle as we go forward.

5 So as issues come up, new safety findings, I
6 think the same framework helps. We know more about the
7 drug's benefit.

8 As the lifecycle continues and as we see new
9 potential risks, new defined risks, I think it helps us
10 put it into the same framework of what we know about
11 the benefits of the drug, the risks of the drug, the
12 value of the drug over time. Are there new drugs that
13 provide equal or greater benefit? What's the unmet
14 need years into the drug's lifecycle?

15 So I think continuing to utilize the framework
16 is valuable and I think companies that bring a
17 structured and thoughtful approach help us in thinking
18 about it as well. We certainly review what companies
19 provide and I think that provides a more -- I think a
20 more detailed and thoughtful discussion when you engage
21 with us.

22 So I think it's helpful. I can't tell you

1 what percentage of companies put it into that formal
2 framework. But I think where it's presented that way,
3 I think there's real value in that.

4 DR. EGGERS: So, go ahead, Rich.

5 DR. FORSHEE: So I'll share just a few
6 thoughts, one set of thoughts on the premarket side and
7 one set of thoughts on the post-market side. I think
8 the main message I would like to give on the premarket
9 side is come talk to us early.

10 And I think in particular, if you're planning
11 on doing anything that is more cutting edge, such as
12 something that's going to potentially have quantitative
13 benefit-risk approaches included or that's going to be
14 doing some sophisticated patient preference, please
15 talk to us very early on in the process. I think that
16 that will provide the best dialogue between a sponsor
17 and the FDA.

18 Regarding the post-market piece of this,
19 particularly on the biologics side, and at the moment
20 I'm thinking more about vaccines in particular, because
21 we have such a low threshold for risk when we're
22 talking about vaccines because they're so widely used

1 and oftentimes they're given to prevent a possible
2 illness as opposed to a treatment of a problem that
3 people already have, we're concerned about very low
4 risks that might be out there.

5 And so, we put a lot of emphasis on the post-
6 market -- post-market side. And this is -- the
7 emphasis has become even stronger since the Food and
8 Drug Amendment Acts that require the establishment of
9 more active surveillance which has led us to be using
10 more health claims data to try and assess potentially
11 very, very low but serious risks that might be
12 associated with vaccines.

13 I think that integrating the new data that
14 comes up post-market into something like a structured
15 benefit-risk assessment, I think we're still learning
16 the best ways to do this.

17 But I think that that's going to be something
18 that's very important and I think that when we consider
19 how to integrate the sort of real-world evidence that
20 is developed after a product is on the market and we
21 think about how to integrate that data, it's oftentimes
22 going to come from observational data, which has its

1 own special issues with interpretation, how to
2 integrate that with the data that's come from the
3 premarket side is something that I think still requires
4 some additional thought. But I think it's an important
5 area that we're going to have to confront.

6 DR. EGGERS: This is a topic that -- this
7 topic of the dialogue between sponsors and FDA is a
8 topic that twill come up in PDUFA VI. It was of great
9 interest there.

10 I just -- I don't have the experience working
11 with the sponsor. But what came up as being important
12 there, hearkening on some things that have been talked
13 about today, was the importance of coming early to
14 discuss the therapeutic context, particularly as early
15 in the development programs because benefit-risk is a
16 consideration early on and having a shared
17 understanding of that therapeutic context early in
18 development can help set stage for decisions and
19 considerations moving forward.

20 So we'll be looking in that as part of -- as
21 part of PDUFA VI about that therapeutic context. If
22 there are no questions, we are -- oh, go ahead. Come

1 on up.

2 MS. DICKINSON: Actually, I think my question
3 has been partly answered already. Sheila Dickenson,
4 Novartis. I had a question about benefit-risk in the
5 post-marketing setting, which I think we've been
6 touching on a little bit.

7 I'm curious are the FDA using the grid that
8 we've been discussing today in the context of post-
9 marketing assessments and do you have examples on your
10 website I could go and look at where you've been doing
11 this? I would very much like to see what you've been
12 doing.

13 DR. EGGERS: So I can take this. The answer
14 to your second question is there probably are no
15 examples out in the public sphere regarding the post-
16 market decisions.

17 But they have been part of conversations in
18 those particularly tough examples exactly to what Peter
19 was describing where you're not sure where a new safety
20 signal emerges and you're not sure where it fits in the
21 armamentarium. And you have to now think what does
22 benefit mean and how can you now measure benefit.

1 So is it utilization? Is it other things? We
2 have now some other indicators of benefit in the
3 setting, new evidence to come in. It does --
4 discussions about uncertainty are as great when you
5 talk in the post-market setting because of the variable
6 data sources as they are when you're talking in the
7 premarket setting where there's just limited evidence.
8 So is --

9 DR. LEVITAN: Yeah. Sheila, one place to look
10 for examples might be the periodic benefit-risk
11 evaluation reports, or PBRERs. Now that they have a
12 structured approach similar to what's in ICH's clinical
13 overview update. In those probably rare cases where
14 there's a radical change in the data and a company
15 can't say its things are the same, you'll probably find
16 a more detailed assessment -- benefit-risk assessment
17 post-approval.

18 DR. EGGERS: Okay. Anyone else? Baruch, yes?

19 DR. FISCHHOFF: I'd like to pick up the
20 question of preference elicitation because I've been
21 sort of reflecting on this all day. And I mean, I
22 think the kind of process that we heard -- you know, if

1 we had a process where we had Telba, you know,
2 understanding the agency perspective, somebody like --
3 I'm taking the previous panel -- Brett, who's familiar
4 with the full size of the suite of alternative
5 perspectives, has seen lots of different preferences,
6 can interpret, somebody like Leah who's able to bring
7 in the heterogeneity of patient preferences, I can see
8 that being a very important discovery process that, in
9 a way, would have kind of a hologram of the complexity
10 of anything else.

11 Just like, you know, if you've listened to one
12 of the Voice of the Patient things, you know, listen to
13 the whole webcast online, you know, you realize, wow,
14 every bit of this world is equally complicated. So I
15 think that there's great -- and where does that benefit
16 come from?

17 The benefit, people know the science. People
18 who know preference elicitation and people who've taken
19 the care to make certain that people have fully under -
20 - you know, have met the communication standard that
21 Steve and Lisa were talking about so that people who
22 are participants in their -- in this are actually

1 telling you what their -- you know, their answer --
2 you've given them a question that you can answer.

3 And yet, what I've seen in areas that have
4 looked at this -- and so, I think that that's an
5 analytical -- behaviorally informed, analytical
6 perspective can give you a lot.

7 And, but I think that the emphasis on
8 quantification leads you into a very dark place and it
9 leads you into the same I think scandalous situation
10 you have with contingent valuation research or with
11 kind of preference elicitation that's done for cost-
12 effectiveness analysis or discrete choice in a lot of
13 other people where people have displays that are
14 incomprehensible, that haven't been developed to a --
15 you know, that don't actually include the information
16 that people need, where there's no manipulation checks
17 to tell -- to check that there's actually been
18 comprehension, that the analytics are opaque, even to
19 reviewers of their -- of their papers, that an industry
20 of contractors builds up around it and they establish
21 their own conventions about we're going to throw out
22 all the protest responses or we're going to impute

1 values to people who refuse to answer our questions or
2 we're going to use this exclusion criteria or that
3 exclusion criteria.

4 If you pooled all the exclusion criteria, you
5 would have no respondents in most of those -- in most
6 of those studies because they've asked people questions
7 that they can't answer. And if they did think -- if
8 they thought they could answer, it's probably because
9 they haven't understood the question because the
10 displays are so poorly evaluated.

11 So I think that -- you know, I think maybe
12 it's worthwhile using quantitative for the risk side
13 and analytical for the benefit -- for the --
14 quantitative for sort of the scientific, estimating the
15 cost and benefit and analytical for the preference
16 side.

17 You can tell if your risk or benefit estimates
18 turn out to be wrong because you'll have some evidence
19 in the future. If you've chosen to misrepresent -- you
20 know, if you've chosen to misrepresent people's values,
21 ignore heterogeneity in population, who's to know?

22 DR. LEVITAN: You bring -- Baruch brings up a

1 very good point and there's actually evidence that
2 something like this could potentially happen. After
3 CDRH released their draft guidance on patient
4 preference studies, suddenly there were more
5 organizations that described themselves as being
6 capable of doing patient preference studies.

7 Now, we always work with academic or boutique
8 consulting groups that are academic in nature. But we
9 have the funds and time to be able to afford that. But
10 not everyone can. So I think your point is well-taken.

11 And it stresses all the more need to have some
12 type of -- I don't want to use the word guidance.
13 That's maybe the wrong term. But best practice
14 document. ISFOR has the beginning of it. Other
15 organizations are beginning to put it together. IMI,
16 the Innovative Medicines Initiative is working on it.

17 Some documents say if you meet these
18 standards, or the International Academy of Healthcare
19 Preference Research, IAHPR, Ben Craig, an organization
20 like that that puts out this set of requirements and
21 then you could say we followed these requirements will
22 lessen some of the concerns.

1 DR. FORSHEE: So I do want to mention a couple
2 of comments have led me to make this comment. With the
3 quantitative benefit-risk assessments that we've done
4 in CBER to date, we are stopping before we're doing the
5 weighting and valuation component.

6 So we will go so far as to estimate, for
7 example, the number of transfusion transmitted cases of
8 Zika virus that our model would predict and we would go
9 so far as to say but it's going to lead to this many
10 units of blood that would otherwise have been available
11 not being available because of false positives from
12 testing, for example.

13 And so, we will go as far as to estimate the
14 likely distributions of each of the benefits and risks
15 that were identified in the early parts of the
16 exercise. But then, that's usually presented to the
17 review teams and to the advisory committees to allow a
18 more qualitative expert judgment about figuring out
19 what that balance looks like.

20 This isn't to say we would never go to that
21 next step of exploring what the tradeoffs are. But we
22 haven't yet. So that's where we've been comfortable

1 going to the point of estimating the likely
2 distributions of the key benefit and risk endpoints
3 that were identified and then using more traditional
4 expert judgments to make final decisions about how to
5 balances those.

6 DR. EGGERS: Well, with that, as the
7 timekeeper, I'm going to have to end the session. Look
8 forward to further discussions. You can be relieved of
9 your posts. Look forward to future discussions. And I
10 think Graham is going to come up for open public
11 comments.

12 OPEN PUBLIC COMMENT

13 MR. THOMPSON: All righty. We are almost at
14 the end of our meeting. I'd like to thank everyone who
15 came in person and the almost -- there are over 400
16 people who attended via webcast. It's great to have
17 you all here.

18 So this is the open public comment session of
19 our meeting. We have seven people signed up for OPC.
20 I'll go through your names in order in a few minutes.
21 Please keep in mind that this is an opportunity for you
22 to present your comment to us. But we're not going to

1 be responding to comments individually.

2 They will be transcribed and they will be part
3 of the public record. If you don't get an opportunity
4 to speak or you have more comments than you have time
5 for, please feel free to submit them to our public
6 docket.

7 All comments submitted to the docket will be
8 considered the same as anything that was submitted
9 here. The docket will be open until November 18th and
10 you can find a link on our website.

11 We'd like this to be a transparent process.
12 So we encourage you to note any financial interests you
13 may have that are related to your comment. If you
14 don't have any, you can feel free to say that. If you
15 prefer not to provide this information, that's also
16 fine. You can still provide your comments.

17 As I mentioned, we have seven people. And to
18 keep this moving quickly, I'll give all the names now
19 and please line up when the previous person has
20 finished. First, we have Caila Brander, then James
21 Valentine, Angela Lundberg, Jon Furman, Kristen Hsu,
22 Jack Mitchell and Benjamin Craig.

1 We have about two minutes per person. So I
2 won't have a timer. But please respect -- oh yeah,
3 there's a mic in the middle. You can just line up
4 there, using the free mic, yeah. And make sure to hold
5 the mic close because people on the webcast, it can be
6 hard to hear. Yeah, that's perfect.

7 MS. BRANDER: Great.

8 MR. THOMPSON: yeah, so you can start us off.

9 MS. BRANDER: Okay. Hi. I'm Caila Brander.
10 I'm the policy coordinator at the National Women's
11 Health Network, which is a nonprofit advocacy
12 organization that works to bring the voices of women
13 consumers to policy and regulatory tables. By choice,
14 we do not accept financial support from drug or device
15 manufacturers. We submitted lengthier comments to the
16 docket. But we just want to raise up three key points.

17 The first is that we don't believe that the
18 current overreliance on the post-market research and
19 review is sufficient to determine if drugs are safe for
20 a diverse population. First of all, the FDA's adverse
21 event reporting system only captures a fraction of the
22 actual number of adverse events that occur.

1 Additionally, drug companies do not fulfil
2 post-market research requirements in a timely manner,
3 if at all. Overall, the number of post-market studies
4 with delays doubled between 2009 and 2011.

5 Flibanserin is a recent example of a drug
6 mentioned earlier, a female sexual dysfunction drug,
7 that was approved two years ago despite serious safety
8 concerns when the drug was mixed with alcohol.
9 Therefore, the FDA required three follow-up post-market
10 clinical trials to determine if indeed the mixture with
11 alcohol was a serious safety risk.

12 But the three clinical trials, one of which
13 was supposed to be completed in December of 2016, are
14 still listed on the FDA website as pending, meaning
15 that they have not begun.

16 The safety of women and people of color should
17 not be dependent on the incomplete reporting systems or
18 an industry which can choose to delay or ignore the
19 FDA's post-market requirements.

20 Secondly, to ensure that a drug is safe, we
21 need to have great inclusion of women and people of
22 color in clinical trials in the premarket review stage.

1 And third of all, we encourage the FDA's effort to
2 incorporate patient perspectives into the drug approval
3 process.

4 But we encourage there to be transparency
5 about the financial support that patients are receiving
6 that bring them to the table and encourage there to be
7 transparency for drug reviewers to know when
8 pharmaceutical companies have funded patient testimony
9 at public meetings.

10 In closing, we call on the FDA to make sure
11 that the drug approval process is safer for women and
12 people of color by addressing these concerns. Thank
13 you so much for the opportunity to speak today.

14 MR. THOMPSON: Thank you, Caila. And next, we
15 have James Valentine.

16 MR. VALENTINE: Thank you, Graham. Good
17 afternoon. My name is James Valentine and I'm an
18 associate at Hyman, Phelps & McNamara. While I've
19 worked with eight of the nine patient communities that
20 will have hosted externally led PFDD meetings through
21 the end of this month, I'm here today providing
22 comments on behalf of just one of those clients, the

1 Myotonic Dystrophy Foundation.

2 On September 15, 2016, the foundation held the
3 first ever externally led PFDD meeting under FDA's new
4 letter of intent process, which brought together over
5 200 community members. As FDA is probably aware from
6 the PFDD meetings it's hosted, the PFDD meeting took
7 many months to plan and required a considerable
8 resource investment by the foundation to pull off a
9 meeting of this magnitude.

10 MDF was happy to do so, knowing this meeting
11 would help to establish the therapeutic context for
12 myotonic dystrophy. According to PDUFA V, this was the
13 intent, as part of FDA's structured benefit-risk
14 framework, to have the PFDD meetings inform the first
15 two rows of the framework. Drafts of these two rows
16 are even included in the appendix of every voice of the
17 patient report.

18 This leads me to what I was asked to request
19 of you today. Given that FDA has passed the torch to
20 patient communities to host these externally led PFDD
21 meetings, the foundation would like to ask that FDA
22 commit to using these Voice of Patient reports to help

1 FDA reviewers establish the therapeutic context in
2 product approval decisions.

3 Such a commitment would include stating how
4 FDA will distribute these materials to relevant FDA
5 review staff. This would also include telling us, the
6 involved and affected patient communities, how
7 reviewers are being directed to use these materials.
8 For example, when filling in the structured benefit-
9 risk framework for a particular product, as a starting
10 point, should the first two rows be prepopulated with
11 the draft provided in the appendix in the Voice of the
12 Patient report?

13 In addition, we hope that for each new drug
14 approval, the agency will commit to tell us how PFDD-
15 related materials, including the Voice of the Patient
16 report and the draft benefit-risk framework, are used
17 in each individual drug review, something that would be
18 consistent with its requirement under the 21st Century
19 Cures patient experience data provision.

20 This will allow patient communities to assess
21 to what degree their efforts are making a difference in
22 drug development and review. I should note this is not

1 a onetime determination for each patient community.
2 For example, earlier this month, MDF hosted a follow-up
3 session at its annual meeting to do a deeper dive in
4 CNS-related symptoms to supplement the information
5 generated at its initial PFDD meeting.

6 In closing, thank you again for the wonderful
7 opportunity to host the first externally led PFDD
8 meeting and to share our thoughts about the use of
9 PFDD-generated information in benefit-risk decisions.
10 We hope we can be a resource to you as you consider
11 these issues in the future. Thank you.

12 MR. THOMPSON: Thank you, James. Next, we
13 have Angela Lundberg.

14 MS. LUNDBERG: Hi. My name is Angela Lundberg
15 and I traveled from Minneapolis, Minnesota at my own
16 expense to share my perspective as a patient with you
17 today. Thank you for giving me the opportunity to do
18 this.

19 I have been harmed by antidepressant
20 medication and I was not warned of the risks before
21 taking it. In 2015 and 2016, I was prescribed SNRI
22 antidepressants. I was not depressed or anxious when I

1 was first prescribed these drugs. However, the first
2 SNRI made me feel anxious. So my doctor recommended
3 that I switch to a different SNRI, Effexor. And that's
4 what I did.

5 After about a month of switching to Effexor, I
6 was suddenly hit with severe anxiety, agitation, panic,
7 restlessness, insomnia and feeling like I was jumping
8 out of my skin. I was also -- oh, I had extreme
9 obsessive thoughts and fears racing through my head
10 constantly. I was severely depressed for the first
11 time in my life and sobbing uncontrollably for no
12 reason. I also felt as though my head wasn't attached
13 to my body, like I was having an out-of-body
14 experience.

15 Looking back, I think I was experiencing
16 something called akathisia. It's a known side effect
17 of antidepressant drugs. I also had suicidal thoughts
18 for the first time in my life. And for the first time
19 in my life, I went to the psychiatric ER because what I
20 was experiencing was so unbearable. Luckily, I was
21 able to find a psychiatrist quickly to help me safely
22 stop taking the drug.

1 Months of my life were stolen by these drugs.
2 While I had the adverse reactions, I couldn't work. I
3 couldn't drive. I couldn't leave the house. I
4 couldn't even be upright for several weeks. The only
5 thing -- the only reason I was able to hang on and not
6 hurt or kill myself was I kept telling myself it's not
7 you, it's the drugs. It's not you. It's not you.
8 Hang on.

9 Even after tapering off of Effexor, it took a
10 long time to feel like my normal self again. This was
11 a terrifying experience and the worst thing that has
12 never happened in my life. If I had known that this
13 could happen, I never would have taken these drugs.

14 I know now patients that are desperate for
15 treatments and are willing to take a risk, or they
16 think they are. But it isn't until your life is turned
17 upside-down by a terrible adverse reaction to a drug
18 that you realize that even a small chance of a risk can
19 happen to you.

20 MR. THOMPSON: Angela, can you provide some
21 concluding thoughts?

22 MS. LUNDBERG: Sure. I just want to say

1 please keep in mind that patients deserve safeguards.
2 We need to be able to trust the FDA to make sure the
3 benefits outweigh the risks for the drugs that the FDA
4 approves and that patients know exactly what these
5 risks are. I almost lost my life because of a drug and
6 I don't want anyone else to suffer that way. Thank
7 you.

8 MR. THOMPSON: Thank you, Angela. Now, we
9 have Jon Furman.

10 MR. FURMAN: Hello, everybody. Jon Furman
11 again. Don't have any conflicts of interest. It looks
12 like I'm about to talk about what it looks like when
13 things go wrong, when things go badly. Specifically,
14 what can quinolone antibiotics teach us about risk-
15 benefit assessment?

16 My experience with this class of drugs, I was
17 first given this -- one of these drugs in 1999 and
18 quickly developed neuropathy, chronic fatigue and
19 bizarre central nervous system issues, including pretty
20 much what you just heard from the previous speaker.

21 The doctors, my PCP, specialists couldn't
22 diagnose what was happening. They had no idea what was

1 going on, couldn't tell me anything. Subsequently, I
2 was given more quinolones, five times over the next 13
3 years. Each time, my conditions worsened. And I
4 personally didn't put it all together until 2012.

5 Unfortunately, some things have gotten better
6 and some of the symptoms are permanent. So I've had to
7 learn how to deal with them. I've talked to -- since
8 2012, I've talked to hundreds of people personally that
9 this has happened to with these same drugs. Usually
10 their doctors didn't catch it either. Some of these
11 people later on died from their condition. Often
12 suicide was what they chose to be the final answer
13 there.

14 So we have a situation with an entire class of
15 drugs and you've got to ask how many people have been
16 affected by this and didn't even know what hit them.
17 I'm thankful that the FDA has update warning labels on
18 all quinolones in the past couple of years to something
19 that's close to appropriate. It looks a whole lot
20 better than it did in the past. Some of the
21 information is there.

22 But these drugs were on the market for 20-plus

1 years before that happened. When the FDA recently
2 updated the warning label, they also created a term,
3 FQAD, which stands for fluoroquinolone-associated
4 disability, which indicates both disability and a long-
5 term nature, if not permanency of the effects of these
6 drugs.

7 So a couple of thoughts on this. The FDA,
8 when it came to quinolones, did not do a good job
9 premarket or post-market on risk analysis. These drugs
10 became very commonly used drugs. And as they became
11 commonly used, they became first-line antibiotics when
12 they were really never intended to be used that way.
13 They were supposed to originally only be used when
14 other drugs failed.

15 MR. THOMPSON: Jon, can you give us some final
16 thoughts?

17 MR. FURMAN: Well, sure. Glad to do that.
18 The situation with quinolones indicates to me a
19 catastrophic disaster essentially of risk-benefit
20 analysis. It's come to my attention that when the FDA
21 indicates a drug is safe, and I know there's some
22 complexities in how that happens, that that's generally

1 believed. Risks, on the other hand, are often ignored
2 by prescribers.

3 So it is very important that the FDA get risk
4 assessment right as quickly as possible and as
5 completely as possible. And you know, a final thought
6 here. You know, I remember there was a slide earlier
7 about creating a moonshot-type framework for risk-
8 benefit analysis. And you know, I'd like to advise
9 that that's admirable. But we want to avoid equally a
10 Titanic-type situation. So please proceed carefully.
11 Thank you.

12 MR. THOMPSON: Thank you, Jon. Next, we have
13 Kristen Hsu.

14 MS. HSU: Hi. My name --

15 MR. THOMPSON: You can hold it. That's fine.

16 MS. HSU: My name is Kristen Hsu and I'm here
17 on behalf of the Amyloidosis Research Consortium. The
18 ARC is a patient-led organization founded in 2015 with
19 the vision to make material and significant
20 contribution to the curability of amyloidosis.

21 Amyloidosis is a group of rare, misfolded
22 protein diseases that are progressive in nature and

1 fatal. There are currently no FDA-approved treatments
2 for any type of amyloidosis. But the landscape is
3 changing and this is a really exciting time. There are
4 a number of companies with products in late-stage
5 development and additional products underway.

6 However, with the risks of the difficult
7 environment that come with rare diseases, these
8 treatments cross multiple divisions. There is
9 generally a lack of understanding of the natural
10 history of the disease and an unclear benefit-risk
11 framework with few clinical endpoints and considerable
12 uncertainties. The value proposition is a concern for
13 a number of companies developing products.

14 To help with this, ARC organized an externally
15 led patient-focused drug development meeting in
16 November of 2015 and we quickly submitted a Voice of
17 the Patient report shortly thereafter. These efforts,
18 we believe, are critical to understanding the disease
19 and the needs of the patients.

20 The concern though is there's not yet a clear
21 directive or path on how these become ongoing tools
22 that will be embedded in the complex and detailed

1 review processes. The PFDD meetings, for example, are
2 immensely resource-intensive for a group like ours and
3 we hope that they have an ongoing impact beyond the
4 members of the FDA who we were grateful were able to
5 attend.

6 Similarly, with the Voice of the Patient
7 report, understanding how and where that document fits
8 in with the review process and whether there are
9 opportunities to ensure that they don't become outdated
10 as the landscape evolves and that they can be updated
11 and used as part of the review process and also that
12 there be an online repository for any externally
13 submitted documents like ours.

14 We think this is a critically important
15 program and we applaud the FDA for the care with which
16 it's been implemented. We hope there will be
17 additional opportunities for groups like ours to engage
18 further and ensure that these efforts have longevity
19 and impact within the benefit-risk framework.

20 MR. THOMPSON: Thank you, Kristen. Next, we
21 have Jack Mitchell.

22 MR. MITCHELL: Thank you for the opportunity

1 to speak today. I'm Jack Mitchell, director of health
2 policy for the National Center for Health Research.
3 NCHR provides objective research information and
4 promotes public health and legislative policies on
5 behalf of patients and consumers. We accept no
6 pharmaceutical or medical device industry funding. So
7 I have no conflicts of interest to report.

8 NCHR would like to commend FDA for holding
9 this day-long panel on the progress of benefit-risk
10 analysis, which is ultimately the foundation of all the
11 agency's regulatory decisions. We've heard today from
12 a variety of experts, both inside and outside the
13 agency, about FDA's efforts over the past eight years,
14 which have produced some very positive outcomes for
15 drug reviewers, industry stakeholders and patients
16 alike.

17 However, we are here today to ask for even
18 more attention to be directed to the patient
19 perspective in this critical benefit-risk decision-
20 making. I'm not a clinician. But as a former FDA and
21 HHS official and as a senior Senate committee
22 investigator overseeing public health issues, as well

1 as with my current role at NCHR, I've heard from a
2 significant number of patients from different
3 perspectives over 25 years.

4 It's truly disturbing how often patients who
5 have been harmed by a drug or medical product have felt
6 a sense of betrayal because they believed, fairly or
7 not, that they had counted on FDA to ensure that
8 medical products are safe and effective and that they
9 had been fully informed of the risks involved.
10 Unfortunately, safety information is far from fully
11 known when many drugs and medical devices are approved.

12 As we know, patients don't often fully
13 understand these risks, if at all. While those who
14 follow FDA know differently, many patients assume that
15 when an FDA advisory committee recommends an approval
16 and FDA agrees and signs off, the medical product is
17 safe without reservation or condition. Often, of
18 course, that is not the whole picture.

19 Approvals and safety ramifications can be
20 hotly contested and disputed among different
21 knowledgeable experts who have equally good intentions.
22 Most patients -- and this is a medical device, not a

1 drug issue -- but most patients know very little, if
2 anything, about the 510(k) substantial equivalence
3 program which governs most medical device approvals.

4 Most patients have no idea that sophisticated
5 surgical implantable devices are approved with very
6 little clinical evidence or human trials, nor do they
7 know that five year ago, the Institute of Medicine, now
8 part of the National Academy of Sciences, recommended
9 in a detailed report that the entire 510(k) process be
10 scrapped as it was unable to established safety and
11 effectiveness. FDA turned down that recommendation,
12 with minor changes to 510(k), which is still the
13 governing -- the main governing medical device approval
14 system.

15 FDA must also always remember its critical
16 role as a voice for patients and to ensure that
17 clinical trials are large and diverse enough to
18 evaluate risks on a premarket basis wherever possible.
19 We also ask that FDA do a better job in enforcing the
20 completion of required post-market studies, which too
21 often are frequently agreed to, but not initiated, let
22 alone finished.

1 The near-term elevation of the patient
2 engagement can be a watershed event and an opportunity
3 to amplify the voice of patients both within the agency
4 and publicly. Patients, after all, are the primary
5 underlying reason you are doing benefit-risk analysis
6 in the first place. I thank you for your time and
7 attention.

8 MR. THOMPSON: Thank you, Jack. And our last
9 speaker will be Benjamin Craig. It looks like Benjamin
10 has left. Going once, going twice? All right. We'll
11 now move to some closing remarks from Theresa Mullin.

12 CLOSING REMARKS

13 DR. MULLIN: Well, it's been a long day. So I
14 could just say thank you and let it go with that. But
15 I guess I would like to try to give you a brief
16 summary, a quick summary of what we've been hearing
17 today. First of all, I do want to thank you for coming
18 to this meeting, especially those of you who have come
19 from far away to share your perspectives with us today
20 and for those of you on the phone.

21 And we've just heard a lot and learned a lot
22 in this meeting. And I'll just try to not do justice

1 to it, but try to cover some of what I think are the
2 highlights based on my notes.

3 And the day began with Rich Moscicki going
4 over -- you know, kind of setting the stage here for us
5 that this is -- our benefit-risk assessment is really a
6 part of our public health function. We regulate drugs,
7 devices and biologics, at least on the medical products
8 side. We don't regulate the practice of medicine.

9 So what we can do is try to determine whether
10 products are safe and effective for their intended use.
11 And I think what this framework is supposed to be doing
12 is helping us. And it is helping us communicate better
13 that benefit and risk.

14 We have heard from speakers today that there
15 are ways to make that even more effective and
16 accessible as a source of information to prescribers.
17 And we heard from Dr. Hammad earlier today about the
18 importance -- we're working way upstream of what some
19 people are thinking of, which is the point of care.
20 And so, you know, we need to work -- continue to work
21 on making this information even better presented.

22 We heard from Mary Thanh Hai about how we've

1 been looking at this framework to see how well is it
2 working for those purposes of organizing our thought
3 with a lot of -- you know, it's millions of pages
4 actually of information that often go into these
5 assessments. How does it help us to weigh all of that
6 information and try to communicate and distill a
7 decision from it?

8 We heard from Valerie Overton. She works at
9 ERG, that her evaluation, and including all of those
10 interviews and all of those applications show that it
11 is overall positive. It is being pretty effective in
12 terms of how it's communicating the information.

13 And then, we heard about the ICH experience
14 and how the information has helped there. Now we have
15 a fairly standardized structure for sponsors, drug
16 sponsors to use to submit that information to support
17 this kind of approach to assessment.

18 At the EMA, they're taking an even further
19 structured approach and they're trying to figure out
20 now how to even go after the different types of
21 uncertainty that are involved in our decision-making
22 and to try to deal with those in a very productive

1 manner.

2 Swissmedic told us about -- Clause was telling
3 us how they practically approach the benefit-risk
4 assessment in our post-trust society and the challenges
5 that are presented by that.

6 In addition to Tarek confirming that the
7 structured benefit-risk approach was, I think, as he
8 put it, a no-brainer in terms of how useful it was, he
9 did raise a variety of other methodological,
10 philosophical and practical concerns that I think would
11 keep us busy for perhaps the next 10 years and well-
12 employed in that work.

13 Becky Noel told us we needed to keep pushing
14 the benefit-risk framework to be further used and
15 integrated into the approaches that we take at the
16 agency as well as what's being done by industry. And
17 how do we make sure there's good connection between all
18 of these efforts that could be siloed if we're not
19 careful?

20 And then, we heard from another colleague in
21 the Center for Biologics, Jeff Roberts, telling us
22 about how he's been using the framework for vaccine

1 decision-making, which has a very sort of different
2 approach to benefit-risk acceptability. And the
3 framework seems pretty robust for the internal
4 regulatory decision-making for that purpose as well.

5 And then, we had an afternoon session where we
6 did talk more about the patient-focused drug
7 development and the patient-centered efforts that the
8 various centers are employing, which we consider to be
9 pretty complimentary, very much a work in progress.

10 We would agree that nothing is happening as
11 quickly as we would like it to. But there is so much
12 to be done and we want to do it right. So it's going
13 to be a little frustrating in terms of how long it
14 takes us to get good tools in place that we can use, we
15 can use correctly and reliably and transparently and we
16 do move things forward.

17 As Brett Hauber put it, there are a lot of
18 tools in the toolbox. But we need to understand how
19 they work and where they're appropriate and how they
20 might work best.

21 Leah McCormick gave us more information about
22 the Psoriasis Foundation's experience and how far

1 they've been trying to go to help look at that
2 heterogeneity across a population because that's very
3 important in understanding what the views and what's
4 most important to a population.

5 And then, Alicyn Campbell talked more about
6 the use of the benefit-risk framework in the context of
7 oncology and the importance of that holistic approach,
8 not only looking at benefits, but also making sure you
9 integrate into that burdens or risks. And she raised
10 the question about what kind of patient-focused
11 information is really relevant to the patients. And is
12 it time to start thinking about a patient-oriented
13 label and presented a presentation of that information.

14 And then, in our last panel, Baruch Fischhoff
15 gave us an overview of key methodological
16 considerations and the pitfalls in a lot of these
17 judgment tools and approaches and what we need to be
18 trying to keep in mind as we go forward to evaluate
19 critically and report candidly, which I like very much.

20 Rich Forshee talked about benefit-risk being
21 complex and iterative and it involves a lot of
22 participants. And that's still true at FDA. It's been

1 true all along and maybe getting more complex. We
2 don't need to use quantitative methods for all
3 decisions. But there may be a subset where it really
4 is helpful to explore uncertainties and do sensitivity
5 analyses around our decisions, not just for premarket
6 review but for other public health decisions that
7 regulators have to make as well.

8 And then, Steve Woloshin and Lisa Schwartz
9 seamlessly -- amazingly seamlessly, actually -- made a
10 presentation showing us how they think this information
11 is very valuable.

12 But they had some ideas for how we can make it
13 better and how we can make it more accessible and maybe
14 make it more available so that the primary care doctor,
15 as well as the specialist can have access to the kind
16 of risk information that FDA puts into its reviews. So
17 that can continue to make its way into the points of
18 care so that that's well-understood and maybe made more
19 accessible to patients.

20 And then, we heard from Bennett telling us
21 about how we might better -- they use the information
22 to better organize their thoughts and distill

1 information within their companies. And they're
2 looking forward to how we're going to be integrating
3 this into our guidance in a few years.

4 And Pete talked about the value of benefit-
5 risk as a communication tool. Not all decisions
6 probably require that I think is the view you generally
7 hear from us here, but that maybe 10 to 15 percent of
8 decisions really do warrant that extra work to try to
9 work up and put all the assumptions on the table and
10 that effort to get all the assumptions out there and
11 maybe extrapolate and look at benefit-risk out in the
12 indicated population is worth our doing. And to have
13 the tools to do it.

14 And finally, I'll just say Clause then warned
15 us about not to make the benefit-risk framework into a
16 Swiss Army knife that had too many features and
17 functions and just to really focus on a few key
18 features that are the ones you're going to use all the
19 time, structuring decisions, thinking about that, maybe
20 looking at a balanced scorecard methodology to try to
21 bring information together in kind of a simple
22 structure.

1 And then finally, I think Baruch ended with
2 concern about the potential for abuse of these methods.
3 And I'll just end with telling you that when we were
4 talking about these commitments, the patient-focused
5 commitments and other PDUFA VI commitments to the
6 energy and commerce committee staff, you know, maybe
7 months ago it seems at this point, but it was for the
8 purpose of this reauthorization.

9 We got questions from the congressional staff
10 about these methods and weren't we concerned that it
11 could be used to manipulate patients' perspectives and
12 that inappropriately and that we would -- the method
13 would be used inappropriately. Companies would do
14 things that weren't appropriate.

15 And all we could do was reassure them that
16 regulators are the most skeptical people that at least
17 I've never met. They hardly believe anything you tell
18 them. And they are definitely going to be very
19 skeptical of things that are submitted.

20 And I think that they're going to worry about
21 model opacity and they're going to worry about too much
22 clever use of -- they're going to be very concerned.

1 And so, that's why we're taking the time to make sure
2 that what we're doing is the right way to do it and
3 that the reviewers all know it.

4 So this capacity-building idea and getting the
5 information out within the agency is we think critical
6 to move this forward because we're not going to accept
7 anything that doesn't look right and that we can't open
8 up and look inside of and make sure it works properly
9 so that we can assure patients -- we're doing the right
10 thing for patients.

11 So on that note, I'll let you all go home and
12 thanks very much again for coming here today.

13 (Applause.)

14
15 (Whereupon, the foregoing adjourned at 5:10
16 p.m.)

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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
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I, BENJAMIN GRAHAM, do hereby certify that this transcript was prepared from audio to the best of my ability.

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September 27, 2017

DATE

BENJAMIN GRAHAM

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