U.S. FOOD & DRUG ADMINISTRATION

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Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA's Office of New Drugs

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KEITH FLANAGAN: Okay. Good morning everyone. My name's Keith Flanagan. I'm the director of the office of new drug policy, in the office of new drugs and I'll be serving as one of today's moderators. Dr. Jim Smith, raise your hand -- is deputy director of the division of clinical policy, in the office of new drug policy. He will also serve as a moderator today.

This meeting is an opportunity for stakeholders to make specific, actionable suggestions, where policy clarity or scientific discussion could promote effective drug development. This is a particularly opportune time for this meeting, as OND is currently in the process of reorganization.

You will see some divisions represented in front of you that just stood up this week, and others who are in a state of transition. We expect this reorganization will further strengthen our review functions and we're excited to have the participation of both longstanding and new division directors. If you were unable to register in advance to speak today, you can share your views by submitting a written

comment to the docket, which will remain open through January 7, 2020. For your reference, the docket number is FDA-2019-N-3453. And the docket can be accessed at www.regulations.gov. We have a full day today. Before getting started, I'd like to briefly go over some logistics that will help keep the meeting running efficiently.

If you haven't already done so, please sign in at the registration desk, so we can send any follow-up information after this meeting. Also, if you're presenting today, please make sure you have signed in. This will help keep us on track. Today's agenda includes a fifteen-minute break this morning, a one-hour lunch break, and a fifteen-minute break in the afternoon.

We ask that you return promptly from the breaks and lunch, so that the 28 registered speakers can fully utilize their allotted time. If you are ordering lunch, you'll need to place your lunch order and pay at the lunch kiosk by 10:00 AM. The cost of a lunch box is $11, cash or credit. Each lunch box contains an apple, chips, cookie, bottled

beverage and a sandwich or salad of your choice. Keep your payment receipt, as you'll need to show it when picking up your food at lunch time. For any members of the media present, FDA press officer Nathan Arnold is available to help you. Nathan, please stand up and identify yourself. Please direct all media questions to him. The Wi-Fi network name and password are available at the registration desk.

With respect to the agenda, the times listed on the agenda are approximate. If we finish one session ahead of schedule, we'll move right into the next part of the agenda. Registered speakers should keep track of how the meeting is progressing, to be sure that they are ready when it is their turn to present. Following our opening remarks and introduction to the panelists, we will have public presentations that represent a variety of perspectives across a range of topics pertaining to effective drug development.

These presentations are organized into four sessions to provide opportunities for breaks and lunch. The sessions are not limited to a particular

topic. Regarding ground rules, we respectfully ask that each presenter limit their remarks to the time you have been allotted. If the moderators need to ask you to wrap up, please conclude as quickly as possible, so that we may remain on schedule. No participant may interrupt the presentation of another participant. After each presentation, the panel may have a minute or two to ask questions of the presenter. Therefore, I ask that each presenter remain at the podium after your remarks to allow the panel this opportunity.

Only the panel may ask questions after the presentations. I will announce the first speaker of each of the four sessions, but not the subsequent ones. So, please approach the podium when the slide that lists your name and affiliation appears on the screen. After presentations from the first session, we'll take a fifteen-minute break. Then speakers from the second sessions will present. Session two will followed by lunch from about 12:15 until 1:15.

After lunch, we'll hear presentations from session three. Those presentations are followed

by a fifteen-minute break, and then sessions four. After the presentations, I'll make brief closing remarks to adjourn the meeting. The record of this meeting will be transcribed. So, please remember to use the microphone when speaking. The transcript will be accessible through regulations.gov, in the website for this public meeting, in about thirty days. Any comments that aren't presented today can be submitted through regulations.gov, using docket number, again, FDA-2019-N-3453. With that, I'd like to thank Dr. Patrizia Cavazzoni, deputy center director, for being here today, and invite her to the podium to deliver opening remarks.

PATRIZIA CAVAZZONI: Good morning and welcome to this public meeting, which, as you have heard from Keith Flanagan, will be first and foremost a listening session. FDA is currently engaged in multiple, high priority initiatives to facilitate effective drug development. What do we mean by effective drug development?

These are development programs that leverage best available scientific knowledge to

characterize the benefit risk of a drug and generate the data necessary to support product approval while maintaining FDA's regulatory standards. This meeting is an opportunity for OND division leadership to receive input directly from the public. As you can see today, we have representation across the OND review divisions. This endeavor aligns with other ongoing efforts to modernize the new drug review program, as is it supports the scientific leadership of the OND review staff and provides a venue for OND review division leaders to hear directly from stakeholders.

Our purpose is to solicit specific actionable policy suggestions for the OND review staff. We are particularly interested in efforts that can be implemented in the near term and that cut across multiple therapeutic areas. A note about the fact that there are current, ongoing, separate initiatives around real world evidence and patient focused direct development, so these topics are not going to be the focus of this meeting.

Topics that are of particular interest

today and where we would like to hear from the public include input on where OND can provide additional guidance or prioritize scientific discussion to improve clarity and encourage effective drug development. In other words, how can we promote effective drug development across the wide variety of products we regulate? There have been many advances in the field of medicine with respect to discovering the underlying and molecular underpinning of disease, thereby enabling precise targeting of drugs. But these advances have not permeated all areas of medicine. We would like to hear from the public on how OND could facilitate drug development for diseases not currently amenable to targeted therapies.

We have seen a rise in the implementation of novel trial designs, such as master protocols, particularly among programs for serious and life-threatening diseases like cancer. We are interested in stakeholders' views on the advantages and disadvantages of extending these innovative approaches to additional therapeutic areas.

There is already a portfolio of FDA

guidances addressing drug development issues, not specific to a particular disease or indication. We want to hear whether stakeholders have experienced variable implementation of these guidances across the office of new drugs and across review divisions in a way not explained by case-specific features. Are there specific areas where additional clarity on the agencies current thinking is needed? Novel approaches can bring additional uncertainty. How could the office of new drugs promote effective drug development programs in the face of the tension between encouraging innovation and relying on existing regulatory precedent? I look forward for today's discussion and I would like now to call Keith Flanagan back to the podium.

KEITH FLANAGAN: Thanks, Dr. Cavazzoni. Now I would like to ask our panelists to introduce themselves, starting with Dr. Smith, please.

JIM SMITH: My name is Jim Smith. I am the acting deputy director of the division of clinical policy in the office of new drug policy. And as Keith mentioned, I'll be one of the moderators for the

session.

NIKOLAY NIKOLOV: Morning. My name is Nikolay Nikolov. I'm an associate director for rheumatology, in the division pulmonary, allergy and rheumatology products.

WILEY CHAMBERS: I'm Wiley Chambers. I'm representing ophthalmology.

SHARON HERTZ: Sharon Hertz, director of the division of anesthesiology, addiction medicine and pain medicine.

HARPREET SINGH: Harpreet Singh, acting division director of our division of oncology products two, which houses thoracic and head and neck malignancies, as well as CNS, cancers, rare tumors and pediatric malignancies.

THERESA MICHELE: Hi. I'm Theresa Michele. I'm the division director for non-prescription drug products.

LOUIS MARZELLA: Good morning. I'm Lou Marzella. I'm the director of the division of medical imaging products.

SHARI TARGUM: Good morning. I'm Shari

Targum. I'm associate director for biosimilars, in the division of dermatology and dental products.

HYLTON JOFFE: And I'm Hylton Joffe. I'm the director of the division of bone, reproductive and neurologic products.

LYNNE YAO: Good morning. My name is Lynne Yao. I'm the director of the division of pediatric and maternal health.

DRAGOS ROMAN: Good morning. My name is Dragos Roman and I'm the acting division director for the division of gastroenterology and inborn errors products.

OZLEM BELEN: My name is Ozlem Belen and I'm the acting division director for the division of transplant and ophthalmology products.

LISA YANOFF: Good morning. I'm Lisa Yanoff for metabolic endocrine products.

TIFFANY FARCHIONE: Tiffany Farchione, acting director for the division of psychiatry.

NICHOLAS KOZAUER: Good morning. Nick Kozauer, acting director of division of neurology two.

ERIC BASTINGS: Good morning. Eric

Bastings, acting director, division of neurology one.

ANN FARRELL: Ann Farrell, division director of division of hematology products.

ANGELO DE CLARO: Angelo De Claro, acting division director, division of hematologic malignancies one. We handle acute leukemia, MDS, CML and drug products for hematopoietic stem cell transplantation.

NICOLE GORMLEY: Hello. I'm Nicole Gormley. I'm the acting division director for the division of hematologic malignancies two. And we regulate and handle products related to CLL, non-Hodgkin's lymphoma and multiple myeloma.

STEVEN LEMORY: Steven Lemory, acting director of the division of oncology products three. We handle GI malignancies and melanoma sarcoma.

JULIA BEAVER: Julia Beaver, director of division of oncology one, which handles breast, genitourinary malignancies and GYN malignancies.

DEBRA BIRNKRANT: Debbie Birnkrant, director, division of antivirals.

SUMATHI NAMBIAR: Good morning.

Sumanthi Nambiar, director of division of anti infectives.

KEITH FLANAGAN: Thank you. The panelists are here to listen to the views of the public. They will in listen-only mode. However, as I mentioned previously, they will have the opportunity to ask question following each presentation if they choose. I thank the division directors for their participation today and salute their collective scientific leadership. Also, thanks very much to Drs. Woodcock, Stein and Temple -- Bob, wave -- for their continuing engagement.

It's now time to begin the public presentations, starting with Session 1. Again, I'll announce the first speaker, but not subsequent ones. So please approach the podium when the slide that lists your name and affiliation appears on the screen. After your remarks, please remain at the podium to allow the panel an opportunity to ask questions.

The first speaker for Session 1 is Peter Pitts, President of the Center for Medicine in the Public Interest. Mr. Pitts?

PETER PITTS: Good morning. My name is Peter Pitts, Center for Medicine in the Public Interest.

Opportunities and priorities for FDA's Office of New Drugs, yes, please. Very timely. I am very honored to be here this morning.

Enthusiasm is common, but commitment is rare. Per the FDA, "Modernizing our operations helps us perform our mission effectively in an environment of rapidly-evolving science, changing stakeholder expectations, and new statutory authorities and responsibility." So I guess from the beginning, we recognize that the words that are being spoken are accurate; the question is how do we actually make them happen? How does the rubber meet the road? Because the status quo is a harsh mistress. And nowhere is that more true or more dangerous or more interesting than when it comes to medicine's regulation.

What senior agency management says publicly about the value and urgency of regulatory innovation has yet to permeate through its review divisions. This disconnect is causing a lack of faith

within the broader healthcare ecosystem that FDA can be a potent ally in advancing patient access to new and important medical technologies. That is not a good thing. Faith must be restored and reinforced. And there must also be a similar review of the disconnect between the pronouncements from the upper echelons of the biopharmaceutical industry and the actual research and development programs undertaken by their companies.

In short, that means blaming the FDA for everybody's problems is really not the best way to move things forward. We can all make things better. Don't place the blame; fix the problem.

Part of the solution is increasing regulatory velocity through this reorganization of the Office of New Drug Policy. The 21st century FDA requires greater regulatory certitude. In other words, that similar situations are treated in similar ways within divisions and across divisions. And this new policy function, the new OND policy function, can help enhance the knowledge and comfort of reviewers so that new initiatives such as real world evidence, basket

trials, adaptive clinical trials, master protocols, synthetic trials, and so forth, are more regularly accepted as part of the FDA review process. Accepting change is difficult. More difficult for some than for others.

And this means nothing less than accelerating an OND-wide review of the current and dangerous stasis of the regulatory status quo.

The most potent way that FDA can enable innovation is by being a partner in advancing new approaches to both drug development and regulatory science. And this begins at the conceptual policy level. Regulatory ambiguity does not instill confidence in an already high-risk development environment.

The OND policy shop as being reconfigured must be able to provide closer coordination between senior agency leadership views on advances in regulatory science and those of divisional line reviewers.

In some respects this new office could act as a translator, as a MapQuest to new ways of

approaching regulatory science.

Regulatory velocity means generating heat rather than light. The intent is to provide greater consistency and nimbleness regarding the appropriateness of new tools and techniques for drug developers. This is as much a scientific issue which we'll discuss today I'm sure, as it is one of social and cultural calibration across therapeutic review divisions.

Sometimes even brilliant scientists have a hard time viewing new ideas without being threatened by them. This is human nature, and it's as true for reviewing drugs as it is every place else. That's got to change. That has to be addressed, it has to be acknowledged, it has to be fixed. The FDA has to be a leader in regulatory science. The science of developing new tools, standards, and approaches to assess safety, efficacy, quality, and performance through true expertise and leadership rather than for simply being the FDA. Having the badge doesn't necessarily make you the expert. This is a collegial approach that everybody's got to participate in. FDA

can be first among equals and lead, and I believe that's the appropriate role to take.

Let me share with you five ways to achieve regulatory velocity. It begins with a general review of the current and danger of stasis of the regulatory status quo. And let me give you five things that we can do right now. We have to address the dangers of heterogeneous approaches to regulatory policy and the need for closer coordination between senior agency leadership views on advances in regulatory science and those of divisional line reviewers. Press releases saying all the right things and exciting lots of people isn't the same thing as making it happen on the divisional review level.

Again, the need for greater regulatory certitude that similar situations be treated in similar ways. When you have that disconnect, it scares developers away from investing in newer, more exciting, riskier programs.

Three, the need for additional resources for and better training of divisional review staff in new regulatory science techniques. We can't

assume that just because the science is out there, that FDA review staff at any level, at every level really knows how to work with that information. The need for more flexible approaches to agency-sponsored communications that does not compromise review integrity or sponsor resources. Past PDUFAs have called for more and more regular meetings, and that's happened. There's a backlog. It's got to be addressed. We don't need just more communications; we need better communications, we need flexible communications. Not just meetings, but phone calls and emails. How can we use technology, how can we be smarter in the use of time?

And again, let me repeat, the need for additional resources for and better training of divisional review staff in regulatory science techniques. This doesn't happen for free. This requires resources, it requires time. This is a PDUFA conversation.

Our FDA initiative is behind the eight ball. Well, everything starts with policy predictability. Back to the OND Office of New Drugs.

The best way to avoid resistance to change is to try to uncover it before implementing that change. The FDA's reorganized Office of New Drug Policy can act as regulatory MapQuest for advancing regulatory science. Is this achievable? Signs point to yes. Thank you very much.

JIM SMITH: Thank you very much, Mr. Pitts, for your presentation. We have a question from Dr. Marzella.

LOUIS MARZELLA: I wonder if you could elaborate on the need for improved communication. What specifically do you see as the most critical needs that need to be addressed?

PETER PITTS: I think the most critical need to be addressed is not allowing programs to mire within the review process because of untimely communications. I'm not saying that we want to do away with process. Process is urgent. But I think a greater nimbleness in providing feedback, on straightforward questions, even though it remains obviously non-binding advice, it's certainly something that should be investigated. There are too many times

that I've heard from sponsors that requests for communications on relatively straightforward questions are delayed when a full meeting isn't really necessary. So I think a more flexible approach to that type of communication is called for.

WILEY CHAMBERS: Can you give us an example of what you're talking about? What kind of timeframe would be an acceptable timeframe?

PETER PITTS: An acceptable timeframe for communications?

WILEY CHAMBERS: Correct.

PETER PITTS: I think that becomes a sponsor project manager type of situation. I think obviously if a sponsor wants a more detailed and profound conversation and to receive some type of feedback, more time is necessary. You can't get ten people in a room in 15 minutes. But if the sponsor determines they really just want a simple phone call with a specific person, I think that should be able to be arranged in a much more truncated manner. I don't know if I've got a specific day, week, two-week type of proposition, but I think generating a phone call

conversation through a project manager to stay within process certainly can be done you'd think within a week, two weeks on the outside.

SHARON HERTZ: You mentioned it would be non-binding. What exactly does that mean?

PETER PITTS: Well, that's a really good question. What does non-binding advice mean? Advice that you get from the agency obviously speaks to what the agency thinks is the right answer, but obviously it's within the sponsor's purview to do whatever they feel is best for their program. In my experience, non-binding advice is generally viewed as binding advice for those who want to make sure their programs move forward aggressively and in a positive direction. If the agency wants to move forward and say we're going to create non-binding advice and binding advice, that might be interesting, but I don't see that on the table. Non-binding advice I think is understood as being solid advice relative to agency thinking that the sponsor can take or not take.

SHARON HERTZ: And just one further question. You mentioned the desire to be able to

simply get somebody on the phone. How do you see that integrating with the sentiment you expressed on keeping things consistent within the agency if anybody can get on the phone with a sponsor at the sponsor's request?

PETER PITTS: Well, I don't think it's anybody. Obviously you want to make sure the person that the sponsor is speaking to is the appropriate person and doesn't speak out of school. You can have a meeting in person and have a solid conversation on a wide variety of issues. You can have a phone call with one or two persons and have a solid conversation on a much narrower level. And I think that's really what's being called for. If programs are being held up, if decisions are being held up on the sponsor level because of the lack of a that-sounds-right or that-doesn't-sound-right from the appropriate person within the appropriate division, I think that's something to consider.

JIM SMITH: And we'll take our last question from Dr. Bastings.

ERIC BASTINGS: You are calling for

additional resources. Can you elaborate on that? What sort of resources are you calling for?

PETER PITTS: Money. Let me be blunt. I think this requires funding. It requires federal funding. It requires a significant amount of federal funding. I think as we think about PDUFA, when you fund things through PDUFA, you get the money. But you also have measurements and goals. And I think an important point is if you don't measure it, it doesn't count. And I think the ability to measure how the agency is doing relative to new types of utility of new scientific tools or sponsored communications, I think that's something that would be smiled upon certainly within the development community. And I think that having better-trained staff on the FDA side and new scientific techniques is absolutely essential. Because minus that, nothing happens, and the problem just gets worse.

JIM SMITH: Thank you very much for sharing your thoughts today, Mr. Pitts.

PETER PITTS: Thank you.

JENNIFER HAMILTON: Good morning.

Thank you for providing me the opportunity to speak with you today. My name is Jennifer Hamilton. I am Head of Precision Medicine at Regeneron Pharmaceuticals. And today we'd like to talk to you about novel applications of genomics data for innovative drug development.

So first we'll quickly review historical and current uses of genomics data in the drug development process. We'll talk about recent advances in the utilization of genomics in drug development, what we can learn from these new approaches and how ideas on how we might be able to use this information for regulatory decision making and labeling.

Today we'd like to focus on efficacy primarily. And at the end of this we'll be talking about how we can work together to brainstorm in a collaborative way on how we can advance our collective knowledge and recommendations for the utilization of genomics data in regulatory decision making and product labeling.

So the key message today is that

genetic information or genomic information should be more broadly utilized by the FDA as a component of the efficacy and safety evaluation of new drugs.

So how have we been using genomics data? We have been using genomics primarily for target identification and validation. We've been doing this for decades. This is done by genome-wide association studies, of cases versus controls, of family studies where diseases run in families.

As the technologies have advanced, it's led to the rise of the field of pharmacogenetics, which is the study of genetic variants and the association between drug safety and efficacy. As of yesterday according to the FDA website, there are now 387 instances of pharmacogenetics information being used in labeling.

So some examples of how we're using genomics in labeling are related to adverse drug reactions or lack of efficacy. For example, there are many variants in CYP genes related to absorption, distribution, metabolism, excretion. Just one example of this is that CYP2C19 is required for metabolizing

the clopidogrel prodrug to its active form. And so variants in the gene effect whether or not the drug is active, and therefore the efficacy of the drug.

There are also examples where variants have been associated with hypersensitivity, such as the HLA-B variants that have been associated with severe hypersensitivity reactions to abacavir.

As the field has evolved, we are now using genomics to select patients most likely to respond. Some examples of this -- this is not an exhaustive list. But some examples are when the target of the drug is a genetic mutation or variant. That patient has to harbor that mutation in order for the drug to be efficacious.

One example of this is the BCR-ABL fusion gene, which results in a mutant protein that drives chronic myelogenous leukemia and is the drug target for nilotinib.

Variants in non-drug target genes have also been associated with drug efficacy. For example, mutations in the RAS pathway, which is downstream of EGFR, affect the response to treatment of EGFR

inhibitors.

So what's new? So we have had just a tsunami of improvements in innovations in not only the wet lab, but the computational abilities to generate large amounts of human genomic information. And this is resulting in large databases of human genetic information that are already available and continue to grow.

In parallel, there's been a growth in high-quality, curated clinical data that's available from electronic health records. We link the two together to understand the genetic variants that are associated with that causative disease or increased or decreased risk for a particular disease.

So what's new about this? What's new about this is that the electronic health records provide an opportunity to evaluate the long-term clinical outcomes in patients who have a non-functioning variant of a target gene. The industry is already embracing this technology and using it, and it's growing more and more.

The current state, just a couple of

examples. GSK has partnered with 23andMe. Amgen purchased Ecogenetics, and the Regeneron Genetics Center has a large partnership with the Geisinger Healthcare System.

Just to give you an idea of the scope of these kinds of programs, this is another example where the Regeneron Genetics Center is leading a collaboration with UK Biobank as well as a biopharma consortium. As part of this collaboration, the Regeneron Genetics Center will be sequencing a half a million participants. And this is anticipated to be completed by the end of this year. So you can imagine what we can do with this kind of data.

So our hypothesis is that the genomics can qualitatively predict long-term, target-related efficacy and safety outcomes. So if a drug is truly mimicking the clinical phenotype that's identified in these genomics studies, the expectation is that it will recapitulate the clinical benefit that's also observed in these studies. This opens the door to use more and more biomarker endpoints as registrational endpoints and may also affect whether or not large

clinical outcomes studies are necessary or if perhaps the scope of them can be reevaluated in the context of what we know about long-term clinical benefits.

So as more and more of this data is available, it's important for the information to also be readily available to providers and patients to help them understand the potential clinical benefits and risks of new therapies.

I'll give you one example of this. The PCSK9 inhibitors came about because there were findings that in patients who carried loss of function alleles -- and what means is that the gene is not functional -- in PCSK9 had a significantly lower LDL cholesterol relative to subjects who do not carry those mutations. And in fact there was a significant decrease, an 88 percent decrease in coronary heart disease in people who harbored these loss-of-function mutations.

This led to the development of anti PCSK9 antibodies, which were shown to significantly lower LDL cholesterol, which recapitulated what was seen with the genotypes in this original study. The

labeling for these drugs don't include any information about what we know about the blocking this pathway with the genetic information.

So we then went on to do clinical outcomes studies. And the clinical outcomes studies did in fact corroborate what we learned from the genetics, which is that patients who have been treated with PCSK9 inhibitors have a lower incidence -- accumulative incidents of cardiovascular events, which is shown here as a composite endpoint. And still even though the clinical outcomes data corroborate the genomics finding, the genomics finding is not in the drug label.

And so what we would like to do is open up the dialogue about industry FDA collaboration about establishing data and regulatory standards for novel applications of these genomic datas to not only regulatory decision-making, the need for long-term outcome studies, but also for labeling.

So we propose that this be done by a stakeholder engagement, public workshops led by the FDA or in collaboration with industry groups,

formation of expert working groups, which could then result to white papers and eventually draft guidances for public comment.

It's important for the industry to have a formal guidance from the FDA on how we can apply these genomics data. And it's also important that we harmonize these approaches with global agencies. And we think by working together, that we will be able to implement smarter drug development and make this a reality through the application of genomics data. Thank you.

JIM SMITH: Thank you very much. Dr. Chambers?

WILEY CHAMBERS: What percentage of patients or even their physicians do you think know their genetic information in sufficient detail to be able to use labeling if you were to do it as you suggested?

JENNIFER HAMILTON: Thank you for your question. The specific labeling that I was addressing was not necessarily the genotype of the specific patient, but what we've learned from the

genomics about the lack of that pathway.

So using the PCSK9 inhibitors as an example. We know that the patients who have a loss of PCSK9 activity have significantly lower LDL cholesterol and a reduction in coronary heart disease events. So that's the information that we think is important to include in labeling. It's not that the patient needs to know their genotype necessarily. The only time the patients and the physician need to know their genotype would be if it's required for drug treatment. For example, a companion diagnostic.

JIM SMITH: Dr. Marzella

LOUIS MARZELLA: I had sort of a broad question regarding your appeal for more collaboration between FDA and industry. How do you see and practice this being realized, and do you have any concerns about potentially being able to carry this activity in a precompetitive space?

JENNIFER HAMILTON: Sorry, I missed the last part of that question.

LOUIS MARZELLA: The concern is always with being able to conduct such activity in a

precompetitive space. So I wonder if you have some thoughts about the practical challenges of this collaboration.

JENNIFER HAMILTON: So I think the collaboration needs to be on a non-product, non-target focus basis. It needs to be very general on the kinds of data that the industry is generating and how we can apply it to drug development. So I don't personally have any concerns that there's a competitive concern here. I think all of the industry wants to get together to figure out how we can use these data more effectively for smarter, more efficient drug development.

JIM SMITH: Dr. Roman

DRAGOS ROMAN: Do you see any potential benefit of using genomics in the constructing natural history studies, you know, in the area of precision medicine?

JENNIFER HAMILTON: We certainly do look at genomics as part of our natural history studies. And we not only look at genetics, which is what we focused on today, but we also look at

transcriptomics when we have tissue samples, for example, of the target tissue affected by disease that we can study. And I think that's another thing that we should be evaluating as part of how we can apply genomics. Not just limiting it to what we can learn from DNA, but from RNA transcriptomes as well.

NIKOLAY NIKOLOV: Hi, this is Nikolay Nikolov. Do you see a difference or do you make a difference between monogenic and polygenic diseases and how this approach might differ?

JENNIFER HAMILTON: That's a really good question. Obviously it's much more straightforward when we're talking about monogenic diseases. But when you're talking about something like lipid lowering, for example, which we know is polygenic, and there's even studies looking at polygenic risk scores for cardiovascular disease related to LDL cholesterol. There's still evidence that the inhibition of that pathway is associated with long-term health benefits. And so I think if something like LDL cholesterol for example is polygenic in a more general population when you're not

talking about patients with familial hypercholesterolemia for example. So we know it's polygenic in those cases. Yet the inhibition of this pathway very potently reduced LDL cholesterol and was associated with cardiovascular outcomes.

So although it's more straightforward to understand in a monogenic disease, I think we already have the example in a polygenic disease with the PCSK9 inhibitors.

JIM SMITH: Thank you very much. Oh, I'll take one more question from Dr. Birnkrant.

DEBRA BIRNKRANT: Thank you for your presentation. I think one of the main issues with using genomics data for regulatory approval are related to data provenance. So for example, are the data robust and reproducible, have the data been validated, is there a record of where the data came from and how the data were generated, annotated, and manipulated? Who owns the data? Can you say more about how the Regeneron Genetics Center and the UK Biobank capture these important features of data provenance and what standards you currently use?

JENNIFER HAMILTON: So what I can say is that those are all really important questions that I think need to be addressed by this partnership. So genomics data in general from these large consortiums, the companies that get involved with them have access to the data. The individual genetic data is not made public, and so for things like that, we cannot do that.

But the overall aggregation of that information and the interpretation of that information would all be part of an application. I think what is required for those standards is part of what we want to discuss in a collaborative way with you and other industry partners.

JIM SMITH: Thank you. And I'm sorry, I missed Dr. Yanof. Did you have a question?

LISA YANOFF: My question is along similar lines. Can you clarify at this time what is the -- how standardized is the technology to actually derive the data across the different databases?

JENNIFER HAMILTON: So there's a number of computational approaches that can be taken.

I think that part of, again, the discussion about the data that we use to support these kinds of claims, we have to talk about how to standardize that. There are many different ways to mine a data set, many different ways to discover and validate a data set. And so we need to develop the standards in order to establish how that should be done.

LISA YANOFF: My question is actually about the collection of the actual data. So the technology to assess the genetic profile. Is it the same method being used across all of these databases?

JENNIFER HAMILTON: So there are different ways to sequence. You can do whole exome, you can do whole genome. The approach that's taken by the Regeneron Genetics Center is to do whole exome sequencing, coupled with dense variant arrays and imputation. And the combination of those three approaches gives us essentially a whole genome sequence.

There may be other companies who maybe are not doing exactly the same thing that we are.

They may be focused on whole exome. Whole genome I think is coming as the technologies become faster and cheaper. So I would say that it's not totally standard across what everyone is doing. But certainly the way we manage those data and how we interpret those data is something that can be standardized.

JIM SMITH: Thank you very much for your presentation.

JUDITH PRESCOTT: Thank you for the opportunity to present today. I am Judith Prescott. I am an Executive Director at Merck and Company, safety assessment and laboratory animal resources, presenting today on behalf of the IQ DruSafe Preclinical Leadership Group on a broad industry perspective and proposal for cross-divisional guidance for the development of therapeutics for severely debilitating and life-threatening indications.

So as a high-level definition, SDLT diseases or conditions are those which cause major, irreversible morbidity and/or the likelihood of death is high despite available therapies. So this may include such indications or conditions as amyloidosis,

inborn errors of metabolism, and advanced stage heart failure. And because there is existing ICH guidance that facilitates the development of SDLT therapeutics for advanced cancer, today's presentation is focused on non-oncology SDLT conditions for which there is no adequate therapy.

For your reference, I've included a link to a publication at the bottom of this slide that does describe a proposal for a streamlined approach for the development of SDLT therapeutics.

So the rational for the development of a cross-divisional guidance relates to the benefits of an agreed approach across the divisions and the need for a clear and early-defined development path for SDLT therapeutics.

Now, we certainly do acknowledge that there are existing guidances and FDA programs that do provide the opportunity for flexibility to expedite the development of these types of indications. However, this does not obviate the need to seek regulatory input for each program on a case-by-case basis. And this can then cause delays in the

availability of SDLT therapeutics to patients.

And we're certainly not proposing the discouragement of these interactive communications between sponsors and the FDA, but proposing that in addition to the opportunity for that engagement and consultation, that clearly defining a development path and having consistency across the divisions will provide that baseline of regulatory expectations so that sponsors understand that and that will facilitate development.

I'd also like to point out that while this is a proposal for an FDA guidance, our clinical trials do often include countries outside of the U.S. And in this situation, obtaining global regulatory agreement in a timely manner is compounded in these situations. And as such, the tendency is then for sponsors to default to the most conservative position.

So by creating, developing a cross-divisional guidance at FDA and taking the lead on development of a harmonized international guideline, this will facilitate global development and benefit patients in the U.S. as well.

So this proposal is not intended to modify the benefit-versus-risk considerations that currently apply to clinical trials, but it is rather intended to focus on the patient and provide greater flexibility for very serious conditions with adequate therapy.

So for example, by initiating first-in-human in patients and allowing those patients to extend their therapy beyond the duration of the toxicology studies as long as they are deriving benefit and not experiencing unacceptable toxicities, this will enable earlier and continued patient access to potentially beneficial therapies while maintaining the standards of safety and efficacy.

This would focus on those studies that are essential to support patient safety in light of a medical need and would allow rapid advancement to proof of concept in patients. And by understand that proof of concept, this would obviously contribute to the benefit-versus-risk considerations and inform decision-making by the patient in consultation with their healthcare provider on trial participation and

continued therapy.

So as far as the development of a cross-divisional guidance, there are existing guidance documents that do provide a foundation for this. This includes ICH S9, the guideline as well as the Q&A for the development of therapeutics for patients with advanced cancer. And this guideline has greatly facilitated the development of these types of therapeutics.

There is also the FDA guideline for SDLT hematologic disorders. Again, this is for the non-clinical development of pharmaceuticals. And this is a guidance that demonstrates how this type of guidance may be developed for non-oncology therapeutics.

Now, because there is no broadly agreed or universally accepted criteria for SDLT conditions, and certainly criteria for severely debilitating, we do acknowledge that defining a scope for this type of guidance is going to be challenging, particularly in light of the fact that this is intended for cross-therapeutic application.

However, by defining those criteria that would be required for an applicable SDLT condition and providing a list of examples, this should define the limits and ensure the appropriate application of the guidance.

And again, I've provided as a reference at the bottom of the slide a very recent publication that does describe some of the considerations for defining SDLT conditions as well as a proposal for defining scope.

So in summary, we believe that a cross-divisional SDLT guidance would enable consistency across the divisions for a shared therapeutic context and will have significant impact for patients with high unmet medical need. Thank you very much.

JIM SMITH: Thank you. If I might actually open with a question. Within SDLT diseases, there are some that are perhaps quite prevalent and others that are, as you know, very rare. And there could be other factors or modulators if you will within SDLT diseases that might influence recommendations regarding what a development program

may look like, either from a non-clinical or a clinical standpoint. Could you share any thought you might have about what some of those factors may be since, as you said, not all SDLT scenarios are the same?

JUDITH PRESCOTT: Yes. So as far as the factors that would be considered as part of the development, is that your -- that is your question?

JIM SMITH: Right. What other features of an SDLT disease might modulate what the package might look like? So I threw out prevalence as an example. But perhaps rapidity of progression. But there could be other factors that from a policy perspective we might be interested in defining or providing recommendations about, what a package might look like under certain scenarios. And I'm wondering if you can articulate what some of those important scenarios or categories might be within SDLT.

JUDITH PRESCOTT: Right. So as far as those things that may -- it's the impact on the quality of life and, as you said, the progression, if it's rapidly-progressing. But it certainly should not

-- life expectancy, the duration of life expectancy should not be a consideration for that, particular criterion on life expectancy must be less than a certain duration, say a year for example. But those types of things if there is rapid progression to disability or the potential for significant injury or functional impairment would be a consideration. The factors such as whether it leads to major disability. And this would be such things as significant reduction in health-related quality of life, such as a patient having permanent loss of independence in their daily activities such as healthcare, would be a situation where there are recurrent hospitalizations due to the SDLT condition, or life-threatening conditions. Those would be the types of things for consideration.

JIM SMITH: Thank you. Dr. Roman:

DRAGOS ROMAN: There is a natural tension between the desire to go into drug development for SDLT conditions and rare diseases and the need to have some particular information that would ensure some safety of the to-be-developed drug. And I'm referring to safety in animal studies. And also we

have to recognize that in rare diseases there are very few patients, so the safety database would be very small. So this tension between not having enough data and going directly into humans or having data that may prove reassuring but at the same time will delay drug development, you know, create a natural tension that we all recognize. What would be in your view a reasonable balance between going faster into drug development and having a limited pharm-tox program and at the same time ensuring patient safety?

JUDITH PRESCOTT: Thank you for your question. So I appreciate that need for the balance. Right? Certainly this is not intended to compromise the standards for safety or efficacy. And so that balance I think has been achieved very well in the area of oncology for advanced cancer. And so given that the medical context for these SDLT conditions is similar to that, I do think that the ICH S9 does provide an example by where you can have -- so as a proposal, you could still have a complete package of the non-clinical data to go into first-in-human. One-month tox studies, your gene tox package. You

could build your safety pharmacology endpoints onto one of your tox studies. And you would have that package going to patients directly, and then you could extend those patients. And that would be the situation, because of that risk benefit and the unmet medical need, that they would stay on therapy if they're deriving benefit and not having unacceptable toxicities beyond that one month duration, similar to what is done now for advanced cancer. And the proposal is that in general you consider the risk versus benefit in light of the unmet medical need. And so you would not compromise the safety, but consider what are those nonclinical studies, for example, that are needed in the context of the unmet medical need in order to inform clinical monitoring and would be meaningful to clinical monitoring.

So for example, you could potentially waive some studies that wouldn't be meaningful in that situation.

JIM SMITH: Thank you. I think there's actually a few more questions. And just to keep us on time, I'm going to ask that we keep the

questions brief and the responses succinct so we can keep moving. But Dr. Bastings?

ERIC BASTINGS: My question was very much about whether the idea was to apply the non-clinical approach for oncology SDLT or whether there would be a specific approach for the non-oncology indications. So I started to hear beginning of a response about this. But my question was really whether there would be a specific framework developed for the situation or whether we would simply adopt the oncology approach:

JUDITH PRESCOTT: So I'm sorry, I did not quite follow your question. You're asking the framework for whether it would be across all therapy areas?

ERIC BASTINGS: I was asking whether you would simply use the oncological approach to the non-oncology indications, or whether you would develop a specific framework for the non-oncology indications.

JUDITH PRESCOTT: Thank you very much. Yes. So I think that the oncology approach for

advanced cancer does serve as a very good foundation for that. There may be some aspects of that for consideration. But it is a very good framework for that.

JIM SMITH: DR. Yanoff?

LISA YANOFF: Thank you. So going back to your Slide 3 where you outline that lack of divisional agreement on development plans can lead to delay. And then you say this results in case-by-case considerations for each program. I think it would be helpful for us as we develop policies to know in a little more detail about that, whether those difference you feel were really related to the things possibly Dr. Smith outlined about differences in the diseases. Or can you give us an example of where you felt that those differences should not have mattered and yet different decisions were made?

JUDITH PRESCOTT: So without giving a specific example, I think that -- so the intent here is really that having that broad agreement across the divisions and for sponsors to really understand what the regulatory expectations will be for these types of

conditions serves as a baseline by which they can then understand how to make decisions regarding development.

So for example there may be one division that takes a much more conservative approach than another. But there is that uncertainty that sponsors have prior to first-in-human not really understanding what are going to be the regulatory expectations, because it's very much case-by-case.

So I think that combination of having that baseline understanding of what generally are the regulatory expectations in conjunction with the opportunity to have the interactions with FDA would really facilitate development. And it would do this in a manner whereby for one example they're in a recent publication by OHA which actually came out last month. They indicated that even for some sponsors that pre-IND meetings, sometimes the IND meeting -- or when they submitted the IND, it went on clinical hold. And so having an understanding of the regulatory expectations going in would give sponsors an understanding of what are the critical questions to

ask in that pre-IND meeting. Because if you don't ask those critical questions, which could happen, particularly with sponsors with less drug development experience, they could still go on clinical hold with submission of the IND. And so that's a manner in which if you had that general understanding going in rather than a case-by-case determination, that that would enable sponsors to understand the right questions to ask.

JIM SMITH: Thank you, Dr. Prescott. And that actually was the last question. So I appreciate your presentation today.

PAUL MELMEYER: Good morning, everybody. I am Paul Melmeyer. I am the Director of Regulatory Affairs at the Muscular Dystrophy Association. Just a moment or two about us before getting into the topic of the presentation.

The Muscular Dystrophy Association serves the neuromuscular disease patient community in a variety of ways, but really focusing on innovations in science and innovations in care. Within science, we are one of the main research funders of

neuromuscular disease research, primarily focused in clinical research, doing everything we can to bring new treatments to the neuromuscular disease patient community. And then within innovations in care, we have a network of care centers. That's about 150 care centers across the United States that actually provide care and support to those within the neuromuscular community.

So within neuromuscular diseases, we're in a bit of a Dickensian situation in which it's the best of times and worst of times. And I'd like to start with the good news. The good news is that we have really seen some unprecedented developments of neuromuscular disease therapies and approval over the course of the last five years. By our estimation, there are 11 therapies on the market currently for neuromuscular diseases, eight neuromuscular diseases in total. And eight of those have actually been approved within the last four years. And we're hopeful and encouraged for new therapies coming to market over the course of the next several years.

The challenge is that there are still

plenty of challenges within neuromuscular diseases. And even though we have eleven therapies available currently for eight diseases, there are still over 43 diseases within the overall neuromuscular disease family, I guess you could say, many of which are not enjoying the same therapeutic developments.

In addition to that, many are quite variable. And when you talk about mitochondrial disease, for example, whereas that could be considered one disease, it's actually over 600 different diseases with a variety of different genetic underpinnings.

And that brings me to the unique challenges that we find within neuromuscular diseases. There's still a stark lack of disease understanding in many neuromuscular diseases, including amyotrophic lateral sclerosis, for example, mitochondrial diseases for another, and a variety of others. Within these same diseases, there are oftentimes lack of biomarkers which make it difficult for the variety of innovative opportunities in development to be taken advantage of, such as the use of the accelerated approval pathway within many neuromuscular conditions. There is

extensive heterogeneity within neuromuscular diseases that oftentimes can be originated from a variety of genetic and mitochondrial underpinnings. Oftentimes we're talking about extremely small patient small populations with specific genetic mutations. Maybe only a handful of individuals in the entire United States maybe the entire world with that specific condition.

Neuromuscular disease can be incredibly severe. Oftentimes for individuals born with certain neuromuscular diseases, they can lead to death, unfortunately, quite quickly.

Oftentimes pediatric populations are included within neuromuscular diseases. Some neuromuscular diseases are centered in pediatric populations. And we still oftentimes are using archaic endpoints within trials within neuromuscular diseases. Uniformly within the neuromuscular community certain endpoints such as the six-minute walk test are strongly disliked, yet we are still using them within development.

So the way that we see developments

going within neuromuscular disease is we're excited for the advent of a variety of innovative approaches. And this is really just a smattering of these. And of course these approaches are nothing new to the panel in front of me. I don't expect anyone to slap their forehead and think, oh, of course we didn't think of that, of course the FDA knows each and every single one of these. But we still believe it's important for the patient community to be emphasizing that these flexible approaches should be used across all neuromuscular diseases.

We are excited for the advent of platform trials within neuromuscular conditions. We are aware of at least two ongoing right now, one being within ALS, another within Duchenne muscular dystrophy, which is co-led by I-ACT for Children, the Critical Path Institute, and Parent Project Muscular Dystrophy.

We are also excited for the implementation of adaptive clinical trial designs, open label studies, and the further implementation of broad trial eligibility criteria. We are hopeful for

broad use of expanded access programs in situations in which perhaps broad trial eligibility criteria can't be utilized in specific neuromuscular conditions.

Remote and mobile data collection is going to be particularly important within neuromuscular diseases due to the ambulatory challenges of individuals actually getting to trial sites.

The use of patient-preferred endpoints is accelerating, and we also hope for the rapid trial timelines due to the severity of the diseases that we're discussing.

So on to our request specifically for FDA. What we do hope for is a more structured transparency in extensive disease-specific guidance development process. What we have seen already within neuromuscular is a handful of diseases-specific guidances coming to finalization, coming to fruition, including Duchenne muscular dystrophy and most recently ALS. We are hopeful that additional disease-specific guidances can be developed within the remainder, or at least when appropriate, the remainder

of neuromuscular disease conditions. We understand of course that community shares responsibility in this. There's opportunities for the community to develop disease-specific guidances, and that's oftentimes happening within neuromuscular conditions. But we also are hoping for a collaborative relationship with FDA in doing so.

And once guidances are developed and finalized, we are closely watching the full implementation of those guidances and the mechanisms discussed within to ensure that those within the industry and the drug development community are actually able to use the mechanisms that have been informally endorsed, one could say, by FDA within the guidances.

And not only that the guidances are fully implemented, but they're implemented consistently across review divisions, as we've been hearing from two of our previous speakers.

We are curious and we're eager for patient and advocate engagements to be fully implemented within the new CDER structure. We're

really looking forward to working with the New Policy Office within OND as well as better understanding specifically how the new structure within OND is going to be impactful on patient engagement within these new divisions and new offices.

And then finally, just continued collaboration with the patient community. We have enjoyed a very strong collaboration with a number of offices within FDA, including the PACE office, the office responsible for patient-focused drug development meetings and the associated initiative, and the patient affairs staff within the Office of the Commissioner.

So just a moment on MDA's role in all this. Of course we're here for that patient education. We are here to work with the patients in bringing them up to speed on everything that FDA is doing and all the opportunities that FDA offers to those within the neuromuscular community.

We are here to support and participate within these patient participation opportunities to offer regulatory and policy support if appropriate and

if warranted. We also are conducting an externally-led patient-focused drug development meeting in Pompe disease on March 9th. We are collecting patient preference information through our OneVOICE program, and finally, our neuromuscular disease observational research data hub, which, as you can see, became MOVR, which is an incredibly tortured acronym, so apologies for that. But this gathers genomic and longitudinal clinical data across diseases to hopefully better track the natural history of the disease and do everything that is cited here. Thank you.

JIM SMITH: Thank you very much. Dr. Singh?

HARPREET SINGH: On Slide 8 you talk about remote and mobile data collection. And I was wondering if you could describe the efforts that MDA has been involved in thus far to decentralize clinical trials or in essence bring the trial to the patient in terms of technology and infrastructure.

PAUL MELMEYER: Absolutely. So we're excited for some of the innovations happening within this area, including on clinical outcomes

assessments that would actually allow for some of the data within clinical trials to be collected at home rather than within the clinic or within whatever venue a patient would otherwise be requested to go to.

We have our clinical care centers, as I mentioned earlier, and clinical care coordinators that work very closely with patients. And really from them hearing specifically the challenges that clinical trial participant oftentimes brings. And from that we are taking those lessons and implementing that within our policy and regulatory efforts such as talking about it here, but also within our research efforts and working with the industries that could be developing these tools, collaboratively working to ensure that these tools are getting to patients as quickly as possible, being used within clinical trials, and then can be also if not endorsed, at least accepted by FDA within the context of these clinical trials.

JIM SMITH: One more question from Dr. Roman.

DRAGOS ROMAN: One of the

difficulties of conducting clinical trials in small patient populations is the availability as well as the small numbers. So you seem to advocate on one of the slides the need for broadening inclusion criteria. Do you have a solution for that or a recommendation how that can be achieved?

PAUL MELMEYER: Absolutely. So we understand enrichment studies are still oftentimes necessary and oftentimes the best way forward in achieving clear safety and effectiveness signals from innovative therapies. If it is impossible due to the heterogeneity of a disease for truly broad eligibility criteria, that is when we would want to see broad expanded access being explored by FDA as well as the company with the therapy. As well as just additional considerations of if there is to be kind of a central trial in a sense of the data that's going to be primarily generated from a very small patient population due to the heterogeneity of the disease, that there can be additional arms of the trial that could be considered for those who don't necessarily qualify due to the heterogeneity, but could still

benefit from the therapy nonetheless.

JIM SMITH: And last question from Dr. Bastings.

ERIC BASTINGS: An approach that can be used in that situation is to enroll a broad population but conduct the primary analysis in a more defined, maybe biomarker or some other way. So do you endorse that kind of approach of enrolling a broad population but possibly doing the primary analysis in a more restricted population?

PAUL MELMEYER: Yes. Primarily we are interested in any therapy that's coming to market having the most appropriate but broadest label available and possible for patients so that that can then result in wider patient access upon arrival to market, hopeful arrival to market. So if that means that we are able to use that approach which will then generate a label that can be most useful to patients, then that is something that we support, absolutely.

JIM SMITH: Thank you very much for attending today and sharing your thoughts.

ART KRIEG: Hi. I'd like to talk

now about oligonucleotide therapeutic programs. And in the first part of my talk, I'm going to talk about programs for ultra-rare diseases, including conditions with single patients who have unique mutations that don't occur anywhere else. And I'm going to be making a proposal inviting the OND, and we'll be reaching out to other stakeholders at the FDA, as well as non-commercial stakeholders, including people who may be here at this meeting, to join us at a workshop to advance this discussion beyond what we can do in this short talk today. We're planning on holding this in the Bethesda are in March or April of next year. And then we have a Doodle poll set up for those of you who may be so inclined to indicate your availability for that.

For this first part of my talk, my affiliation that's relevant is I am a co-founder and past president and a board member of the Oligonucleotide Therapeutics Society and I'm also on the faculty of the RNA Therapeutics Institute at the University of Massachusetts, where we have an interest in this.

So a brief background on the OTS. This is a nonprofit organization founded 15 years ago with a mission to foster academia and industry-based research and development of oligonucleotide therapeutics, bringing together industry and academia. Because we really need both in order to make progress there.

Our website is shown. We have about 500 members. We are very international and roughly evenly divided between academia and industry. We just had our annual meeting last month in Munich, where there were over 600 attendees. We had 154 poster presentations and so forth. And we make a special effort to involve students and post-docs there. So we provide funding for their travel awards.

We have a journal, we are on Twitter. And our members are very passionate about the potential for oligonucleotide therapeutics.

It's been a long time for our field. Since the dawn of this when the first companies became involved, investor started getting into this, was in 1989. And at that time the only tools that we really

had in terms of the chemistries were basically phosphonothioate modification to native DNA and RNA, which are too rapidly degraded to really make useful drugs. And with the phosphonothioate chemistry briefly, it just really wasn't up to the task of making therapeutics. It's very difficult to get it to work. It's taken billions of dollars invested into the field in the decades since then to reach the point that we're at today, where we now have multiple different chemistries that work as modular building blocks.

So that's one of the neat things about oligonucleotides. Because we're targeting the genetic code, RNA or DNA, once you have building blocks like this, you can target any gene, you can target any mutation using those same building blocks just rearranged to whatever the target is that you're going after.

So in the early decades of technology, there was failure after failure. We now have multiple approved drugs, most of them just in the last three years, including multiple different platforms. And

there's not time to go through all of these, but the earliest platform was antisense oligonucleotides. And there's two major types of those. Gapmers, cleave targets -- and there's several approved drugs based on that mechanism, and there's a second platform based on blocking targets; Mixmers and the exon skipping oligos, Nusinersen and eteplirsen are good examples of that. So those are two very robust platforms. Those can be used for many more targets and many conditions. And in addition to that, we have RNAi, the latest generation of RNAi compounds. Two doses a year can provide therapeutic effects, again, across a wide range of targets. And these are technologies right now that are highly effective for liver targets. They're becoming effective in the CNS, and they'll be extending out to other tissues as well.

And the other platforms I won't talk about, but there's multiple different technologies coming together here. And the innovations are not over now; they're continuing and that's going to be accelerating.

So where does the field go? Well, the

companies are leading the way here for the common diseases. What I want to talk about today is how do we extend this technology to diseases that are not common, where there is no commercial incentive. Because unlike any other drug platform for therapeutic development, oligonucleotides are fast and they're relatively cheap. For small molecule drug discovery, it takes an army of chemists years and years to get a new drug. For biologics it takes a smaller group, but it's still years and years, and it's very expensive. Oligonucleotides, because we're targeting the genetic code, you can accelerate that process and a single lab can actually generate a new therapeutic to treat a condition.

An example of that that you're going to hear more about from the next speaker is Mila, a young girl with Batten disease. Mila had a unique genetic mutation never before reported. And Tim Yu, a professor at Boston Children's, recognized that that mutation could be addressed with an oligonucleotide therapeutic. Now, Dr. Yu had never worked on oligonucleotides before. He had no prior experience

in this field. But he reached out to people who did, including a lot of our members. And within less than a year from when he identified the mutation, he conducted the screening of the oligos and actually generating cells from Mila and so forth, and began therapy within less than a year from identifying that mutation. Only oligonucleotide therapeutics make that possible.

Now, Mila is the first of the patients who are going to be treated with this kind of approach, but there are many others. And what I want to spark your excitement about today is how do we extend this to the thousands and tens of thousands of other people out there who could benefit from these technologies. And that's why we're having this meeting early next year, because we really think there's huge potential here. And the companies aren't going to lead the way. We need to bring together other stakeholders who see this potential and can bring the resources to extend this to more patients. And that's why we want to have this meeting.

So we're thinking start out 40 to 80

attendees. I don't know how many people we're going to have. The Doodle poll just opened a few days ago and people are signing up. The objectives are really going to be to define a process to connect patients and other stakeholders with the resources for this. We've already been getting emails from academic centers around the country and internationally who have read the paper in the New England Journal a couple of weeks ago reporting Mila's case and want to know how they too can help patients at their institutions take advantage of the potentials of these technologies.

Now, I don't want to trivialize this. Most patients with rare diseases are not likely to benefit from this kind of a therapeutic. And the first challenge here I think is to establish the criteria for patient enrollment; what patients are we going to start off treating with these technologies? Then we have to have a process for selecting patients for this. The worst thing in the world I think would be to have something like these stem cell clinics springing up all over the place that are offering

therapies with very little scientific benefit. I think this has to be rigorously, scientifically driven. There have to be people who are making decisions on what patients are going to come into this based on a risk-benefit analysis. And we have to establish standardized protocols for how the oligos are screened, the CMC, the safety testing, and so forth. And we have to establish then pathways for patient dosing. This all has to be done in dialogue with the FDA of course.

Secondly, in my remaining ten seconds, I'm just going to comment that my other affiliation is I am at Checkmate Pharmaceuticals. We are doing cancer immunotherapy. And there was a seminar just yesterday on approaches to neoadjuvant treatment that was co-hosted by the FDA and the MRA. And for those of you who aren't already aware of that, I think there's a great need there for developing new endpoints, surrogate endpoints for approval of new cancer immunotherapies. Thank you very much for your time today

JIM SMITH: So perhaps I can ask

you about the second part that you didn't have time to get to briefly. It appears from your slide, you're addressing the challenges of early stage cancer therapies. And I'd like to broaden that, that many chronic diseases may have an early stage where there is a potential to benefit was well, to either halt, slow the progression, or even reverse the disease. And as you point out on your slide, that could lead to lengthy clinical trials and whatnot. Do you have any recommendations for the type of a data package that might support a surrogate endpoint in that situation?

ART KRIEG: Yes. Well, let me first start by where the field is at right now, at least for neoadjuvant cancer. The first approval of neoadjuvant was in breast cancer where the first approved drug was based on a data set of around 10,000 patients followed for close to a decade. And the drug that was approved there I believe had already been approved in the advanced metastatic setting.

And what I've heard from individuals with a strong regulatory background, which is not me, is that in order to get a new drug approved, maybe

it's going to be a little less of a data set than that. But when I'm talking to investors to invest in our company -- because we are a small biotech company, we have to raise money to run these programs. The investors can see how the pathway goes forward for the advanced setting. For the neoadjuvant setting, they can't see that. Because the only understanding they have of a data set to approve a surrogate endpoint is based on the breast cancer example. And we're not going to be generating data sets like that in a small biotech company. And even large pharmas are scared of getting into something like that, because it takes so long and costs so much money. When you're thinking of other investments, that's not where you're going to put your money.

JIM SMITH: Thank you. In the interest of time -- I know we have to more talks before our break. So thank you very much for presenting today.

JULIA VITARELLO: My name is Julia Vitarello, and I am Mila's mother. And thank you, Art for painting a bit of the backdrop of Mila's story.

Three years ago, Mila was diagnosed with Batten disease, which is a rare and fatal neurodegenerative condition. There were no treatments. There was no cure. I was told that my at the time very outgoing, seemingly incredibly healthy little daughter, who was skiing and hiking and singing the ABCs like every other kid, was going to lose all of her abilities and die in five years.

And there's a lot more I could tell you about what happened over the last three years, but really what's most important is that in the year following her diagnosis, as you just saw from Art's presentation, an incredible effort was made by Dr. Timothy Yu and his team at Boston Children's Hospital, along with many others, to give Mila the chance at a treatment that was looking very promising for her in the lab.

And at that same time, Mila was losing her abilities by the month, even by the week. She lost her vision completely, she lost her ability to speak. She was losing her ability to swallow and to walk at the same time that a promising drug was

getting close to be able to happen.

And as a mother, as Mila's mother, I faced the question of the risk of treating Mila versus the risk of not treating Mila. And the answer to that was very, very simple for me. The risk of not treating Mila was very obvious every day. Her life was suddenly taken over by seizures, which took up most of the 12 hours of waking time that she had a day. She was losing everything so incredibly quickly that I knew exactly what her course was going to look like over a very short period of time. And no child with this form of Batten disease has ever lived.

So what happened afterwards was that Mila ended up receiving this treatment, which was a drug called Milasen. And she received that starting almost two years ago. And Mila was seven going into this treatment, which has quite progressed. But despite that, we have seen some really promising signs. And because of Milasen, which we have learned since then was the very first drug tailored to one single patient, Mila's quality of life and our life as a family -- I'm just incredibly grateful for where we

are today. Mila turned nine years old two days ago, which was a big milestone for us.

And I'm here to thank the FDA. Because the entire team at the FDA was incredibly thoughtful. They listened. They were very careful in understanding the risk-benefit analysis for Mila. They ensured that -- all of you ensured that Mila's drug was rigorously tested and that it was safe for Mila, but at the same time understood the urgency and the promise that this drug possibly offered. So thank you for being collaborators, for being partners with Dr. Yu and his team and all of us in really assessing her specific situation and allowing us as a family and as a nine-year-old girl to have a second chance at life.

I'm always very honest about Mila's situation. I don't know what her future holds. She was seven years old when she began this treatment. She had lost a lot. But despite losing a lot before that, it was a long shot. I have seen a lot of promising things. It is not black and white; Mila's life is not magically perfect. But many of her

symptoms have -- some of them have greatly improved. Some are stable. Some are not doing as well as I'd like, but we're learning. Because Mila is the first, and we have to learn a lot about dosing. And as Art implied, this is promising, but there is still a lot to learn.

So I just really wanted to thank the FDA. I went into this thinking that the FDA were these guards at the gate and that maybe wouldn't get through. And I realized afterwards that this was a discussion, it was a collaboration with Dr. Yu and his team, and it was an explanation of the potential of the drug, but also where Mila's life was headed and what her risk of not treating was like.

And so to end, I just wanted to show a very short little compilation of very recent, in the last probably month or two, videos. Just short, little video clips and photos of what Mila's life is like, really thanks to you allowing Mila this opportunity to have Milasen.

For right now it sounds like the audio is not working. So we're going to do it without the

sound, which is actually fine. And if we can fix it later, that's great.

(Video plays)

JIM SMITH: Thank you very, very much for being here. If I could ask one question. We would anticipate that parents, family members, other patient advocates would want to engage with FDA in partnership along with our academic investigators in future situations where individualized therapies are being developed. From your experience, what went well and where might we improve in future cases?

JULIA VITARELLO: That's a really good question. I think Dr. Yu and I have had an ongoing very good relationship of -- Dr. Yu has been very honest and upfront from the very beginning of the promise that Milasen might offer, but also the reality of this, that we really don't know that much. And we went into this knowing that Mila's cells -- you know, her brain cells, some of them were in a process probably of dying that may not be able to be stopped, and other ones were potentially in a place where they could be stopped, and that Mila's disease is obviously

extremely complicated, and there are many different symptoms, and that this was not a magic cure and that our hope was that we could potentially stop this disease. And in fact what we're seeing right now is in line with what we had talked about from the very beginning, which is that some symptoms have improved, some of them have stabilized, and some of them are not doing as well. And I think that setting expectations from a PI to a family is extremely important, as you know. And I'm sure I don't need to tell all of you that when you have a parent like myself who is being told that their child is going to die, it's something that I can't even put into words. I mean, the rest of my life just disappeared that day. And so you cling to anything that looks like hope.

And I think that in this case, like Art explained, is there is actually in fact a lot of promise in this platform. But we have to be realistic, because every disease is different. We don't know until more children -- I hope many more children across many diseases are given an opportunity like this. Hopefully it will be in time for them, and

hopefully we'll learn a lot from this to understand what we can stop and help and improve and what we can't possibly.

And expectations for parents is really important. Communication between PIs and parents, very transparent expectations, even to the point where up until honestly days practically before we moved to Boston to begin Mila's treatment, Dr. Yu did not promise this was going to happen because he was working with all of you. This had never been done before. And we didn't even buy plane tickets. You know? We moved at the very last minute. And so transparency, honesty, is incredibly important.

And I can't speak for Dr. Yu, but I know that Dr. Yu and his team and myself all took a very honest and collaborative approach with all of you guys. And I know that you all did the same with us in the sense that we told it exactly as it was. I wrote a letter and I gave it to the FDA through Dr. Yu that really explained towards the end this is where Mila is today and this is where she was three months ago. And I listed very specific symptoms. And I was very

honest in that letter, and a little bit nervous, to be honest, to say the truth, which was I didn't know if we started this treatment even one month later whether or not it was in time for Mila and I might change my mind. And that was honest. And so that would be kind of my advice.

JIM SMITH: Thank you very much again.

JANICE SORETH: Good morning. I am Janice Soreth, a former FDA-er for life, and now back, two years after having retired from FDA in the role of a consultant and advisor to industry.

Thank you, Dr. Cavazzoni, and your team of organizers for letting me present today. It's truly an honor and a privilege. It's especially an honor and a privilege to be the last speaker before the break. So I'll try to cut to the quick with regard to my specific actionable policy recommendations.

But before I get to them, let me take us back in time a bit to when FDA rose to the occasion to address in a timely fashion an area of unmet

medical need. And I'm speaking here to HIV infection and the AIDS crisis that prompted an epiphany when HIV infected patients and their advocates made it perfectly clear that the patients are waiting, time is of the essence, and the usual development path and rules and regulations wouldn't suffice and didn't apply.

It was a hard-won epiphany, patient-led, patient-focused, with a clear articulation of the level of risk that patients were willing to shoulder. And it catalyzed a timely collaboration and communication amongst the clinicians and scientists of all types within the agency and necessarily with sister agencies and the whole clinical trial network of patients, academicians, treating physicians, and healthcare professionals and industry, to rapidly get to a point to translate what we understood of the science at the time into a clinical trial with endpoints, surrogate markers, surrogate endpoints that appeared to be likely predictive of clinical benefit.

My focus in making three specific recommendations for consideration for policy pivots

has to do with patients at this time in various therapeutic areas, adults and children, areas of unmet medical need where there are no approved treatments or there may be some, but they are woefully inadequate, but that's all that we have.

So my first recommendation is for further enhancement and streamlining of the process for identifying and validating surrogate endpoints.

My second recommendation is particular to those areas of unmet medical need in children, specifically those pediatric conditions or diseases that primarily occur in children, or they occur in both children and adult populations, but they're different enough in kids in terms of their presentation or progression such that extrapolating from an adult efficacy trial isn't the way to go. It won't suffice.

And the recommendation is that in those scenarios that the agency permit the pediatricians in the agency to take the regulatory lead. I say that as a trained general internist. So I'm speaking from my own depth of ignorance when it comes to understanding

pediatric disease, taking care of pediatric patients over and above my own two kids.

And last but not least, my third policy pivot for consideration is that consistently agency clinical and scientific leads be proactive and willing to be part of the scientific development that translates into clinical trials, an endeavor that invariably involves risk-taking.

I said I would be succinct, and that's it.

JIM SMITH: Thank you very much. Dr. Yao?

LYNNE YAO: Thanks, Janice. Good to see you. I have a question for you about the pediatric recommendation you made. I'm fascinated about it. Could you elaborate more about what you mean by taking the pediatric experts and FDA taking the lead there?

JANICE SORETH: I can speak to this directly from when I was on your side of the table. And I think that my own observations are that there is inconsistency in different therapeutic areas,

different offices or divisions. And this is not to point to anyone in particular, but simply to say that there is inconsistency at the end of the day with how the pediatric input is taken. And at times it was taken as a recommendation, take it or leave it. At times directors of a given endeavor who themselves were not experts in the pediatric domain took it or didn't take it.

And I think in those arenas where the pediatric expert is the expert in the given disease or condition, it's more than a recommendation, or I'd like to see it be consistently viewed as more than a recommendation, like this is the way to go.

I think along the lines of if you don't play the game, how can you be expected to make the rules. So without getting into nitty-gritty, that's what I'm talking about; that there would be a policy determination that even if the lead of a given endeavor structurally or org-wise was not a pediatrician, that at the end of the day if there is a divergence between which way to go in the trial or the endpoints or whatever, that the pediatric expertise

would rule, would take precedence over someone having a certain title. Does that make sense or is it still too vague?

JIM SMITH: I believe we have one more question from Dr. Farchione.

TIFFANY FARCHIONE: So if I could maybe follow up and sort of expand on Lynne's question. So I can think of an example where this would really apply, would be for instance autism spectrum disorder. And I guess I'm wondering in a case like that where for instance I happen to be a child psychiatrist, which is helpful, how you would envision peds taking the lead in a situation like that where you do have the pediatric expertise within the review division. And I think we collaborate pretty well with peds, but how would you envision a situation like that?

JANICE SORETH: Well, I think when you have pediatric expertise at the top of a unit, that's kind of a no-brainer, unless there's a fundamental disagreement amongst or between the pediatric experts which way to go. But frankly I

never saw that at the agency, and I haven't observed it from the outside. It's the opposite. It's when the programmatic director of an office or a division or whatever who doesn't have pediatric expertise thinks that this is the way to go. And the input from the pediatricians is otherwise and sometimes it's not taken. And I think in those scenarios, that's a decision not made in the best interest of patients; in this case the pediatric patients and their parents and guardians. I was at the agency long enough that the pediatric rules and regulations didn't exist when I joined the agency. So I saw -- I'm older than god. So I saw it through its stages of iteration.

JIM SMITH: Thanks very much, Doctor. We're going to take a 15-minute break, which means we start off again at 11:07.

(Break)

KEITH FLANAGAN: Okay, we are going to now proceed with Session 2. As with the previous presentations, I'll announce the first speaker, but not subsequent ones, so please approach the podium when the slide that lists your name and

affiliation appears on the screen.

After your remarks, please remain at the podium to allow the panel an opportunity to ask questions. The first speaker for Session 2 is Elliott Levy, SVP of Global Development at Amgen. Dr. Levy?

ELLIOT LEVY: I want to thank the panel for giving me the opportunity to talk this morning about topics that we're passionate about and in particular, I want to spend a few minutes talking about innovative trial designs, which are, I believe, a life and death matter for the pharmaceutical industry.

The state of pharma R&D is not well. There are areas of (indiscernible) good health in oncology and in rare diseases, which conceal the fact that we underinvest and in some cases, dramatically underinvest in many important areas of human health.

I find it particularly shocking that of the 59 new medicinal entities approved last year by the FDA, not one was in the area of cardiovascular disease, which is the most common cause of death worldwide.

One of the major reasons for underinvestment is the perception that based on fact that clinical trials, clinical programs in these areas take too long, cost too much and carry too much risk. Innovative trials, it's a term that encompasses many different methods, including platform trials, the use of real world evidence as a compliment to or as a substitute for clinical trial evidence and other methodologies.

But what I thought I would show you is just an example from our own hands of the value of one particular innovative methodology, that's the adaptive design. This slide, it represents the results of a study design process, a phase II trial for lupus in our organization, where we've modeled out three characteristics, comparing a traditional design and an innovative design using response adaptive randomization, interim success and futility analyses and longitudinal modeling.

And the panel on the left shows that the probability of reaching an incorrect conclusion, the panel in the center, the number of subjects and

the panel on the right, the average time to a decision.

And in each panel, we show the outcome of the traditional design versus the innovative design, if -- whether -- assuming the drug doesn't work on the left, or that it does. And you can see that in each case, whether the drug is efficacious or not, the probability of reaching an incorrect conclusion is reduced by the innovative adaptive design.

The average number of subjects is dramatically reduced and the time to a decision is shortened. We believe that by incorporating these methodologies throughout the -- our clinical portfolio, that we can dramatically change the prospects for success in medicinal development, particularly in areas of common diseases, which today receive insufficient investment.

So we think there are three opportunities for us to partner with FDA to promote the adoption of innovative methodologies. And the first is really around timely advice and engagement.

We're delighted to be participating in the complex innovative trials pilot. Sorry.

But we think that more contact with the agency is needed. We recognize the value of having firm binding commitments that are arrived at through formal dialogue, but we would ask for the agency to consider options for making contact with sponsors more frequent and less formal, more information sharing, less -- more asking and less telling.

I think we can learn much from each other. We'd also encourage you to seek options to share learnings with the clinical trial community more actively, perhaps by publishing case examples on the website or in Q&A documents.

We are used to working with non-binding feedback. The vast majority of the agency feedback we receive worldwide is non-binding, and of course, we work with many others such as payers, who have a significant impact on our work, who provide only non-binding guidance. So while we welcome the binding guidance, we shouldn't let it prevent us from opening up additional channels of communication.

Expertise and know how is a critical challenge, not just for the agency, but for the industry sponsors who seek to adopt innovative methodologies. Equally important is a broad understanding that's shared not only by the statistical experts in these methodologies, but by the clinicians who will need to interpret the results.

We would encourage you to enhance your capacity in bayesian adaptive designs and modeling and simulation, which is a critical capability for evaluating innovative trials. We understand that the agency has retained external consultative support. We feel that's helpful and could be extended.

I would acknowledge that our industry sponsors have the same challenge in finding and developing or promoting talent that can work with these innovative methodologies, so we were very sympathetic, but we need to work closely together.

We also believe it's important for, again, for the different divisions which will interpret the results to share a common basis or

understanding for these methodologies, and would encourage you to work to develop not only your statistical staff, but your clinical review staff.

And then finally, the global nature of the programs represents a challenge. It's difficult to move forward with large data collecting exercises, when different important regulatory jurisdictions have differences of opinion about the validity of the science. And it's seeking and building a consensus with multiple regulatory authorities.

It is so time consuming that it offsets a great deal of the value of using these methodologies. So we would encourage you to, as you have, to seek opportunities to build close relationships with other progressive health authorities around the world, perhaps building on the cluster approach, incorporating innovative designs into one of the existing clusters or forming any -- an additional cluster, and looking for other opportunities to engage with the regulators and stakeholders and public discussions around these methodologies.

And again, just to emphasize, although I've -- my example was one of adaptive designs, there are many other types of innovative methodologies that will acquire the same kind of concerted approach, if we are to truly take advantage of them.

I wanted to also highlight one other area, where we think that a closer and more open frequent interaction between the agency and the drug developers could be a value and that's in determining when post-market safety studies are required.

The -- I have not seen systematic studies of the effort that's required to comply with post-marketing safety requests, but I believe from my own experience that multiple companies, that between 10 and 20 percent of the resources and effort that we deploy in clinical development are spent fulfilling post-marketing safety requests and other post-marketing requirements.

We, like many companies, have invested heavily in the development of resources, sentinel-like resources that we believe could be of considerable value in safety evaluation, and in many cases, could

allow us to adequately assess a known and potential safety risk without the standing up of clinical trial.

And but, we find in certain cases that the FDA determines that a trial is, or other study is necessary, but for reasons that are unclear. And pregnancy registries we think are a good example of this issue. Their shortcomings are, I think widely acknowledged. We believe that there are acceptable alternatives using real world data resources, but to date have been unable to have an open dialogue with the agency around these, despite having put proposals forward.

So we believe that the agency where it conducts a robust evaluation of where sentinel is sufficient should provide sponsors with sufficient information and analysis and rationale to understand the deficiencies of sentinel or a sentinel-like approach.

And we would encourage the agency to consider whether another type of database study in these cases could be sufficient, recognizing that sponsors have invested considerable time and effort

into the development of sentinel- like capabilities that could perhaps be useful for this purpose. And that's it. Thank you.

KEITH FLANAGAN: Thank you. Dr. Yao?

LYNNE YAO: Hi. Thank you for your comments. I'm interested in maybe getting a little bit more detail about your comment about other types of database studies that could replace or be evaluated before requiring a pregnancy registry study. Could you maybe provide a little bit more detail about what type of study that might be? And --

ELLIOT LEVY: Well, we did prepare a worked example for consideration at the time of approval of one of our products, a database study that we thought would be more informative than a traditional pregnancy registry. And so, I think we'd be happy to share that example with you, if you'd like.

KEITH FLANAGAN: Thanks for putting this thoughtful presentation together. On slide five, you flag that advice on design features

that FDA has done, unacceptable would be helpful. Which types of design -- could you be more specific or granular about the types of design features that are front of mind for you, please?

ELLIOT LEVY: Well, I think that one of the major challenges in bringing forward these sophisticated response, adaptive designs is the adjustment for multiplicity, where there are, you know, today, to my understanding, the traditional statistical approach is maybe inadequate, and instead, we have to rely heavily on modeling simulation to help us understand the operating characteristics of the study.

You know, I expect that over years and with experience we'll become comfortable working together using modeling and simulation to replace traditional statistical approaches to corrections for multiplicity. But today, I think the field is very much in its infancy, and it would be enormously beneficial to begin to share examples of cases where you feel we've come forward with a good proposal, and others could adopt similar approaches in, you know, in

assessing criteria for success of the studies. Is that helpful?

KEITH FLANAGAN: One more question from Dr. Roman?

DRAGOS ROMAN: One of the slides you make the suggestion that the FDA considered contracting third party statisticians to help, well, this is continuous hiring and training continuously and everything in the agency. But could you elaborate a little bit more about that in the context of the fact that most of these issues are proprietary, you know, trial related issues and statistical issues, and you know, this proprietary information has to include some difficulty in sharing some of the information. I didn't know if you have any thoughts on that.

ELLIOT LEVY: So your concern is that if you had a product under review in front of you, you'd be precluded from consulting someone outside of the agency to help to evaluate the statistical approach (indiscernible) --

DRAGOS ROMAN: Well, I mean, I think that that'll be proprietary information. I mean, I'm

not working for a company, but I would assume that sharing that information, which is proprietary to myself would be problematic.

ELLIOT LEVY: Yeah. Well, I don't -- you know, I don't know the procedures that the agency requires for engaging expert consultants in cases like this. From the sponsor's perspective, we would be quite open to disclosing proprietary information if it were necessary to support that appropriate assessment of a scientifically novel package.

DRAGOS ROMAN: Thank you.

JIM SMITH: Thank you very much, Dr. Levy.

KATRIN RUPALLA: Good morning. I want to thank FDA very much for the opportunity to present today. I am Katrin Rupalla. I am a Senior Vice President of Lundbeck and heading the Regulatory Affairs, Medical Documentation and R&D, QA organization.

I'm focusing my presentation today on the CNS area, but I would like to highlight that actually the area stands exemplary for diseases where

we don't have a deep understanding of the biology, and where innovation and methodology is almost as important as innovation in the lab in order to advance the field.

Why is it important to use CNS as exemplary therapeutic area here? We have a high unmet medical need, which will even increase for the rest of the aging population. And usually also, the field is considered a graveyard of drug development, which you have seen with recent (indiscernible) and Alzheimer's programs, for example.

We also would like to highlight that the efforts of the FDA that you have taken, for example, in the development of the early Alzheimer's guideline in the recent years, and also for the use of breakthrough designation in the past couple of years, even starting in 2014.

I'm following the outline of the questions that were asked for this public workshop. Where I put the OND provide additional guidance or prioritized scientific discussions. I have to say, I am coming out of oncology for the last 20 years, and now trying in the CNS area.

And I was reflecting on why is it so difficult to apply breakthrough designation and advance early, pick something, pick the winner early and move on. And at the end of the day, it all comes down to outcome measures.

You have a very objective or a much more objective outcome measures in oncology, or in HIV, where you have lab parameters or images, where you can clearly measure a size of a tumor and the shrinkage of a tumor.

It's much more difficult in diseases where you rely on, you know, questionnaires. Can you do well today? Can you walk today? And it often depends on the mood or other circumstances, and also, where you have a high placebo effect.

So outcome measures in the development of new outcomes to use tools that have been developed 30 to 40 years ago, which may even not withhold scientific scrutiny today is a primary area of, you know, where the methodology could push forward, drug innovation in this field.

Also establishing frameworks for

evidence collection in the real world, because many of the diseases, you know, you can have years of progression. In order to establish long-term benefit, it would be very important to collect long-term data in the real world evidence.

Also, you know, to see how can we develop add-on products and having specific guidance's on combination track development, similar to the oncology guideline, about how to establish, you know, like the efficacy of each component in a regimen.

Again, and it comes very similar to what the previous presenter said is that we need to develop regulatory approaches similar to oncology and use it to the full extent available to products being developed for dementia and cognitive impairment, such as the innovation coming out of the oncology division of the Real Time Oncology Review, which have recently applied to many of the approvals, trans diagnostic approaches.

I will quickly touch base on this follows very much the tissue agnostic approval in the oncology field, optimizing use of breakthrough

designation covered with the advancement in innovative trial design.

Innovative trial designs really also is applicable across therapeutic areas. If you look for an example in CNS or neurology, actually you do have symptoms that are common to different diseases, like cognitive impairment, or psychosis. So you can actually leverage master protocols like basket designs or umbrella designs or platform trials also for these areas of this disease area.

Also, you have on neurology, you have a common hallmark, which is for example, tauopathies. There are several diseases that link to tauopathies, and over expression of these tauopathies, and a specific hallmark of the disease.

And coming back also to the previous speaker, one of the reasons also reflecting on the differences between oncology and CNS is when you look at a CNS development program, where you have a high placebo effect, not so sensitive measures of outcome, as we just discussed.

It takes you usually a Phase I, Phase

II randomized placebo controlled study in order to understand, do you have a track that's really working or not. And then we talk about five years until we actually know we have a track that is innovative or is actually not working.

So finding new, you know, like adapting new methodologies like the previous presenter was saying about adaptive designs and using Bayesian designs in early development could actually already, you know, like facilitate, pick the winner, but also facilitate the use of innovative regulatory pathways.

Again, here it's more like highlighting why I am focusing on the CNS area. We have very objective measurements to say there is much less activities in terms of approval. Approval usually takes longer, much less breakthrough designations. It's just to highlight that there are clear differences between the therapeutic areas.

And how can OND promote effective track development is offering more opportunities to interact with the sponsors, that's coming back also to the previous speaker, and maybe not always

related to a project, but facilitating the scientific discussion.

When we look at our development programs, challenges are often not specific to one project, but go across different projects. So debating the science, debating the challenges around the methodology in scientific meetings with the agency would be very welcome.

Then I think, and it's by coincidence that Friends of Cancer will speak after me, but just to say in oncology, the meetings that the oncology division had with the Friends of Cancer Research Organization to facilitate and provide a platform to push forward our new methodologies, agree on the challenges, set priorities of which challenges should be addressed is a very important activity of the FDA as well.

And then, the development of guidances in a timely manner, such as the innovated trial designs. And we are very much looking forward to work with the new organization of the FDA and relevant key stakeholders because we believe this is -- this, you

know, CNS and development of new drugs in these challenging areas will require an all-hands on deck approach. Thank you so much.

JIM SMITH: Thank you. Dr. Farchione?

TIFFANY FARCHIONE: So you mentioned taking a trans diagnostic approach. And I can see where that's very appealing in cancer, where we know a lot about the pathophysiology of the illness, like right down to the genetics and everything.

But you know, in psychiatry, we don't have that. So and that makes it hard for me when I'm looking at something to say, well, you know, is this symptom, is the pathophysiology of this symptom the same in one disease versus another?

So how would you suggest that -- what would you suggest that we could do to encourage companies to really explore the pathophysiology a little bit more? Because I mean, I think that we share the same frustration with just relying on, you know, a rating scale. So --

KATRIN RUPALLA: You know what? Coming back, and that's the challenge versus the oncology

area, right, where you have, you know, a historical controls that are, you know, describing at least what the response rate is previously.

Your tumor agnostic approach was also used for rare diseases so far, right? So rare mutations or rare, you know, like is MSI high, for example, a mutation of burden. So it's also linked with the biomarkers as well.

I agree it's most probably you know, like it's finding something like tauopathies, maybe an area where you can start establishing some of the methodology for other areas to come. I think like you said, for outcomes you know, like schizophrenia or psychosis or dementia, cognitive impairment will be more difficult, but if you have an area like the tauopathies that is already driven by a certain hallmark, that may be easier to say across these tauopathies, you have one symptom, you know, can I have different subsets that -- for example.

You know, like as if -- I think that would be most probably the easiest approach to start with something that's more defined in this space.

JIM SMITH: Dr. Bastings?

ERIC BASTINGS: Yes. You're calling for integrated and (indiscernible) approaches in the absence of regular biomarkers. Can you elaborate on that?

KATRIN RUPALLA: So I think again, I want to extrapolate a little bit from oncology. In neuropath oncology clinical trials, you have almost in every trial now, whole genome sequencing after patients. And getting biomarkers and understanding the genome.

Working now in the CNS area, we don't do any patient sampling or very little sampling. It's spinal fluid, SMRI, but genetic testing has not been fully implemented in the science of neurology in clinical trials.

So you know, like I think at the beginning, it will require a commitment to collect this data and you know, understand what we can do. But also, in the area of big data, I think the more data you will accumulate in the future, the more it'll be possible to find potentially some genetic markers

also relevant for CNS diseases.

So integration both you know, from the sponsor side, you know, like the willingness of patients to provide the patient sample, and developing further guidance on like the previous speaker on genomic testing and use of the data.

JIM SMITH: And one final question from Dr. Chambers?

WILEY CHAMBERS: So following up on that, you -- do you think people are not doing genetic markers in some of these other diseases because the FDA is stopping them from doing it?

KATRIN RUPALLA: No. I -- for me, this is why I call it integrated approach, right, is -- I think that needs to be commitment from -- you don't collect usually data if they are not in some form useful for regulatory decision making or at least to advance the science, all right?

So if -- and I think here, it is advancing the science and you know, the regulatory acceptability, if you find a mutation or if you find a common hallmark, would the FDA be open to a discussion

based on this data and the use of this data in the submission?

So that's why I think an integrated approach is, you know, like I said, it needs a commitment from all parties, you know, like that we have to make advancement in the field using -- doing testing, acknowledging the data, harvesting the data, and then also accepting the data on regulatory submissions.

JIM SMITH: And we'll get one more question in from Dr. Birnkrant.

DEBRA BIRNKRANT: Thank you for your presentation. So we've heard this morning, not just from you, but from others about various types of clinical trial designs and using master protocols on platform protocols, but we didn't or haven't heard much about formation of clinical trials networks. Is that also part of your approach to be able to address these types of less common diseases that are difficult to study?

KATRIN RUPALLA: No. I can't answer. You know, sorry. I can't answer. I don't know what

we are currently doing on the clinical network side, so sorry.

JIM SMITH: Thank you very much for your presentation.

MARK STEWART: Thank you for the opportunity to present or to discuss some potential opportunities to help prioritize some of the efforts that are going on in the office of new drugs. But first, thank you for your continued efforts to recognize the importance of seeking input from outside organizations.

And I think it's been exemplified in terms of the outward facing nature FDA's had over the past several years, and recognizing the fact that there's always an opportunity to strengthen the agency.

So Friends of Cancer Research, we have and continue to be continuously involved in this intersection of science and advocacy and policy. And based on our interactions with a variety of stakeholders, including FDA and other PhRMA companies and actually organizations and patients, I'd like to

share a few areas that are based on some learnings from our activities and working groups and white papers that we've put together over the past few years.

So the first thing I'd like to focus on is facilitating the use of innovative trial designs, and maybe even more broadly is facilitating the use of innovative drug development strategies. I'd like to acknowledge FDA's role in -- and putting out guidances for adaptive designs and master protocols that really help illuminate strategies for addressing concerns around IRB reviews and informed consent forms, and even addressing issues related to sample size and patient population, treatment arm and endpoint selections.

But beyond just the issues of developing one of these master protocols, I think where the rubber meets the road is really how to implement them. And I think there's opportunities here for improved interactions between FDA and those that are trying to implement these innovative trial designs.

And I have similar themes of what have been previously discussed. And I think just you know, I can add an example here based on our experience with our lung cancer master protocol lung map, which is a master protocol that involves multiple sponsors.

And as you could suspect, it's critical to really have this master protocol launch in a uniformed manner. And that requires having each of the arms that consists of different sponsors having timely feedback, typically in a uniformed fashion.

And we've seen that alignment on launch is critical as sponsors manage competing priorities, and even potentially drug supply issues. And so, it's not ideal to have a drug waiting as they're waiting for other sponsors to clear their timeframes.

And so, I think more real time interactions for feedback on items that don't constitute a regulatory decision could be helpful in those instances. However, we do recognize the need for this multi-level review for full agency decisions, but a point person for informal, non-binding feedback can certainly help address FDA concerns earlier,

ideally even before any formal FDA submission or even interaction occurs, which our hope is that that could result in more balance and time and resources, but ultimately improve the efficiencies for the trial and ensure timely access for the patient.

The next area is streamlining the development and review of drugs. And we recognize that the regulatory review process for drugs is a resource intensive undertaking for both the sponsor and the FDA that's tasked with assessing the drug's benefit and risk.

Improvements in the efficiency of this process can have significant impact on the resources and time required to complete a drug review, and importantly, bringing these new therapies to patients more quickly. And I'd just like to highlight the real time oncology review pilot that was initiated by OCE and ask whether there'd be opportunities to incorporate that more broadly within the agency and helping to improve the efficiency and process.

Building off of work we did last year on a white paper that consists of a multi-stakeholder

working group, I think it was recognized that the benefit of real time oncology review will ultimately be realized once we're able to move from supplemental applications into the reviewing new drug applications, recognizing, though, there are challenges that will need to be considered both from a CMC perspective that might need to be built into the real time oncology review.

And so, looking at a potential expansion of the real time oncology review that potentially expands from a more simple supplemental NDA to a more complex supplemental NDA, and eventually making its way into breakthrough designated new molecular entities that might involve companion diagnostics and etc., and really cataloging at each step, kind of the learnings and the processes to ensure that there's a more appropriate roll out of that pilot.

The last area I was going to focus on was just encouraging innovation while managing uncertainty. And I think FDA's certainly done an incredible job, particularly with the oncology space

with this. But as we've begun seeing successes with oncology, we're continuing to push the envelope.

And it was mentioned earlier that now we're starting to look at opportunities for disease interception, and neoadjuvant therapies. And with that can result in trials that have very extended lengths of five, 10, 20 years before you might get the clinical endpoint that you're trying to measure. And in those instances, surrogate endpoints will be critical.

And so, how can we capitalize on the best available evidence today to help ensure that we're able to help patients now rather than having to wait five, 10 years down the line and paralyze ourselves as we try and create the perfect biomarker before we're able to make any progress?

And so, while I may not have a specific answer as how to do that, I think even the meeting yesterday that was noted earlier with MRA around the use of pathological complete response, I think these dialogues will be important to help inform potential guidance and help inform how these clinical designs

could be ultimately designed.

In addition to managing uncertainty, there is uncertainty from the regulatory perspective in terms of whether the drug's truly beneficial within the context of a clinical trial that's being reviewed by the FDA. There is additional uncertainty from a patient's perspective, as these drugs come onto the market.

And asking themselves, do the patients that were included in this trial look like them? And so, I'd encourage looking at opportunities and certainly applaud FDA's role in releasing draft guidance around broadening eligibility criteria to ensure that we have as much information as we can as early in the drug development process, so once they are on the market, patients are able to make the most informed decisions as to which therapy is best for them.

In addition, I recognize that there's other venues for the discussion of real world data, so I'll focus my discussion just on the use of contemporaneous or historical clinical trial data. So

I think there is a wealth of information that's available.

And while single agent -- single armed trials alone may yield important safety and efficacy signals and have certainly been relied on for regulatory decision making in certain clinical and regulatory contexts, external controls, whether it's using clinical trial data or even real world data, I think provides an additional -- it provides opportunity for additional context and supplementary evidence to really understand that treatment benefit.

And so, guidance on how to appropriately incorporate these types of data into a clinical design study I think are important. And when endpoints from different clinical trials are able to be compared to one another are also of importance.

And so, I just will end by just also asking, well, one, recognizing the efforts that FDA has undergone and the multiple pilots that they've begun to initiate. But to ask that there be some form of impact monitoring. And identifying metrics that could help us understand the benefits and successes or

lack thereof of some of these pilots that can help inform the next steps for the community, and really understand the benefits that these innovative trial designs and programs have to offer. Thank you.

JIM SMITH: Thank you very much. We'll take a couple of questions. Dr. Joffe?

HYLTON JOFFE: Hi there, yes. I've heard from a few presentations now this idea of non-binding feedback, you used the word informal feedback? And I'm still quite fuzzy on what we mean by that. You know, usually when we give advice to industry, we vet it through the division director. Are you talking about -- or a deputy director -- are you talking about feedback that's given by a primary reviewer, for example, which may or may not jive with what the division director would say so?

One question is, what are we talking about byinformal? What are we talking about by non-binding? What type of advice is this, that you think would be helpful to get in this manner, if you could provide some clarity? Thanks.

MARK STEWART: Sure. Well, I think in

terms of just informal interactions, it would be more probably on the reviewer level. And just to have that feedback earlier on, to really get an understanding of where there could be potential concerns prior to the formal submission could help trial this as they move forward with the formal design that goes into the submission.

So you know, I think it's certainly -- it's context dependent and I think it will just depend on the situation. But in terms of, you know, our interactions with the master protocol for lung map, I think having that interaction early, so then, once it is submitted, we can ensure kind of a timely launch, particularly when we're trying to juggle different needs of sponsors.

And each might be in a different timeline, but for these master protocols, at least what we've been hearing is that it's important that there really be a unified launch for these.

JIM SMITH: Thank you. So that we can get in two more questions. Let's try to have succinct questions and answers. Dr. Gormley?

NICOLE GORMLEY: Yes. So you mentioned that the use specifically of a lot of the oncology pilots that are ongoing, the RTOR, etc. And oftentimes, you know, we seek feedback on a case by case basis. So after an RTOR or an application has gone through the RTOR pilot, you know, seeking feedback with that individual sponsor, etc.

And I was just -- you mentioned the importance of capturing, you know, larger, more global or widespread metrics. And I just wanted to get your thoughts as to what you thought would be meaningful metrics that would indicate, you know, success of such pilots.

MARK STEWART: Sure. I'm sure I'll miss some, but I think even time. So the time it takes from a submission of a -- or the IND to the NDA and even the NDA then to the approval and understanding whether there's any impact on that.

Even though the number of studies that might be required within that clinical development program could be important. I think from a patient perspective, understanding if, as part of streamlining

drug development, does that mean, you know, a decreased number of patients that might be required to answer a question? And so, those are just a few that come to mind.

JIM SMITH: And Dr. Beaver?

JULIA BEAVER: Sure. Just following up on Dr. Joffe's question regarding the earlier advice in facilitating the use of innovative trial designs. It sounds like you mean more like almost a pre-pre-IND type interaction or, do you think even just involvement of FDA on the working group for that type of project might suffice?

MARK STEWART: I think we certainly saw the benefit of that, and even when the initial discussions around this concept of a lung cancer master protocol was underway, FDA was certainly involved in those discussions. So I think we've seen the benefit in that, and whether there's a way to capture that and other aspects for other people, I think would be helpful.

KEITH FLANAGAN: One final question. We want rapid informal iterative feedback

from reviewers, and at the same time, we want to treat similar situations similarly. Do you have any comments on how to reconcile that tension?

MARK STEWART: I'm so sorry. Can you repeat that?

KEITH FLANAGAN: On the one hand, you're advocating for more rapid informal feedback in development and review of medical products, right? On the other hand, and at the same time, we want a consistent approach so that different therapeutic areas treat similar clinical situations similarly. Can you comment or make any suggestions concerning that tension?

MARK STEWART: Sure. That's a good question. I'm not sure I have the exact answer for you because I do recognize as you go down this path of having these informal interactions, that there is this opportunity that you might get -- you might lose uniformity in what's being put out there.

And so, I think even to the extent that you -- that somehow, these discussions could be catalogued in a way or even communicated more broadly

within the divisions could be helpful. And I guess the types of interactions that I'm thinking about would be more around kind of the strategy and not necessarily around kind of the regulatory and decisions that are being made, so more of kind of an academic discussion, are types of interactions that I'm more thinking about.

JIM SMITH: Thank you very much for your presentation.

RUSSELL REEVE: All right, well thank you. It's good to be here. This is a really exciting time in clinical development, lots of exciting innovations occurring. And I'm glad to be here. It's also challenging times. Let's go onto slide two.

Okay, so I'd just like to set the top or set the stage of the common areas that we're seeing of innovation that are really the hot topics right now. We're seeing three broad areas that are classified here. One is the area of innovation and types of evidence that we have efficacy and safety that we will accept or would rely on.

For example, using external comparators

to augment the concurrent control groups or the use of real world data that are strictly using clinical trial data. There's also the trial designs that's reflected in the protocol. We've talked a lot about master protocols, which are a very hot topic right now, adaptive designs, modeling simulations, and precision dosing, which we haven't talked enough about here, but I'll talk about a little bit later.

Then you also have the trial designs on the operational side, on the virtual trials, which allow more patients to be involved in the clinical trials, therfore connected devices which speed up our collection of data.

And all of these work together. We need to keep that in mind. They all work together to improve on each other and have actually synergistic effects. So I would ask that we try to support that. Okay, next slide.

Okay. So some of the obstacles that we're seeing to incorporating these into more of a clinical development. One thing we have to keep in mind, and I like innovation, but not every trial is

really suitable for innovative methods, so we have to accept that fact.

So identification of these cases where innovation is useful is very helpful. Identifications where they're not useful -- helpful is also very important. So if you can come up with some case studies, some examples, some ways of talking about how to differentiate these, that would be very helpful.

There's another issue that we've seen here is really the lack of expertise in these innovations. Of course, we don't want to engage in areas that we don't have expertise in, but it takes some time to do that.

We -- and as a statistician of course, I view statistical expertise as very important, but it is also expertise and innovations throughout the whole trialist community, all right, the medical (indiscernible), the pharmacokinetics, the operational sides. We all need to understand the benefits, the concepts of these innovations, how they benefit us, really the suitability of any given application of innovation to a particular trial or a

particular problem. So the more we can do to support that.

More case studies would help. More exposure and conferences and simulation games. And I like simulation games. I'm a simulation person. But simulation games can really help us to understand how a problem may work out. You can try various interactions, see what happens. You can -- and it doesn't hurt anything because it's only in (indiscernible).

And you can get a lot of experience very rapidly on how these innovations interact with each other and have -- if you get the right answers or not. And I think this would be true on both the regulatory side as well as the industry side, and working together could be very useful. Okay, next slide.

We want to talk a little bit about master protocols, and the fact that they're using a lot more Bayesian analysis and adaptive design concepts within them. One of the issues that we're seeing with the Bayesian analysis and Dr. Levy pointed

out that Bayesian analysis reduced sample size, speed up time, have a lot of benefit to them.

But one of the issues we're seeing is that it's a completely different language from the frequentist's viewpoint that we've all come to know and love. So we need really training throughout the whole trialist community in what this language entails and what we can expect from it.

Okay. I do want to talk a little bit about precision dosing because I don't think we've mentioned that here. This is an innovative method. Precision dosing really is -- provides a mechanism to provide a dose for each individual patient, the right dose for each individual patient or a small subgroup of patients.

All right, this is very powerful -- it has been well known throughout the pharmaceutical community, but I don't think it has really been well known in the statistical and general medical community. And there were benefits of that.

And the past really has been used in narrow index -- or narrow therapeutic index drugs, but

the benefits really can extend much beyond the narrow therapeutic index drugs to almost every drug that has a dose response curve to it.

And in fact, we have shown that it can reduce the sample size fairly substantially in some cases. And if your objective really is to take a Phase II design and find the right dose according to Phase III, it will -- has the highest chance of finding that dose. It is superior to judicial fixed designs, it is superior even to adaptive designs.

Okay. I just want to highlight some of the innovations we see in -- often in orphan indication in Gaucher disease. And the reason why I highlight this is because these are what's going on there, but they're also applicable to the broader development community as well and other disease areas.

So if you look here, there is a lot of natural history trials. We have single arm trials, screening studies, you know, biomarker studies. And these are all types of studies that we can incorporate into the general -- into our general development for other disease areas as well.

Okay, if you look at slide number 6 here. What have you learned from this? Well, patient registries and natural history studies are really very important for clinical development. They give us a lot of information. They help us understand the disease process, the metrics we use, how the metrics vary over time in the disease and how those metrics vary across sub populations and understanding sub populations is very important as well.

And also, the statistical modeling should be incorporated into the clinical programs. And one last thing to highlight here is that we really need -- if we're going to have innovation, we're going to have to accept that it's not going to look exactly like our traditional approaches. It's going to be different.

And so, encouraging the -- that experimentation is going to be important to moving our art of clinical development forward as a discipline. Okay.

Now to drive adoption. We really need to show the benefits of these innovative methods. And

it helps to have specific applications that we apply them to and compare them to a traditional approach with metrics here.

So for precision dosing, for example, we actually -- there is mathematical proof that it reduces the sample size. But most of these, you are not going to get that. You are going to have to rely on simulation methodologies to do that.

In the platform trial cases, what we've actually done is we've built examples of a platform designs as well as the traditional designs and we compare them both for costing and for timelines. And that's been very helpful for our clients to understand the benefits of that.

And finally, my last slide here. If you can have forums that we can really get together and discuss on a scientific basis these innovative designs, bringing together the regulatory academics industry, all talking about that.

And what we've found is that having a session like hackathons, where people can get together and talk about designs and the problems together with

different viewpoints, that has been very helpful in the past, and I highly encourage us to work together to create those in the future as well.

And I'm running out of time here, but having conference sessions, where we can really talk about these innovative designs and in some sort of detail. A lot of the conference talks we talk about are fairly high level. I'd really like to see us really getting in the details of what's going on, how the recruitment rate affects randomization ratios or the timing of the adaptations, for instance.

And the more interdisciplinary, the better, because we need everyone working together, so I would encourage interdisciplinary work. Thank you. Thank you for your attention.

JIM SMITH: Thank you very much.

ANN FARRELL: Just a quick question. You talked about the forum for discussing innovative designs. And were you thinking disease focused or more broadly? Because I think it's a little different given sort of where the field stands for certain diseases.

RUSSELL REEVE: Yeah, I mean, it can work -- depending on the fields. I mean, (indiscernible) has been doing that in adaptive designs for a while. And that has been very effective. I think there is also some broader general principle forms that's also very helpful.

Because some of the learnings you'd have say in neurology can carry over to like rheumatology. And the mathematics is similar, even though the disease itself is a little bit different, yeah. You're welcome.

JIM SMITH: Thank you very much for your presentation. Appreciate it.

PETER SCHIEMANN: Good afternoon. Yes, it is. My name is Peter Schiemann. I am a managing partner of Widler & Schiemann, it's a consultancy, global consultancy based out of Switzerland and Zurich. And I'd like to thank the ladies and gentlemen of the FDA very much for giving me the opportunity today to contribute a little bit to this discussion.

I myself and my colleague Beat Widler,

whom some of you might know, had some brainstorming of what to present today, because as a consultancy, you get to know about many problems of your clients, what works, what does not work.

And finally, we came to a conclusion to submit two topics of which then I was told you choose. And we could not decide, so I brought you two topics today, which I also want to send a disclaimer upfront. So those are ideas.

It's supposed to be a brainstorm food for thought. We're not claiming to have solutions to the very detail because you will see that both topics, one we called flipped clinical trials, the other one of indication, one standard dose protocol, multiple IMPs require quite extensive discussion and review to make it actually happen.

So without further ado, excuse me. So the flipped clinical trials. What is this about? So there are two aspects to it. One, the problem statement as I've listed it here. When you have patients, for example, suffering from a serious disease, but they're, you know, it's not so much

progressed. I'll give you an example, multiple sclerosis, they usually treat it by the GP's at the very beginning.

And today, however, clinical trials in general take place at specialized clinics, and therefore, patients needs to be convinced to change their treating physicians in order to partake in a clinical trial.

And this very often, and I have a close friend who is a GP and who stopped working in clinical trials because of that. And supporting them, actually. For patients, this means disrupting the relationship with the treating physician.

Usually, you have a very close relationship, as most of you might know, who are sick in the past. And for the GP, this results also in losing a patient, usually to a big clinic, and not having access to the hospital records as well.

As a result, the GP may not be very enthusiastically support participation of his or her patient in a clinical study. And for the patient, this could result in additional burden, for example,

having to travel to the institution, being exposed to an unknown environment, etc.

So that said, how could a solution look like? You see it says solution, but again, as I said, this is an idea, it's not necessarily a whole solution. What we could do -- and before I get into this slide, as I said, I come from Switzerland, and there's currently a pilot, a very interesting pilot ongoing at the ETH in Zurich at the (indiscernible), at the university hospital there, which are actually trying this out, what I am going to talk about in a second.

And my colleague Beat Widler is an advisor in this pilot. So patients having treated by the local GP and remain with a physician who knows them best. So this of course implies again a problem because most of the GPs are not very familiar with clinical studies, and we know from research from the Society for Clinical Research sites that about 40 percent of GPs who have participated in a clinical study for the first time quit because of the effort that is involved.

Now how to remedy that? There is a need to leverage the proficiency in clinical trial conduct of the hospital treating physician. So the idea here is to have a mixed investigative team basically.

So GP investigators would not only have only basic GCP knowledge and/or GP investigators can use systems that are maybe not fully compliant, computerized systems validation comes to mind, for example, electronic health records they're using.

The second part is we could design trials, especially longer term trials in such a way that visits requiring specialized equipment or exams, baseline, end of treatment visit, etc., are contacted at larger institutions that have extensive experience in the conduct of GCP trials, where interim visits are conducted by the patient's GP.

Of course, this always depends on the (indiscernible), I know that. And we also need to challenge classic endpoints, and that comes back. And I feel a little redundant with something that I am saying now, and also in the second topic, with

colleagues that have spoken earlier, we need to also -- there's classic endpoints.

For example, multiple sclerosis, the time 25-foot walking test, which is actually currently done at the University Hospital in Zurich. So we could use modern technology, for example, with the help of apps to monitor the movement pattern of MS patients.

I mean, we all use our smart phones, smart watches, or Fitbits, etc., to measure our fitness and things like that. Why don't we use modern technology in clinical trials and to think a little bit more innovative? And if it's better than the walking test, why not use that, even if we know it's not 100 percent perfect?

And for example, all follow-up visits of safety could be done by the GP's office. So the question to FDA, would you be able -- would you be open to that approach, and also, of course, changing established endpoints when it's supportive of modern technology.

Now the next part has already been

touched upon also by some speakers here. We were wondering and we have had lots of experience in clinical studies supporting clients with protocols. Only part of our clients were using templates, and even those templates were not, let's say, the best.

So there's a lot of problems at the moment, and as we know, especially when providing those protocols to the PI's, then in the studies, they have to familiarize themselves. And you reviewing those protocols at FDA probably also know exactly what I'm talking about. That the consistency in the conduct in describing a clinical trial in the protocol, which should be the work instruction actually for the site is not always very good.

Now what could we do? We could use standardized protocols, for example, across a disease or a therapeutic area. One would only change for a trial what needs to be changed. Based on the latest research, results availability of biomarkers.

And as colleagues earlier said also, it may be genetic research and analysis, innovative endpoint determination and so on. As a result of such

standardization, the whole approval process of the protocol would be much easier and faster, not only for FDA, but also for IRB's, for example.

And in addition, of course, now looking at the physicians being involved in the clinical study, they would not have to re-learn the "bible" every time they participate in a new protocol, because when -- once they have become familiar with a template, they will know what to do.

So the big advantages could be for treating physicians and patients, increased familiarity of trial procedures with treating physicians, including GP's, over time optimization of trial conduct by implementing learnings from previous trials, while being able to limit changes to the template.

FDA would need to spend less time to review. Standards could be even endorsed by FDA. I know this is, you know, a very bold statement, but I am pretty sure eventually this could be something that can happen.

The advantage for sponsors could be

lengthy protocol development. Writing iterations can be avoided on the basis of a recognized standard. Discussions with FDA on the design of the protocol could be accelerated, and the protocol would undergo much faster if there are review and approval, while avoiding hobbyhorse comments by any reviewers.

I mean, we know that we don't know everything, and sometimes, we focus on what we know best. And there are sometimes discussions emerged that are slowing down the process. Time and money could be saved, and patients getting access to new medications much earlier.

Now again, the question to the FDA, would you spearhead such an initiative. For instance, leading a pilot in a crowded disease area. I can imagine as I have been working with CTTI in the past, that that might be a forum to discuss this matter, maybe, and we would be happy to work with FDA and relevant stakeholders on this in the future. Thank you.

JIM SMITH: Thank you. Dr. Lemory?

STEVEN LEMORY: So you call them

flipped trials. We've sort of termed them decentralized trials. But and I have a support for them because, you know, really you see there's a geographic inequity in clinical trial participation now depending on where you live.

What do you think are the biggest sort of hurdles from the systemic standpoint, and even from a reviewer division standpoint, it's okay. But you know, if I think it's okay. And then, I'm mostly interested in can the protocol be followed? Are patients protected?

And so, I'd want to see a sponsor, you know, provide assurances of that beforehand. And I don't see why that couldn't happen. But as far as more systemic issues about the IRB's or you know, inspectors within the agency or other bodies, you know, worldwide, what are the big global issues that have to be, you know, solved before sort of it gets done at a more, you know, a more frequent --

PETER SCHIEMANN: Yes, I completely agree with your comment. Of course, we have to start small somehow, so there needs to be a -- let's say,

call it a controlled environment, in which to run those tests and to see whether it can actually work.

But what we've seen so far today, there is lots of room for improvement. And we had a discussion earlier this morning here that innovation in our industry is sometimes very hard to come by, meaning changes in the procedures and how we do things.

I'm thinking about medical writing. I am thinking about protocol design in general. Every study is unique. And there are interests of several groups. I think if this can be driven more from the agency point of view saying, look guys, this is about drugs in this indication and this is this class of drug, you have reviewed all the protocols on that and you know what works and what does not work.

Each individual sponsor, they don't. They sit in their own little bubble, right? So I think here, FDA can play really a key role pointing out what is actually working and what is good? What is not so good? And also say maybe -- I'm leaning a little bit out of the window now, but also telling

sponsors how many data points are actually enough in a clinical study to make it easier.

Because that was exactly the discussion I had with my friend who's a GP who stopped working on clinical trials, just they wanted me to collect over 100 datapoints. I cannot do that. This is actually impossible. And they cannot -- they don't use the data, actually, for the -- for determining whether the drug is good or not, you know, quote unquote.

And that's why I think there needs to be a concise environment in which this should be tested. Maybe as I said, you know, in one area and run a pilot, see if it works, get all the stakeholders on board. And I think over time, this can lead to a vast improvement.

JIM SMITH: Okay. I know we're eating into our lunch hour, but we're going to figure that out. We've got another couple of presentations, but actually, we do have a couple more questions, so hopefully we can keep the answers relatively focused. Dr. Yanoff and then Dr. Bastings?

LISA YANOFF: Thank you for your

talk. I'm wondering if you though that we should be aware of any special considerations for pediatrics or would all the same information that you discussed apply, do you think this would be particularly useful or not useful in pediatrics? Or what should be think about?

PETER SCHIEMANN: Pediatric trials, to be honest, I cannot really comment. I think my talk at the moment was focused on adult patients. My personal experience with pediatric studies is that you have to be very careful of the individual situation of the drug and the disease. So at the moment, talking about your colleague's comment to have a kind of a pilot, I would not look into any pediatric indication at the moment.

JIM SMITH: Thank you. And Dr. Bastings?

ERIC BASTINGS: Yeah, so regarding the standardized protocols, who would keep the library of protocols that people can use? How would you see that?

PETER SCHIEMANN: That is a technical

question. If we come to a conclusion that the FDA would actually endorse certain standards so that we have a -- let's say a template for a clinical trial in a certain indication for a certain drug type, then this could be, you know, something that companies could download from the FDA homepage. It would be sitting there and the text that is standard could not be changed.

You can add then your items that are specific to the drug and specific to your company needs, etc., and your design or how many patients you want to include and other points. That could be something that how it could look. But to be honest, this is up for discussion and I think at the moment, in my opinion, much too early to think about. I don't know what your procedures are at FDA to provide such templates to the public. I am pretty sure they are standard procedures.

JIM SMITH: Thank you very much.

PETER SCHIEMANN: You're very welcome. Thank you.

JITENDRA GANJU: Okay. My name is

Jitendra Ganju and I'll be speaking about strengthening the interpretation of data from clinical trials, all right? So let's start with the conventional way with which things get done. So in trial protocols, we pre-specified the primary endpoint.

We pre-specified a list of secondary endpoints and so on, and attached to each endpoint is a single method of analysis. And this is the key part. There is a single method of analysis through which we interpret the results formally.

And the issue with that is, you know, it's our best judgment. We don't know whether what we are pre-specifying is going to be optimal for that endpoint for that upcoming trial. So here is an example of how things can go wrong, if you choose an incorrect model.

So two models were applied to the same dataset. They give different answers and it would lead to different conclusions. I'll come back to this example later. I'll make a couple of side notes.

One is that I've taken very simple

examples to get the point across quickly, and the second is that the examples I've taken are in the public domain, so that others can replicate these findings.

So when is use of a single method risky for any given endpoint? It's risky when we out of necessity cannot do a large trial. It's risky when we are conducting a complex clinical trial and there are just too many uncertainties to feel confident with the pre-specified method of analysis.

What this comes down to is that the risk in the method that is pre-specified is tied to our experience with the endpoint. So I have over here on a continuum, endpoints with which we have varying degrees of experience. On the left-hand side in black are endpoints with which we have more experience, like hemoglobin A1c.

On the right, there are endpoints with which we have less experience, like number of days hospitalized. In the middle in red, the endpoint time to event, it depends on the context. In some cases, we have experience with it, and in some cases, we

don’t.

Here is an example of a time to event endpoint. This is typically analyzed by the Cox model, which makes the assumption that these hazard rates have to be proportional. This is -- this assumption is clearly violated in this example. And the Cox model would not be the best way to analyze such data.

So what can be done? The proposal is that we take an approach that is similar to the way we invest our savings. We diversify our investments. We don’t invest our savings in the shares of one company. We prefer to diversify.

So the proposal is to take a similar approach. Rather than pre-specifying one method of analysis, which we are not certain about, pre-specify more than one method. Combine the P-values from these pre-specified methods, but do it in a way that controls the alpha.

And the method that I’m going to speak about today is something called Fisher’s combination method. And in the next few slides, I’ll show that

the combination approach is very robust. In some cases, it gives more power, and it's very flexible.

So going back to the example we looked at earlier. So the model that had log transformed the covariate give a large P-value. The model that did not transform the covariate give a very small P-value. Now if we were not sure of which approach to use, you can prespecify both.

And take the combined P-value, which in this case is controlled for Alpha, and it gives an answer that's very close to the better performing model. And this is what robustness means. It's insensitive to the choice of a sub-optimal model.

Let's take another example, about the endpoint. Should the endpoint have been log transformed? You're not sure if it should be or it shouldn't be. Do it both ways. And again, it shows this is again an example in the public domain, it shows that the combined P-value gives an answer that's a lot closer to the better performing model.

Let's look at it a different way. If you're not sure about the metric, should it be percent

change from baseline or should I look at data on its original raw scale? If you're not sure you can do it both ways, if you did it for this simulation setup, if you did it using percent change, power is abysmally low, around 30 percent.

If you did the analysis on the raw scores, power is quite high, it's about 86 percent. But if you're not sure, you can propose both methods, assuming both ways of looking at the data are reasonable, and the combined method gives power that is much higher than the method that performs poorly, and it's slightly lower than their better performing method.

Here is a setup, where the combination method actually can give you more power. And this happens when the trial size is small, and there are many covariates to choose from. So in this case, there were 16 covariants to choose from, and the trial size is 20.

So there are many different single models one could have selected. The worst you could do in terms of power is about 20 percent, right? So

you're pre-specifying, you don't know if it's going to work well or not. The best you can do with the single model would be -- would give you power of around 50 percent.

With the combined approach, and here's the important part, even though for this setup, the combined approach includes the model that performed the worst, it gives you more power than the best performing single method.

The versatility of the combination approach comes through with group sequential trials. The conventional approach of doing things is to pre-specify a single method of analysis at each interim time point and at the final time point.

So it's the same method used for every analysis time point. Combined methods are a lot more flexible. And in this case, it's not just the trial results that have to be interpreted. You can actually stop the trial earlier, if supported by a formal method of analysis.

So to take an example, let's just look at a simple case where there is one interim analysis

and one final. Let's just say the conventional approach looks at the log rank statistics. So you would use that statistic for the interim and for the final.

But with a combination approach, you don't have to be so tied in. You can use, for example, a weighted log rank at the interim and a log rank at the final. You can even take it a step up. For the interim, you can pre-specify more than one method of analysis, and for the final, you can pre-specify a different set of analyses, and then do it in a way that controls the alpha.

And as before, the combination method was robust for group sequential studies. So to wrap it up, the limitation, it's -- it is a robust procedure. The limitation is that it doesn't produce an estimate of the treatment effect.

And I would suggest that to build experience with this, one can apply this on trials that have already been completed and look at how the combined approach compares with the method that was pre-specified.

For upcoming trials, one can add this to trial protocols, and again, do a side-by-side comparison of how the combined approach works with the pre-specified, the single pre-specified method of analysis.

There are many ways to combine P-values. There's, you know, you can take the minimum P-value and control the alpha for that. What I've used here is something called Fisher's combination test.

And alpha control is achieved through something called the permutation methodology. And everything that I've spoken about, for the most part, is contained in these three references. Thank you for listening.

JIM SMITH: Thank you.

MEG JARDINE: Well, thank you for accepting our application to speak with you today. I'm Meg Jardine, a physician and a researcher of the George Institute and I'm the member of the International Society of Nephrology clinical trials group and co-chair of the trial design work group

there.

And our (indiscernible) there is to increase the high quality research generation for new trials, for new treatments in my disclosures. In nephrology, we win the wooden spoon for the worst generation of evidence over time. But that is something we're trying to change.

The International Society of Nephrology two years ago held a workshop, and one of the outputs of that was a goal, an ambitious goal that we would have 30 percent of people with CKD, chronic kidney disease in a trial.

So to do that, we obviously need to do something different or we will continue to hold the wooden spoon. And the answer for many of the challenges in nephrology are the master protocol trials. So what I'd like to do is outline some of the key features of those trials and how they would answer some of our problems in nephrology.

Firstly, the ongoing nature of these trials, which has been demonstrated successfully in other indications would allow our relatively low

frequency of diseases to be represented in stable infrastructures that permitted ongoing development of schools in our trial staff both at sites and centrally.

One key feature of master protocol trials is the use of a common endpoint, whether for basket or on (indiscernible) trials. And in fact, in nephrology, we have multiple conditions, generally poorly defined and discriminated from each other, often defined on the basis of the appearance on a pathology slide.

But for all those diseases, and most common endpoints are the same. We look at variations of measurements of the albumin or protein in the urine or it changes in the eGFR. So in fact, we are moving to a common endpoint and a (indiscernible).

In fact, for focal sclerosing in glomerulosclerosis, a rare disease that has been the subject of much interest recently, there is a remarkable similarity in the endpoints that are used, which are around reduction in albuminuria, in this case, in a threshold based analysis. So in fact, we

do have a de facto consensus, or at least we're very close to a de facto consensus on a common endpoint.

We could use the -- yeah, I think these are the old slides. And nonetheless, we'll push on in a more common endpoints, diabetic kidney disease. We are working with the FDA to try and get a consensus on endpoints, reduction in albuminuria, and change in eGFR over time, that would be accepted by regulators and would allow the generation of evidence broadly, but particularly for master protocols.

Master protocols allowed the shared infrastructure, which leads to evidence efficiency, generation efficiency. The master protocol trials allow the use of multiple agents, and this has been demonstrated in previous, in other areas, such as most notably in oncology.

We're now fortunate in nephrology and after quite a few years in the desert, we do have a number of new agents being developed. But unless we get more efficient ways of generating evidence, we won't allow these to be sufficiently tested.

The advantages of course of a master

protocol is the use of a common control arm, which means we can reduce our sample size. Now for context, in the primary (indiscernible), which is a common cause of end stage kidney disease, they remain rare disease at the population level.

For adults, about 0.2 cases per 100,000 people per year. And for children, it's about half that. So we need efficient ways of generating the evidence and of not squandering our patients replicated control arms.

Finding patients for these trials is challenging. In focus (indiscernible) sclerosis again, over the last two decades, the combined registered trials required a little over 2,000 patients, but two thirds of those are in trials that are actively ongoing.

So we need to do more now than we have been able to do in the past, and again, new models and more efficient ways will be -- trial designs will be the way to do that. Even in our more common diseases, diabetic kidney disease, which is the most common reason that patients progress to requiring dialysis,

we still have relatively low incidents.

The recent successful (indiscernible) trials recruited six to eight patients per site. Now compare that with some recent cardiovascular trials, which recruited at least double that. So for sites, you can see the burden, and the advantages of the common and the stable infrastructure would definitely improve the situation.

Master protocol trials give us the advantage of allowing adaptive randomization, which allows the more efficient generation of evidence and the quicker pathways to successful treatments for our patients. And they also allow Bayesian statistical approaches to sharing knowledge across disease states, rare diseases that have similarity can be used to have some sharings, which would allow us to generate evidence in conditions which are impossible to generate evidence in at the moment.

A number of our (indiscernible) diseases are very similar pathologically, hopefully in the future we'll have biomarkers, but again, a low incidence. And sharing the knowledge will enable us

to at least get some evidence.

So master protocols in nephrology would allow patients greater access to trials. They would certainly increase the efficiency of evidence generation, they would allow us to incorporate external learnings, both from within the trials and from other trials.

The net effect would be that instead of having competitive trial endeavors, we would move to a collaboration state, which would allow us to generate our evidence more efficiently.

Now I think there are three ways that the FDA can support this. Firstly, by giving the support to master protocol trials in nephrology that has been given to oncology would be really engender confidence in our community that this is an acceptable way to go.

Secondly, I think a focus on the need for global collaboration. You know, I outlined (indiscernible) sclerosis what the challenges for recruitment are. I think there's acceptance that even in the US, the largest community, there still are not

enough patients to efficiently test these agents.

And so, we need to embrace the global efforts to answer these questions. And lastly, the FDA's support in defining acceptable common endpoints. Now that would help us across nephrology generally, but would particularly help with master protocol trials, if we had an accepted, validated endpoint that was acceptable to regulators that would then again engender confidence in the master protocol approach. So I thank you.

JIM SMITH: Thank you. So the idea of a more collaborative research environment to optimize the amount of information that each participant provides is certainly a laudable one. Other than the endpoint issue, which you just mentioned, what other ways do you believe that the Office of New Drugs could help facilitate that?

MEG JARDINE: I think specific endorsement of the master protocol for nephrology would help. It's not a new design anymore in oncology, and when you speak to sponsors who have worked in the oncology space, they're very

comfortable. But in nephrology it is still new. And somehow, sort of smoothing over that barrier, so to allow us to look over the fence and see that this is a way forward.

JIM SMITH: Okay.

KEITH FLANAGAN: Thank you very much. So we're running a little over, a little behind. So with -- it's 12:42 now, and with the panel's permission, I propose that we reconvene promptly at 1:30. There being no objection, 1:30.

(Break)

KEITH FLANAGAN: Okay, we're going to now proceed with Session 3. As with the previous presentations, I'll announce the first speaker but not subsequent ones, so please approach the podium when the slide that lists your name and affiliation appears on the screen. After your remarks, please remain at the podium to allow the panel an opportunity to ask questions.

The first speaker is Dr. Chou, president of PD Sciences, LLC.

TING-CHAO CHOU: Thank you. Good

afternoon. I'm Ting-Chao Chou. My topic today this afternoon will be very different. It's mass action law based pharmacodynamic for quantitative and efficient drug evaluation guidance, subtitle computerized data analysis of single drug and drug combination in vitro, in animal, and in clinical trial.

I have eight minutes for my lifetime theory of work, so I have to show only the highlights. Those who want more detail, please contact or visit my website or my review article. The pharmacological review article 2006 summarized the theory, equations, algorithms, and application. Up to this week, they totaled 2,300 citations in 941 journal internationally. The PD theory has three major equations.

First, the median-effect equation which is the unified general theory of mass action law. It described that those affect mathematical relationship. The second one, combination index equation for drug combination. It define CI equal one its additive effects, more than one synergism, greater than one is

antagonism. The third one, dose-reduction index equation calculate how much dose reduction because of synergy.

Within the equation is unified theory of mass action law. It's described, the fraction affected, the ratio of fraction not affected equal dose versus median-effect dose to the M's power. (indiscernible) is potency. M is for indiscernible) order which is shape of dose effect curve. So this equation can be -- the (indiscernible) and enzyme kinetics can be the -- one forward. I don't know why.

Okay, Henderson-Hasselbalch equational pH ionization is also the Hill equation like an occupancy and the Scatchard equation of receptive binding. The dose effect curve can be linearized by the median effect plot. Sorry. Eight. Okay. Okay, forward. Okay.

The median effect plot which linearized dose effect curve. The shape is the slope. The X in the set is the potency like ED50, PD50, LD50. So it's universally validated. Okay, The computer

simulation of median effect equation different shape of dose effect curve, become different straight line with different slope. Different potency of the drug, it become different X intersect.

So this is very important new finding although it may be many years old. Any two data point on the straight line signify entire dose effect curve. So the minimum -- only two data point required to simulate entire dose effect curve, if accurate. Okay, so it's very powerful tool. This especially important in vivo, like in animal or clinical trial. You cannot have too many doses. So minimum, only two data point required.

Okay, now talk about PK and PD. PD model is mass action law. It describes dose effect mathematical relationship. PK is only the intermediate state of PD. PK has no model. And so it's so important, make it very clear, this compare PD and PK. PD for what drug does to the body and it's (indiscernible) derive equation, it determine efficacy and toxicity.

By contrast, PK is what body does to the drug and is an imperial formula, neither determine

efficacy nor toxicity. It's -- but PK help proper use of a drug. Computer simulation of drug combination synergy using median effect plot and the combination index plot -- equation, I'm sorry, not plot -- equation -- one forward. Okay, so we can calculate -- forward. Further. Further forward. Forward. Forward.

Calculate CI. CI equal one Additive effect, smaller than one synergism, greater than one antagonism. This have been cited 6,000 times in literature and it also calculate dose reduction, (indiscernible) dose reduction because of synergy and also it can -- example, in two drug combination to any drug combination. So universally applicable.

Okay, just my proposed recommendation of two drug combination design. Drug one dose by relationship, drug two dose by relationship , and the combination diagonal at constant ratio. For example, ED50 ratio. Only 16 data point, you determine synergy. You can take two weeks to do it. The analysis took two second, one

or two second to complete the.

Okay, computing software is for pharmacodynamic, pharmacobiodynamic, and bioinformatics. It's offered for free download as a donation to biomedical community. During the past seven years, 35,000 download by biomedical scientists from 129 countries.

This is the example of two drug combination in vivo. Anticancer xenograft tumor in nude mice. On the 10 data point, 66 nude mice and you look at this, at drug (indiscernible). Drug one three doses. Drug two three dose, combination three or four doses. Only this 10 data point generate those (indiscernible) curve, generate (indiscernible) plot, determine synergy. As a (indiscernible), determine synergy and tell you how many fold dose reduction due to synergy.

This entire (indiscernible) only take only one or two second. Next. This is the comparison of drug combinations in vitro, in animal, in clinical trial. In terms of time, cost, sample size, and minimum number of data point, you see in animal clinical trial only 10 data points. Quantitatively

determine synergy. Next slide.

This is a clinical trial, FDA approved, AZT plus 3TC uses 366 patient, but their designs are wrong. It's AZT use single dose. Impossible to determine synergy and also they use statistic P value. Nowhere you can determine synergy with statistic. It should be determined by combination index. Should use based on mass action law, look at another clinical trial.

AZT trial, interferon alpha, use only 36 patient. Used Chou-Talalay Combination Index Method each drug, three doses totally 10 data point. Analyzed synergy quantitatively. This clinical trial very expensive, take four, five years. Look at it day and night different. Next slide.

This comparison of drug combination in the past century, 120 years almost. Ten different method of synergy determination. Here, I compare with a trend of total citation since(indiscernible) publication annual citation per year, CI method predominate because it's the only method of quantitative all the hundred years all the other methods are(indiscernible) non-quantitative and also computer automation.

Next slide. This tell how much CI Method can tell us in drug combination. As in any synergism, how much synergism. Synergies at what dose level? Synergism at what effect level? What the isobologram look like? And How many folds dose reduction because of synergy? Dose reduction reduce toxicity, of course. It can also answer the question for optimal combination ratio, one to one, one to three, three to one -- which is better.

Sequential of combination, A follow B, B follow A or some other which is better. All these can be determined. Next. Thank you.

JIM SMITH: Thank you Dr. Chou.

TING-CHAO CHOU: I have many (indiscernible), 67 supporting slides to FDA. I hope you have time to go through it. This is all the (indiscernible). I think a lot of question people can ask because this very big issue, very important issue.

JIM SMITH: Thank you. Dr. Yao.

LYNNE YAO: So I’m not going to

claim to understand even part of the math behind what you've presented. I do have a basic questions, though, and it does seem that your models rely on basically physical chemistry or physical properties of the --

TING-CHAO CHOU: Correct.

LYNNE YAO: -- drug and I do wonder if you could comment on how, for example, we've used physiologically based PK modeling --

TING-CHAO CHOU: Okay.

LYNNE YAO: -- and how your models would be able to incorporate that or not.

TING-CHAO CHOU: Okay. As we know, our local system is very complex and very diversified. It is impossible to do one (indiscernible), one by one. So my approach was unified theory. Mass action law is basic fundamental for biophysics and biochemistry, the whole biology. So I use this general theory as a large common denominator so simplify very complex biological system to very simple way.

But this only talk about general

principle, not for specific. So this theory supposed to apply to (indiscernible) for any disease, any organ, only tissue, any cell, any gene, any drug. It's universal theory. Mass action law is entire biology basic fundamental principle. So --

JIM SMITH: Thank you.

TING-CHAO CHOU: -- I'm not asking for -- I know, it took me 40 years, so median effect equation alone took me 10 years derived 300 equations before I (indiscernible) simple median effect equation for (indiscernible) now. And combination index equation took me seven years.

This is all on record and it was ignore, nobody care – what are you talking about but now I have 36,000 citation.

JIM SMITH: Thank you.

TING-CHAO CHOU: And 1,269 journals.

JIM SMITH: Thank you very much, Dr. Chou.

TING-CHAO CHOU: Yeah.

JIM SMITH: We appreciation you coming today.

TING-CHAO CHOU: Yes. Okay. It encompasses almost entire biomedical science (indiscernible). So this -- so (indiscernible) actually.

KEITH FLANAGAN: Dr. Fisher.

CHARLES FISHER: Good afternoon. So today, I'm going to talk a little bit about the promise of artificial intelligence and opportunities to use AI to improve drug developments. And in particular, I think that this is a really opportune moment for FDA to build on some prior work in this area to ensure that these technologies ultimately provide the benefits to patients that we expect of them.

So I'm Charles Fisher. I'm the founder and CEO of a San Francisco based technology company called Unlearn AI. After a few years working in pharma R&D back in Cambridge, Massachusetts, I moved to San Francisco and I met two machine learning scientists, Jon and Aaron shown here and we started

this technology company to build new machine learning approaches to improve medicine.

And especially to build machine learning approaches that would improve the efficiency of the drug development process. And when we do this, we build on three kind of foundational principles that I think apply to all areas of machine learning an AI and really, ultimately, to all uses of data.

So the first one, at least our company starts with integrated, curated historical clinical trial data, but the main point there is that we want to start with clean, reliable data so that we can make good decision. Then, we need to build the right tools in order to use those data.

And then finally, we need rigorous evaluation that the tools are appropriate for the task ahead. And as I said, these things apply broadly to uses of AI in other areas. And so the last decade has really brought amazing progress in AI. It's now, your smartphone can translate between 27 languages in real time. Your autonomous cars can recognize all of the different objects in front of them on the road.

Neural networks can draw photo-realistic pictures of imagined faces like this one. This is not a real person's face. They can write scientific abstracts that look like they were pulled straight from PubMed. All of this made possible with approaches that were developed in the last year known as the deep learning. And this is not merely academic. These are not things just for your smartphone.

These are things that are making real impact in medicine. CDRH has now approved a number of medical devices that use AI and they have released the framework for thinking about how AI and software can be used as medical devices. There are a number of ways that AI is being used to improve drug development process.

You could imagine companies that are working on predicting serious adverse events before patients may enroll in a trial. Or, we've heard a lot today about incorporating historical or real-world data to -- into clinical trials as external control arms. And so I'll tell you a little bit about what we

do at Unlearn.

So Unlearn creates digital twins using machine learning. A digital twin is a computational simulation of a subject that is matched to that subject when they enter into a clinical trial and describes what would happen to that particular person if they were to receive a placebo. And so we can incorporate those data into the control arms of trial.

So this work that I'm showing you is part of a collaboration that we did with the critical path for Alzheimer's disease consortium where we have taken data collected from a number of historical Alzheimer's disease clinical trials and trained a machine-learning model that's able to generate these digital twins. And it's described in a paper which is open access nature scientific reports for anybody that's interested in finding it.

So starting with this database, we trained this machine-learning model and using this model we can create a digital twin for each subject in a trial, both in the treatment arm and in the control arm so that you maintain blinding, you maintain

randomization. But each twin acts as an individually matched control for each subject in the trial.

On the right, I'm actually showing an example of one of the simulated subject records, digital records that we can create for a subject with Alzheimer's disease which covers all of the individual components of the composite scores, covers lab tests that you would look at for safety, basic demographic characteristics, all of those data longitudinally simulated.

And so application of this technology could enable one to run trials where fewer subjects receive placebo. It enables you, because you have a matched control for each subject, to get individualized information about responses to therapy. However, the promise of AI approaches, our approach and the approaches that are being developed by a number of other companies really cannot be realized in a vacuum.

So there are a number of questions that people have. Which use cases are appropriate? How do we evaluate the quality of AI-based predictions or

simulations? How do we judge the clinical utility of these tools? So we would recommend that CDER develop a framework much like CDRH has for describing how these AI-based tools may be used within drug development.

There's sort of three concrete recommendations, so one is to clarify how A-based applications for drug development could potentially be qualified within FDA's Drug Development Tool Qualification Programs.

Another is to promote new pathways such as the complex innovative trial designs program in which sponsors and other stakeholders may obtain different types of feedback about specific uses of AI-based tools.

And finally, to develop demonstration projects, collaborations, that can facilitate where sponsors and regulators can have discussions about the use of these tools and understand their advantages and disadvantages, so things like inform within the FDA and then public-private partnerships like those managed through the Critical Path Institute.

So the above concrete actions would alleviate a lot of regulatory uncertainty, both amongst sponsors and technology companies like ours and would open the door to applying these innovative approaches to make drug development much more efficient and to get patients new treatment that they need as quickly as possible.

Thank you.

JIM SMITH: Thank you. Dr. Farchione.

TIFFANY FARCHIONE: So I noticed that in your example, you had Alzheimer's. So I'm wondering, is this model mainly useful for things where you have a fair idea of sort of the natural progression of disease or would you be able to do something like this for a disease where the course waxes and wanes over time? Again, because I'm in psychiatry, I'm thinking things like schizophrenia and depression and --

CHARLES FISHER: Sure.

TIFFANY FARCHIONE: -- along those lines.

CHARLES FISHER: Yeah, so I would

say kind of two aspects to this question, so the first of which is that we tend to work on diseases in which we have data. So that is part of the large reason why we started with Alzheimer's. There's this large, unmet need and companies are willing to share data in order to address it.

The models that we use can be applied across different disease areas if those sufficient high-quality data are available. So we have -- we'll be discussing -- actually we're writing up a paper now on multiple sclerosis which is a disease that has a more complex history and the models work just as well there.

JIM SMITH: Dr. Yao.

LYNNE YAO: Curious about pediatrics again. Does your technology allow for incorporation of information about growth and development and can this be used in peds? And also, do you think this is -- this would be useful for both efficacy and safety or are we focusing right now on efficacy?

CHARLES FISHER: So first question,

so we are looking into some pediatric conditions, yes, especially building off some of the work, some of the guidance out of the Division of Neurology thinking about the use of models for extrapolating from adult populations to pediatric one.

And to get to your second questions which was about safety, so we have taken the approach of trying to incorporate all of the data that you would want, so those include the lab values that you would use for thinking about safety information. The current thing that we have published does not have adverse events in it, but we are looking into also providing information about those as well.

So I think that both efficacy and safety could be improved by using these technologies.

JIM SMITH: And if I may ask one more, it would seem that your digital twin example, you could test that in a regular placebo-controlled random -- placebo-controlled trial a priori to predict, if you will, what patients in the trial would do if they were assigned a placebo and then you have a group that’s actually assigned a placebo and you could

compare.

To what extent has that type of work already been done and what's on the horizon?

CHARLES FISHER: Sure. So we can do that ourselves easily retrospectively. So we have done a lot of work retrospectively looking at historical clinical trials, both ones for which we have access to some data and taking summary statistics off of CT.gov. We are in talks now to do this prospectively.

We're effectively working with sponsors as part of their trial, as like a third arm that enables us to get some of those prospective data.

JIM SMITH: Thank you very much. Appreciate your presentation.

CHARLES FISHER: Thank you.

ANDREW EMMETT: Good afternoon. Thank you. My name is Andrew Emmett. I'm an FDA liaison and head of U.S. regulatory policy for Pfizer. And just as an aside before I get started, I just wanted to say thank you for convening this forum. I go to a lot of FDA meetings and I think on behalf of

the FDA stakeholder community, we recognize what a unique opportunity this is to share our perspectives and thoughts directly with OND leadership and you all have just been incredibly generous with your time given other demands. I just want to say thank you.

I'm going to be talking about three primary topics today, SDLTs, PMR/PMC reform, and adoption of novel regulatory science and tools and methods. I think Dr. Prescott this morning did a fabulous job covering the issue of severely debilitating life threatening diseases and I couldn't agree more that we'd really benefit from additional guidance and stakeholder engagement in this area.

I think we've seen considerable progress by leveraging regulatory innovations in a number of areas of unmet medical need, but there are other therapeutic areas -- congestive heart failure, late-stage diabetic neuropathy, lupus nephritis, advanced Parkinson's disease, progressive multiple sclerosis, to name a few -- where there continues to be unmet medical need.

And like oncology, they're really

characterized by short term survival rates and rapidly progressive disease and in our view, there's equal urgency to spur R&D investment in these areas and we felt that for the SDLTs an ICH S9-like approach similar to what we've seen in the hematologic guidance would be quite welcome.

The benefits, obviously, earlier patient access to therapies for these SDLT diseases, avoidance of necessary use of animals, and reduction in the economic and (indiscernible) costs associated with late stage and end of live conditions. And this all can be done, in our view, in a way that protects patient safety and ensures consistency in regulatory practice.

So how do we get there? As a first step, we'd like to see FDA convene a workshop that define SDLTs across (indiscernible) areas and ultimately establish a pathway towards consensus guidance across therapeutic areas. Now, the current definition -- currently, there lacks a current definition -- consensus definition for SDLTs across broad therapeutic areas, but the hematologic

definition already exists is really quite flexible and we believe would be appropriate to use more broadly.

But we also need to have objective criteria for the conditions that would warrant streamlined and flexible development plans, and this is really critical because depending on the given disease, it may be a non-SDLT or an SDLT, depending on the point of the disease trajectory or an SDLT might be representing a more severe manifestation of a more common condition.

And so we'd like to work collaboratively to develop objective, quantifiable medical, clinical, and scientific data to help define the SDLT patient population, demonstrate the available therapy is inadequate, and that we can -- safety and efficacy of the (indiscernible) drug can be appropriately monitored in the clinic.

And this -- finally, guidance could clearly define the non-clinical development expectations for more efficient clinical -- preclinical and clinical development modeled under ICH S9. Illustrative examples and guidance would also be

quite welcome. ICH guidance in this area would prove most beneficial.

We believe that FDA guidance could help pave the way for ultimate international harmonization that would really foster innovation in this area and provide patients access to urgently needed potentially efficacious therapeutics.

Next, I'd like to speak a little bit to question three in the (indiscernible) novel clinical trial designs, and particularly, we'd like to look at this through the lens of the PMC/PMR process. We're fully supportive of innovation in clinical trials, adaptive trials, master protocols, virtual trials, et cetera, and would like to see that also leverages in the post-marketing setting for PMC/PMRs.

We were quite pleased as we were putting this presentation together to see the FDA issue an updated version of their post-market studies and clinical trials guidance which we really hope will lead to more uniform approach for selecting PMR/PMCs because we have experienced some variation in how review divisions approach both the timing of

discussions around PMC/PMR selection as well as the types of studies involved.

This -- especially when these discussions happen late in the review period, it can lead to insufficient opportunity for scientific dialog around objectives and feasibility, and I believe the process would benefit from standardization and modernization. And three recommendations.

First, the process for determining new PMR and PMCs, both during the review period and in the post-market should be predictable, articulated, clear scientific rationale regarding the scientific questions addressed and, importantly, allow for sufficient time for FDA sponsored dialog and review of study objectives, feasibility design, including the use of nontraditional trial methods -- of novel trial designs.

Second, as the state of the science and the practice of medicine evolve in the post-market, we believe it would be helpful for FDA and the sponsors to periodically discuss progress in satisfying post-market studies, including issues around timelines,

feasibility, and relevancy.

And finally, methodologically sound, nontraditional trial designs and novel data sources should be considered as potentially a more efficient means of generating evidence in the post-market to satisfy a post-marketing commitment. For example, use of real-world evidence in the sentinel network to satisfy PMCs or PMRs or even composite datasets integrated from different data sources.

And we feel that it is very important, consistent with the existing statute, for demonstrating sufficiency of the (indiscernible) system or the sentinel network system prior to requiring a post-marketing requirement under 505(o)(3)B. We also recommend that there be a dialog with the sponsor and the rationale provided to the sponsor as well.

Finally, the third topic I'll discuss is with respect to question five and the topic of regulatory science. Since the Critical Path Initiative was established, FDA and industry have invested considerable time and resources and

consortia, (indiscernible) partnerships, pilot programs intended to modernize drug development and evaluation.

But despite these recent initiatives, it's not always clear how these new tools and methodologies and approaches will be integrated into regulatory frameworks, and importantly, what weight they will be given in FDA decision making across therapeutic areas.

And of our view, regulatory science initiatives and pilot programs could benefit from a structured change management and implementation process across the project life cycle, from the ideation to the initiation of the project to, ultimately, after generating learnings whether to adopt or not adopt a new process consistently across review divisions.

And we believe that this could be based on the principles of change management, of identifying what regulatory practice or tool we want to see changed, evaluating impact of the change on development, review, and regulation; planning and

implementation of the change across relevant offices and functions; and finally, validation and monitoring of, did it have the effect that -- and the outcome that we sought.

And we think a public communication plan in that respect would really be helpful to improve transparency and predictability in this space. And taken in tandem, this type of regulatory science change management and implementation approach could really engender a safe space for FDA and sponsor experimentation and innovation based upon a pre-specified expectation of -- jointly held expectations in the process.

I'll also briefly note that in our written comments, we'll also be following up on question four, examples of variation in FDA guidance, for example, around size and safety databases, waivers of non-serious adverse events for drugs, pivotal clinical trial replication, and application orientation and mid-cycle meetings and we look forward to providing those written comments. Thank you.

JIM SMITH: Thank you. could you

provide any examples? I'm curious in the PMR/PMC space, you're advocating for novel trial designs or innovative approaches. Do you have particular designs in mind that you think are geared toward issues that are generally the subject of PMRs and PMCs?

ANDREW EMMETT: Yeah, I think the post-market provides a unique circumstances where there's additional data sources that are not available, typically, in a premarket setting. I know it's out of scope of the meeting, but additional sources of real-world evidence from electronic health records, claims data.

That's the type of evidence that, one, can help to assess the feasibility of a post-marketing requirement to see if it even makes sense to answer the scientific question at hand as well as opportunities to develop unique sources of evidence to answer that question, depending on the research question at hand and whether the data itself is fit for purpose.

JIM SMITH: Thank you. And not seeing any other hands, I'll ask one more. With respect to

the structured change management approach that you suggested and kind of an implementation plan, are there areas that right now you think might be particularly ripe for an evaluation of OND practice and potential rollout more broadly? Or was it a general process that you wanted to encourage?

ANDREW EMMETT: I think it's intended to be a flexible model that would apply to a number of new regulatory science tools and methods. There are a number of ongoing pilot programs at FDA -- the CID program, the MIDD program, RTOR, et cetera -- and I think that there's oftentimes a question amongst industry of once that pilot concludes, is there a formal process for determining of it was successful or not and then if it was, how is it then democratized to cross review divisions so there's predictability that we can also leverage these tools. So those are the types of examples we've combined.

JIM SMITH: Thank you. Appreciate your discussion today.

CHERISE SHOCKLEY: Good afternoon. Today, we're here from the diatribe Foundation to

bring perspectives from people with diabetes and patient advocates as part of our commitment to diabetes and the diabetes epidemic. Living with diabetes is risky.

You might have to dose insulin, a potentially lethal drug with a narrow therapeutic range, you have a higher risk of heart and kidney complications, and for the most part, you have to handle the roller coaster of diabetes by yourself.

KELLY CLOSE: So patients in general in the United States are the envy of a lot of patients throughout the world because we have so much access to FDA and we just want to say thank you guys for that. There are many regulatory agencies all over the world where patients actually are never asked for their opinion and it's a big deal and it's been really amazing to be in community here today with so many different stakeholders, many patients among them.

And we've heard a bunch of different commonalities today, so appreciation for your increased focus on patient preferred outcomes that contribute to better short- and long-term outcomes,

acceptance of new improved tools for remote monitoring devices, gratitude for harmonization among agencies and divisions, and even more across-division consensus.

Requests for more acceptance of new data metrics is something that we've heard from a number of different constituencies, enabling better information in labels that really help drive improved clinical decision-making and better delivery of care.

And we want all of your work to lead to better delivery of care, especially in diabetes, the number of things that you have approved, the number of products you're approved, what you have made happen, it hasn't yet translated into as much improved delivery of care that we'd like, but we know that it can get there.

And last, we've heard a lot of requests for facilitating even more diversity in clinical trials and that is so important.

CHERISE SHOCKLEY: People spend less than one one-hundredth of one percent of their time in the doctor's office annually. Specifically, people

with diabetes spend anywhere from 24,000 to 110,000 minutes a year making important decisions that directly influence their diabetes care, but they just spend 14 to 120 minutes tops getting decision making help from doctors and nurses.

EMILY FITTS: We really appreciate the FDA's recognition that in order for patients to be successful they must feel supported in their self-management. The FDA has the ability to expand primary and secondary end points that affect patients' medical and psychosocial outcomes, and in doing so, the entire healthcare system can benefit, particularly in terms of expanding productivity and lowering short-term and long-term costs.

In diabetes, the field has measured management in three-month averages through A1c, but people are living those three-month averages on a minute-by-minute basis.

KELLY CLOSE: Am I too high? I need to take medicine. Am I too low? I need to eat or take glucagon.

EMILY FITTS: That is the level at

which people experience their A1c. Like others today who have asked for new data metrics to be considered, we'd love to see this valuable measurement complimented by metrics on time in range, particularly advance glucose profile or AGP.

KELLY CLOSE: So time in range is a real priority for people who have diabetes and clinicians and everybody here knows someone with diabetes. The data shown here from the market research conducted by DQ&A shows that time in range has the biggest impact on the daily lives of any aspect of diabetes. That's true for people with Type 1 and Type 2, both using insulin and not.

There's some really important cultural shifts that are going on right now in chronic disease. One of them is just a greater focus on mental health and on emotional wellbeing, which you can see is greatly needed in diabetes. We'd love to encourage more focus on standardizing and incorporating these measures.

There's also just a cultural shift with anyone who's lucky enough to have access to CTM or to

connected meters in moving to time in range as a way to supplement and compliments discussions about A1c, and this is just a quick look at how a patient's data can show much more or less success, even with a week or two and can enable patients to switch strategies to do better.

A renowned analysis conducted by Dr. Roy Beck and Rich Bergenstal in diabetes care last year showed landmark -- using landmark DCCT data has really validated time in range. This has already been cited dozens of times and come up in multiple scientific presentations all over the world.

As part of our work at diaTribe, we go to many scientific meetings at this moment when researchers give results and they don't say what happened in time in range and how much time is spent in hypoglycemia or hyperglycemia or how much weight change, people are at the microphones asking questions on that. And that is just seen as a very important increased measures.

CHERISE SHOCKLEY: Time in range is the most tangible and meaningful measure of success for

patients, whether or not it's being measured, because it captures variations. The highs, the lows, and in-range values that characterize the life of diabetes in a way that A1c cannot.

It enables us to measure our diabetes outside of the 15 to 120 minutes we spend with our beloved doctors and nurses by providing actionable information that is in context. Research tells us that even just the 5 percent increase in time in range is clinically meaningful.

KELLY CLOSE: So diabetes -- in diabetes, like in many conditions, excursions from the average are where negative costly health events occur, and obviously, everyone wants to bend the curve as much as possible with all chronic disease. We've heard a lot about that today. In diabetes, measuring time in range and out of range to determine appropriate and optimal therapeutic interventions helps us avoid these dangerous excursions, especially on the low end, and that's what helps us avoid severe hypoglycemia in particular.

CHERISE SHOCKLEY: Hypoglycemia is not

only dangerous and frightening for us and our parents and our kids and our friends in the short term, it is a clinically meaningful outcome that significantly affects patients' long-term health. Research shows that hypoglycemia begets hypoglycemia and drives an estimated $7 billion in U.S. healthcare claims, $3 billion in lost productivity, and 300,000 U.S. hospitalizations and ER visits annually.

FDA has an opportunity to establish hypoglycemia as a clinical meaningful end point. This would change our world.

EMILY FITTS: And now, thanks to the evolution the FDA has enabled, we have better tools to measure our diabetes management in a way that enables better outcomes using continuous glucose monitoring systems or CGMs or connected blood glucose meters.

CGM data is a hugely relevant end point for clinical trials and as it stands right now, as we understand it, the side of FDA that approves therapies doesn't het have a formal pathway for accepting CGM data from clinical trials. We believe the FDA has an opportunity to establish more harmonization across FDA

divisions by accepting CGM data in the assessment of clinical trials in addition to A1c metrics.

The data can inform how time in range, A1c, and clinical outcomes interact, helping both patients and healthcare professionals make even better decisions. CGM is now the standard of care for people living with diabetes and how that enables time-in-range thinking is so valuable.

KELLY CLOSE: We know we're out of time. We just wanted to say that we have been so grateful over the years to come in when you've had new guidance documents. We'd love to see the responses to the guidance documents. We have loved how you've made labels easier to read and more patient friendly. We'd love to see even more of that. We'd love for the field to get even more guidance from FDA on diversity in clinical trials. We know some sponsors are doing it really well. Some are doing it less well. It's very challenging for everyone and it couldn't be more important, that's diversity in race, age, many different pieces.

The last thing is, prevention. As a

culture, we are thinking about how to be more healthy, biomarkers of health as it were, and it's not really part of the narrative yet about public health, about how much prevention FDA has enabled on the diabetes front. We say congratulations to them on the CVOT front and preventing kidney disease.

We certainly agree with the former speaker. We would like to see more work there. We'd also just love FDA to have more resources to consider how people can stay healthy and avoid diabetes altogether.

CHERISE SHOCKLEY: diaTribe has so appreciated the chance to be here in the community with so many other advocates today from all over the country.

JIM SMITH: Thank you very much.

KELLY CLOSE: Thank you.

JIM SMITH: Dr. Michele.

THERESA MICHELE: So while diabetes clearly requires the intervention of a healthcare professional to manage appropriately, as someone in the division of nonprescription drug products, I'm

really struck by the amount of time that you catalog that patients spend managing their own disease and I wondered if you had any recommendations for things that would help patients better manage their disease that could be available in the over-the-counter or nonprescription setting.

KELLY CLOSE: We would really love to see CGM, as one example, become available over the counter. We know many people with prediabetes, if they're lucky enough to be able to get a prescription for it to be able to use it and Medicare, obviously, is covering this but not yet over the counter. We think also people are using it even for weight loss, et cetera, and who have really benefitted from work toward preventing Type 2 diabetes in particular in this case.

We also certainly recognize that a lot of work on food policy that's not necessarily happening right here at FDA alone, much of that has to happen elsewhere in the government, but we love seeing you work on good policy. One in nine households is food insecure. There's so many people who are living

in food swamps. All of this would really help people with all kinds of diabetes.

JIM SMITH: Dr. De Claro.

ANGELO DE CLARO: Thank you for sharing your perspectives with us. My question is regarding your comment on how can FDA better improve our job regards to making our therapeutic labels more patient friendly.

KELLY CLOSE: Oh my gosh, so this is amazing. I mean, you've already started doing it, which is fantastic. So just plain English, right. So BAQSIMI is a recently approved product. It's glucagon -- just itself, it's transformative but it's so easy to read this label. Granted, there are challenges to getting patients to read labels at all. It's, obviously, little print, all of that.

The more that you're doing to get this education online and the more that you're supporting patients in this is incredible. This is plain English and this is really easy to understand and we know that was not accidental. That was very purposeful and deliberate and intentional and more of that, more

focus on that would be wonderful.

I don't know if you have any ideas on how to do it or the rest of you, but I'm sure your creative thinking would be wonderful. We know delivery of care is what is really hard once things have already been approved here.

JIM SMITH: Thank you. One more question from Dr. Yao.

LYNNE YAO: So thank you so much for highlighting all of the ways we can work on end points other than A1c. I wanted to actually pick out a smaller point in your talk about prevention because that hasn't come up today, and curious what you think are the barriers to more development in the prevention space, what do you think OND could do to help facilitate that?

KELLY CLOSE: Yeah, this is so exciting. I mean, obviously, on prevention a lot of that is on the screening side and I know that's not an area -- that's not necessarily an area of yours. I think just in terms of thinking about prevention, it's not just binary, like, you prevented it, you have -- I

know that you're looking at probably multiple therapies on the Type 1 side that would prevent diabetes even for a couple of years.

There's amazing anti-CD3 data at the ADA this year that was very exciting. Thinking about what therapies could delay, we saw amazing data from EISD on VERIFY that showed that combination therapy delayed time to over 7 A1c. There probably is -- probably the same thing exists on six -- five and six, so thinking about maybe what would the pathway be on prevention, both for Type 1 and Type 2 would be wonderful.

There's so many different stakeholders in diabetes on all of these questions, like JDRF and Helmsley Charitable Trust and ADA and we know who could contribute to that question really meaningfully.

JIM SMITH: Thank you very much for coming today.

KELLY CLOSE: Thank you.

JAMES LOVE: Is there -- I can just use this to flip through the slides here.

MAN 1: Use the keyboard.

JAMES LOVE: The keyboard? Okay. thank you very much. Hi. My name is James Love. I work for a nonprofit organization. We have office in Washington and Geneva, Switzerland. I'm going to talk today about two issues. The first one is reforming the FDA-managed nonpatent incentives for drug development from (indiscernible) test data, orphan drug, and pediatric testing exclusivity to the priority review voucher.

The primary point is to introduce economic in the design of incentives. I would -- that requires, I think to do a good job, you have to start with transparency of what clinical trial costs are.

Clinical trial costs are really an important issue in terms of determining how many years or months you want to give for an extension of exclusivity in justifying the kind of licensing practices that a government might use and determine if they want to give an exclusive license or how many years of exclusivity they'd like to give a license or what the price should be permitted to be, and yet there's a general mystery about what clinical trial

costs are and we think that that's really a bad thing and we should just -- those are just things that should be known.

And also, averages are not very helpful because if you look at -- I mean, you can build up averages after a while, but there's such a big variance in cost for different products, it's really important to have as complete data as possible to begin to understand more what the economics look like in drug development.

The incentives should be designed to be what's reasonably necessary to induce desired investments. The priority review voucher which is something that has almost a random value, depending on the number of priority review vouchers that have been awarded and the products that might create a demand for it and creates an irrational incentive in the sense that you take a product that doesn't merit a priority review and give it a priority review at the expense of other products, we think this should be replaced with cash market entry awards.

We think you should explicitly consider

the expected and actual value of sales revenue in looking at what incentives might look like. You should make some incentives optional and tied to the affordability or reasonable pricing conditions or introduce a means test. I'll give you a couple of examples. And you should not use exclusive (indiscernible) when it's cheaper to achieve the same result by funding market entry awards or subsidizing research directly.

The original Bayh-Dole Act -- I'm sorry, the original Orphan Drug Act in 1984 conditioned the benefits of the Orphan Drug Act on a finding that the cost of developing, making available in the United States a treatment would not be recovered from the sales of the product in the absence of the benefits.

That was eliminated a few years later. In Europe, they still have a means test in the orphan drug exclusivity. It kicks in after the first five years on the market. You can -- a government can contest whether or not it makes sense to continue classifying a product as an orphan if there's evidence

that the product is sufficiently profitable.

I think as people here know, even products like Humira have qualified for orphan drug status. There's all these different things that you observe. Like when Gleevec first came in the market, they thought it would have 5,000 patients. It now has about 200,000 patients, generated over $50 billion. For a while, it was generating over $4 billion a year. It doesn't make sense to consider those things to have marginal economic feasibility.

This is one suggestion of how you might structure a voluntary incentive. If you had market awards for orphan products instead of just taking everything that had a mechanical 200,000 or more qualification -- patients qualification for determining whether you were eligible for the orphan drug tax credit or the exclusivity provision, to have a fund. It would reward people that develop products.

It could either be used to subsidize the trials like the orphan drug tax credit does now, which was cut, by the way, from 50 percent to 25 percent in the 2017 tax bill, but you could either

subsidize the trials or you could give cash market entry awards or some combination of the two and you could condition it on reasonable pricing conditions or some limit on how long the exclusivity was.

For example, if the total cumulative returns exceeded targets, you could start to dismantle the exclusivity. Now everyone would want to participate in such a fund, but that would be actually a positive thing because the people that actually did participate in the fund would then get more money if fewer other -- if other people opted out, the people that remain in would get more and you'd have a -- you'd target your incentives more efficiently in products that were actually not viable economically otherwise.

I'm a co-author of a paper with Aaron Kesselheim and others on the pediatric extension. When I started working on this paper, the first thing that jumped out at you was there was a lot of cases where the cost to consumers of a six-month pediatric extension for pediatric tests was over a million dollars per child that was in a treatment and in some

cases it was $4 million a trial, and that's not a very well-designed incentive.

The takeaways on this, transparency is essential and you have to look all these different areas of the value chain and the economics, and prices are not the only thing to look at. I think you have to look at the revenues generated by the products. Often, the prices are really hard to establish in the beginning, (indiscernible) make sense for an orphan product, but the revenue, the total amount of money you make off your product is really the relevant thing for incentive.

The last point is on technology transfer, biologic drugs, vaccines, and cell and gene therapies. I think everyone, I think, here understands that in the area of biologics that unlike small molecules where when the patents fall, you begin to see intense competition and prices falling, in the area of biologics and new cell and gene therapies, that's not as much of a predictable outcome.

We made a proposal to the FTC in 2017, but earlier than that we made a proposal -- or we

should say, to the World Health Organization in 2017 and the FTC last year -- of the types of forced technology transfer that would make the biologics market as competitive or more competitive or similarly competitive, the small molecules market.

That may seem like an ambitious proposal, but it’s one that other people are reaching the same conclusion at.

This is a paper that was forwarded to me by one of the co-authors, Julian (indiscernible) sent me a copy of a paper he worked -- he made a similar proposal recently in the journal (indiscernible) medical ethics and he’s addressing the issue that’s not really ethical, to put people into a biosimilar trial when you already have a science and really have -- already have a therapy that actually works and that you really have to mandate the licensing of the cell lines and other technology to avoid having to force people to experiment and take risk in areas where you have products that already work.

Even more compelling, I think, is the

fact that Jeremy Levin, the incoming chair of BIO, has made a similar proposal of mandating after a certain period of years that you license cell lines for biologics, and so the products would be safer for patients.

My wife is a cancer patient. She's a terminal cancer patient on -- she's on her third regime (sic) right now. She's been in chemotherapy for 10 years and she's taken a series of biologic drugs, two of which were not on the market when she was first diagnosed, but some of the people taking the drugs that she's taken, have died. They were friends of ours.

If she was asked to take a bio-similar drug, it would be a difficult moment for us because we know that the drugs she's on right now, she's been fortunate, she's one of those patients that's done better than the average. She's done above the median in terms of patient outcomes, would she want to switch to a biosimilar.

And that's one of the reasons why you have a hard time getting people to switch to

biosimilar products, because if they're on a regime (sic) that actually works, they're reluctant to switch because they don't know how it's going to work and the same way with a small molecule. But if you have deep technology transfer, the same kind of technology -- to move a plant from one location to another location, this would not be such a large issue. Thank you very much.

JIM SMITH: Thank you. Question to my left.

KEITH FLANAGAN: Thanks for your presentation. In particular, most of the discussion today has concerned innovation and clinical and scientific content and kind of the top line takeaway from you is that's good but what about access. We can't think about innovation de-linked from access. Many of the proposals you flagged would require statutory change or --

JAMES LOVE: Some would, not all of it. Some would.

KEITH FLANAGAN: So the question is, with respect to access to innovative new

treatments, are there any things within our administrative or regulatory discretion that you would spotlight?

JAMES LOVE: Yes, I would start with the pediatric extension. Pediatric extension is only available if the FDA makes a request to a company to conduct the study. You don't have to ask the study if it's going to cost $4 million a patient to have a private company do the study, the FDA, I think, the government should have the NIH or someone fund the study.

I think there should be some threshold on the expected cost to consumers when you no longer basically use an off-budget mechanism for finding, and that's something you can do under existing statute. And you raise an important issue. Among the other things that we've proposed, what things do you already have the authority to do and I'll come back to that in the comment period.

KEITH FLANAGAN: Right, we have the docket's open, so --

JAMES LOVE: Thank you.

KEITH FLANAGAN: Thank you.

JIM SMITH: Thank you very much for your presentation. Appreciate it.

ANDREW ROBERTSON: All right, thank you. thanks for the invitation. I'd like to start by thanking the FDA for holding this forum today. I know I'm not the first to thank you guys, but this is a lot of time on your really busy schedule, so I think this is really an important meeting.

My name's Andrew Robertson. I'm the head of regulatory science and policy for North America at Sanofi. As our time is short, I'm not going to touch on a lot of the other proposals that were brought up already. We agree with many of them.

We've actually contributed to a lot of them, but what I'm actually focused on is one specific proposal which we think deserves a little bit more attention, and that's the development of a reliable quality dataset that would capture regulatory processes, outcomes, and metrics and this really all speaks to transparency.

Many elements of what I'm going to be

discussing here have already been described in the openFDA initiatives starting in 2013 under Dr. (indiscernible), but we like to encourage the FDA to actually expand upon this initiative even further and the principles it has captured.

So at the risk of stating the obvious, I'll start with a couple of key points. So we recognize that innovation in drug development relies in part on regulatory predictability and flexibility. We're not calling for absolute consistency across FDA review divisions. I think this is important. What works in one therapeutic area doesn't necessarily work in others and we get that.

But what we are actually looking is the ability to anticipate what the FDA's expectations might be and this would actually give us the ability to meet those before having to wait for guidance or wait for the fifth or sixth case study to actually come forward, and predictability is key.

And like I said, this is built upon guidance. It's built upon case studies, experience, communication with the agency, and most importantly,

it's built on data. There are several public and externally facing databases that could provide important information; however, they have limitations and I'll get back to these in a later slide.

So expanding the concept of an openFDA would go far to build on this predictability and help support and further innovation from companies. A properly constructed database will help stakeholders move beyond anecdote and supposition. It would actually help us take a data-driven approach to inform regulatory strategy in our product development approach.

So -- I'm sorry, keyboard. So it shouldn't be a surprise that companies and researchers can learn a lot by building future profiles around specific products. We're not the only company to do this. This is regulatory intelligence, pretty much.

But by looking across datasets like Daily Med and Drugs@FDA, we can actually stitch together profile snapshots of specific products and the regulatory context. Internally at Sanofi, we've mined close to 50 datasets, actually, either public or

commercially available, to help develop these profiles. And we could take it even further than just actually getting a product by product approach.

We can actually start testing trends and identifying patterns that start to emerge. As the regulatory science starts to develop we can actually anticipate the direction that it's going to go. However, there is no single dataset yet that contains all the relevant information that we would look for.

We have to link and cross reference these datasets to get a composite picture and this is resource intensive. It's inefficient. It's imprecise and bottom line is it's just not scalable. So regardless, though, the data that we can get hold a lot of value. For one, they inform our product development strategy and they enable identification and comparison with similar prior regulatory submissions.

We're able to analyze precedent and anticipate FDA's expectations and preferences on a granular product specific level. Likewise, these data can actually help stakeholders identify issues of

consistency between review divisions.

So we've heard not just today but in other contexts, industry claiming that the FDA is not consistent in its approach. But these claims are really primarily based on observation and experience. They're not necessarily always data. They don't have a foundation in data. What we can do, and this is kind of a call to industry as well, we can and we should be moving this towards a data driven analysis to really understand where these inconsistencies might lie and figuring out why they are there.

This past summer, we published a study that actually looked at this approach a little bit more, so specifically, I know patient experience data isn't a topic for today, but we wanted to use this as an example of what data can actually do.

So we wanted to know how the FDA utilized patient experience data during 2018 drug approvals, so what we did is we took advantage of Section 3001 under 21st Century Cures that requires the public statement from FDA about how they use patient experience data in each of their approvals. What we

did is we actually manually scraped this data.

We combined it with review documentation, cross referenced it to Drugs@FDA and ClinicalTrials.gov databases and we were able to break down the actual application to patient experience data in a number of contexts by FDA office, review division, regulatory designation, and the method of data collection itself.

This analysis helped inform our internal patient engagement strategy and it can demonstrate possible trends within review divisions and it actually serves as a foundation as well, so as we move forward we can actually start seeing which way the winds are blowing.

Third, analysis of these data can actually also help us assess the impact of FDA policies in drug development. Now again, there's several questions that we can ask here relating to issues like, what's the value of an expedited review pathway to a company. What about incentive programs? We heard the priority review voucher program mentioned on the previous speaker and also, other initiatives

that the FDA has implemented or might be considering to implement.

So another study that we actually did, we published last summer which specifically at the FDA Cardiovascular Outcome trial requirement for approved Type 2 diabetes drugs. We did this study in response to the 2018 advisory committee meeting where -- and this kind of stuck with me -- one of the committee members said that they saw no evidence for this CVOT requirement having any impact on innovation and industry investment, so we wanted to look at that.

Again, we thought the claim was based a little bit more on speculation than data, so we cross referenced data from ClinicalTrials.gov, Drugs@FDA, and combined it with the Google patents database as well and we demonstrated what we thought was a correlation between implementation of the CVOT requirement and a decline in industry-sponsored Type 2 diabetes research.

Now, we don’t claim this is causation by any stretch, but our analysis take us one step closer to really understanding what is the impact of

an FDA policy, and then again, as we see this is a big partnership between industry and academic stakeholders and the FDA, can we actually then start developing recommendations to approve upon those policies.

And then fourth, it's worth noting that if properly structured, accessible datasets, that they would actually enable prediction modeling through machine learning. We've seen a huge growth in this area from over the past few years. An earlier speaker spoke to this as well.

These models go beyond traditional statistical analysis and they integrate a wide range of variables to generate a more precise prediction specific to products, therapeutic areas, and clinical programs. So here, I actually pulled an example that didn't come from us but actually came from the FDA.

So in spring of 2018, Hugh, et al. published a model where they used FDA internal data to predict how soon an ANDA application would be filed following a loss of exclusivity and they actually got it to about 80 percent accuracy.

So internally at Sanofi, we're building

similar models to predict timing -- for example, timing of efficacy supplements, will there actually be a -- can we anticipate a shortened FDA review period, can we actually anticipate the resource requirements that would be needed during review cycle. But we are limited by the reliability and accessibility of the regulatory metrics in our process data.

So, look, the potential value of these data are well recognized and Sanofi is definitely not the first to come up with this idea. These are just a sampling of publications that cite the use of these or similar datasets and better understanding how drugs are developed, regulated, and monitored. They're authored by pharmaceutical companies, academic institutions, and the FDA themselves.

Likewise, FDA reports, communications, and initiative have understored the importance and value of regulatory process data and we've seen a couple of examples of this emerge recently. But as obvious as this concept actually is, each of these instances have run into one or more problems. For example, conflicting data between sources, difficulty

in linking various datasets.

There might be unstructured format or the data might be in a PDF format which makes it difficult to ingest. Lack of specificity or granularity regarding metrics and end points, data collected imprecisely across review division. The information might not be timely or there might be delay in access or it may not just be publicly accessible at all, requiring, for example, manual collection or even a FOIA request in some instances.

So this is my last slide, what we were talking about when we were actually saying advance in openFDA. First, we believe that the FDA -- we recommend that the FDA expand on what it's already doing. We understand there is an active knowledge management initiative. We've seen the TMAP for actually updating the internal IT infrastructure. This is an area there's an opportunity for -- to promote reliable and public access to this data. We think there's a lot of benefit that can come from that.

And second, again, I think the word

partnership -- hopefully I said that enough times during this talk -- we kind of think this should be a partnership. We would be able to not only with industry, but also with academic researchers, actually help address things like what does reliable data look like, what does accessibility look like.

We can actually help mitigate the burden of data collection as well within the FDA. We don't want this to be a resource-intensive initiative either, but can we -- and finally, and I think importantly, can we navigate confidentiality concerns. So as I said at the start of my time, we don't believe this is the only idea to advance drug development and Sanofi isn't the first to bring this concept forward.

But we do believe it's a concept with great importance and potential and in this one, like I said, that we think deserves a bit more attention. Thanks.

JIM SMITH: Thank you. Dr. Marzella.

LOUIS MARZELLA: I think that this is a very important talk because it sort of adds meat to the anecdotal sort of concerns that we've heard

regarding the consistency of regulatory approaches. So to what extent is there reliable analysis of -- based on public information of what regulatory practices are across divisions, across diseases, and this would be enormously, I think, useful effort to try to characterize the actual practices, and so can you give us some more insight in terms of how do you see this effort moving forward?

ANDREW ROBERTSON: I think that you raise a really good initial point which is kind of indexing what's already been done and how accurate that is. Some of the reports that we've done internally have actually shown inconsistencies. I brought up the study that we did on patient experience data. There were inconstancies between review divisions on how that data is actually collected.

Another publication that came out about a year, maybe two years ago from Duke Margolis and the Deerfield Institute, they actually tried to index IND start dates. They looked at the FR register as well as Drugs@FDA and they actually found conflicting dates, I think, in about 50 to 60 percent of the time.

So there is an issue that we actually would need to start indexing where are the inaccuracies. So I think there's more that we can go into and we can put those in our written comments, but that's just to say as a cursory -- again, that's an anecdotal response to something which should be a data driven initiative.

LOUIS MARZELLA: The promise, of course, would be to identify best practices and so again, this -- it would seem that this would be an enormously productive effort to try to optimize the way that regulation is done to enhance the efficiency of product development.

JIM SMITH: Dr. Chambers.

WILEY CHAMBERS: Have you put together a list, and if so where, of all of the end points that you would like to see collected?

ANDREW ROBERTSON: We have our list, but I wouldn't suggest you go off of our list. This is -- again, this is why a partnership is important, because if you're going to do this, you may as well do it right from the get-go. So this is where we could

provide a lot of the information that we would love to see gathered.

I think it would be really interesting to see what others are interested in as well and even though this is data driven approach, I think that still it can be question driven and sometimes you don't know -- the questions can actually help anticipate what data we want to collect going forward, so I think that's where at least trying to get a partnership up front to figure out what are we most interested in tracking over time is important.

WILEY CHAMBERS: So I guess I would suggest in the comment period that you include --

ANDREW ROBERTSON: Yes.

WILEY CHAMBERS: -- at least your list.

ANDREW ROBERTSON: Yes, we will. Yes, we will.

KEITH FLANAGAN: Yeah, just echoing and amplifying Dr. Chambers. The purpose of the meeting is to try to gather as many specifics as we can. We make hundreds of thousands of regulatory

decisions annually and so we have to start in specific hotspots.

ANDREW ROBERTSON: Well, I mean, if I can really quickly, I mean, there are some -- sometimes, the data is already captured and it just might be an issue of making it publicly available.

Again, I could point back to -- so in May of this year, there was a draft guidance on actually -- again, RWE isn't one of the topics of this meeting, but on actually tracking RWE use and regulatory decision making, but within that guidance, we didn't see anything about public access and that was actually one of our comments that we submitted to the docket on that point.

So this is trying to -- yes, we get it. There's always going to be more information to collect, but the accessibility of it might be something to work on in the immediate term.

LOUIS MARZELLA: One final --

JIM SMITH: Go ahead, Dr. Marzella.

LOUIS MARZELLA: One final comment, if I may. I think expanding the overview to include

other regulatory bodies and their experiences would also be helpful and this would be information that the manufacturers would have more access to than we would have.

JIM SMITH: Dr. Yao.

LYNNE YAO: So I'm going to ask a question, and if it's out of bounds, I guess our moderators will let me know. So I take everything that you're saying and I think it is important in terms of transparency, openFDA to see how we can increase the efficiency of what we're doing for the sake of getting these drugs out to people.

But I'm colored and influenced by our last presenter, our last speaker, about transparency on the other side. So could I ask you the question about how do you believe the transparency ands reporting revenues in -- my influence this openness of communication?

ANDREW ROBERTSON: Even if that was in bounds, I don't think I have the personal authority to respond to that. So, I mean, I can give you a contact to my vice president if you'd like.

JIM SMITH: Totally fair answer. I'll just add one plug for you to consider during the comment period, because I know we have to move along, but obviously you've heard that there would be interest, I think, from FDA staff as well as on your side to have, perhaps, a better and more rigorous ability to have a window using data into what we do across many divisions over -- on a daily basis.

From a disclosure perspective, obviously, if we were only able to disclose data regarding applications we have approved, that has the potential for selection bias, right. Obviously, we might be able to see the entire spectrum but something for you to consider is whether or not there might be -- if you have any ideas of how to tackle that challenge, since on your last slide in red text you made the point that you need to protect commercial confidentiality.

ANDREW ROBERTSON: Yeah, absolutely.

JIM SMITH: Thank you very much.

ANDREW GUSTAFSON: Good afternoon. I'm Andy Gustafson. I'm senior director of U.S.

regulatory policy and advocacy at GlaxoSmithKline and I'd first like to echo the thankyous from many of the other speakers for your willingness to take the time to hear from us today, some of our considerations during this listening session. It's very much appreciated.

I'm going to speak to -- okay, I'm going to speak hopefully about two specific suggestions we'd like to make during this session. The first one relates to your first question, specifically, around asking where we could suggest agency could improve clarity and encourage effective drug development programs.

And the first topic is regarding the posting of FDA reviews for new indication efficacy supplements. We would like to suggest that sponsors and other stakeholders would benefit and perhaps even FDA themselves, if review summaries for new indication efficacy supplements were posted to the FDA website as is currently done with original new drug applications and BLAs.

I think we know well the review

summaries for NDAs are posted in a very timely basis within about 30 days. The review summaries for new indication efficacy supplements are very rarely published and companies usually have to go through FOI requests and wait considerable lengths of time, up to 12 months to receive those documents.

So we feel that these -- this proposal would have potential benefits by promoting a learning environment where sponsors could gain insights from recent FDA decisions that can be applied to our ongoing thinking and planning regarding development programs and clinical trials.

And this is especially important in the environment that we're working in today, where we're seeing sponsors applying innovative clinical trials, real world evidence, digital technologies, and other topics that we've heard about today and to have a more timely awareness through posting of information like this would be very helpful.

We feel it would facilitate more focused FDA meetings and briefing packages that sponsors would prepare with better informed questions

being posed to the FDA review teams and perhaps even fewer meeting requests coming in if we had greater access to this type of information. It would be very much more efficient to share that information broadly than for individual sponsors or stakeholders to be making these requests through the Freedom of Information processes.

I'd also like to suggest that this proposal relates to FDA question five, where you talk about the tension between, you know, companies trying to decide whether to use an innovative approach versus a more traditional approach, and the more information that we have access to, to build into our thinking or precedents, then perhaps the more willing sponsors might be to go ahead with a more innovative approach in their programs.

The next topic I'd like to talk about related more to question number three, talking about innovative trial designs. And specifically, this suggestion is around the use of historic or external data in clinical development and it is a topic that others have touched upon in the meeting today.

But we propose that sponsors and other stakeholders would benefit from robust scientific dialog and enhanced clarity on the acceptable use of this data in clinical development, especially in trials that are forming the basis of new drug applications to support regulatory decisions for new drug applications, BLAs, labeling changes, supplements, and that nature.

The potential impact, we feel, is for more efficient drug development by utilizing more of the data that's available to form benefit-risk decisions and possibly the potential for reducing patient exposures and reducing development times. We feel it's recognized already that clinical studies that use historical or external data do have a place in drug development.

A number of designs have been proposed in this area and some examples include designs where used to increase precision of a current trial by using historical data from past studies; extrapolation from one population to another, for example, from adults to pediatrics; leveraging data across different but

related disease subtypes within a clinical trial, for example in basket studies; and sharing information about patient responses to different therapeutic interventions.

Similarly, a number of statistical methodologies have been developed to ensure robustness of the inferences drawn when utilizing historic or external data, dynamic borrowing, propensity score matching, synthetic control arms, model based meta-analyses.

But there remains some areas of regulatory uncertainty around selection of the sources of external or historic data to be utilized in the study, analysis methodologies to ensure the robustness of study inferences, and appropriate metrics to evaluate operating characteristics including alternatives to control of type one error.

So we will acknowledge that the use of historic external data is discussed already in several FDA guidances, the ones for rare diseases, one regarding non-inferiority clinical trials, as well as the guidance around adaptive trial designs. But we

feel that there would be a benefit to having a comprehensive singular FDA guidance on the use of this data in clinical development.

So I'll conclude with our two proposals in this area, is one, to encourage a robust open dialog about the appropriate use of historic external data for regulatory decision making through your public workshops that you are very good at pulling together. And secondly, to enhance regulatory clarity through parallel development of a comprehensive guidance document focusing on this data in clinical development.

And that is the conclusion of my talk.

JIM SMITH: Thank you. I can't tell, is that Dr. Hertz? Sorry. Yeah, Dr. Hertz.

SHARON HERTZ: In reference to your comment about posting the memos for the efficacy supplements so that there could be shared learning from those experiences, what are your thoughts about posting the memos from non-approvals which I think could be even more informative to companies and really help avoid a lot of missteps?

ANDREW GUSTAFSON: Yeah, that is an interesting suggestion and I think that was raised in the previous discussion. This proposal that we're making really deals with those that make it through to approval, and of course, there would be learnings from the other side of the coin, those that don't make it through, so I think that's an area for discussion with sponsors to understand the issues that would be -- need to be dealt with in order to develop a comfort level to do those types of things.

JIM SMITH: Dr. Roman.

DARGOS ROMAN: Yeah, I had a clarifying question regarding the use of historic or external controls. Is the desire to have -- was the presentation geared toward primarily rare/nonrare diseases?

That would be my first question because the followup to that is, you mentioned that you have there is a lot of information in the current guidances but not enough, so I'm looking at the rare disease natural history studies for drug development draft guidance which was issued in 2019 and is dedicated to

this topic.

Would you be able to elaborate to us what more would have like to see in that guidance, what is it missing as a reader of the guidance that we maybe didn't pay attention of and that would be helpful for us. Thank you.

ANDREW GUSTAFSON: I think I'll address your first question first around the breadth of applicability, I think we were thinking this. Certainly use of historic and external data has had relevance in rare diseases and other indications. What we're thinking is that this has a potential utility. More broadly and going forward through dialog we can define how to appropriately use this type of data more broadly across a broader spectrum of therapeutic indications.

And I don't have prepared for you recommendations around the existing guidances and I think the suggestion was more around, we've got this topic covered in three different areas so if we're going to try to drive consistency and have a kind of an overarching policy on the use of this types of

data, it would be nice to have it in one place. I will take your question under consideration when we think about submitting replies to the docket.

JIM SMITH: Thank you. And Dr. Yao.

LYNNE YAO: So this isn't a question, just a clarification. Actually, it turns out pediatric efficacy supplements that are submitted under PREA, those that receive exclusivity under BPCA, those medical, statistical, and clinical pharmacology reviews are available online.

KEITH FLANAGAN: Thank you very much. You are the last speaker in session 3, so we're going to aspire to take a 10 minute break and resume at 3:20.

We'll now start with session 4. As with the previous presentations, I'll announce the first speaker, but not subsequent ones. So please approach the podium when the slide that lists your name and affiliation appears on the screen. After your remarks, please remain at the podium to allow the panel an opportunity to ask questions.

The first speaker for session 4 is Frank Sasinowski, Vice Chair of the EveryLife Foundation for Rare Diseases. Frank?

FRANK SASINOWSKI: Thank you, Dr. Flanagan. Thank you for allowing me to be here. I have three ideas that I'd like to share on rare diseases, in particular, since I'm here for the EveryLife Foundation for Rare Diseases. One, it was good to hear the Glaxo representative talk about external controls. I'm going to talk about external controls.

Second, everybody would like to have more intra-OND consistency. I have a few practical ideas. And the third is something that I've spent my career working on with how do we articulate the quantum of effectiveness evidence that's necessary for rare disease therapies? So, those three topics, I'd like to address.

The first is, what about external controls, and why am I interested in having external controls? And I'm interested in it because in the areas in which I'm dealing with, sometimes we have

maybe 100 patients in the United States with a rare disease. We're going to have a very small trial. Even if we can have 20 subjects, it's almost a miracle. And in that case, with these rare diseases we don't know the pathophysiology. We don't know all the ideologies.

So just by chance, we cannot know that we will not by chance have in the control arm or in the investigational arm a misrepresentation of those who are more likely to progress rapidly. So you could have a Type 1 or a Type 2 error by chance in the gold standard, a randomized control trial.

So my approach has been to tell sponsors for a long time that whenever possible, you should always depend upon other external controls, that is both a patient as their own control. As soon as a sponsor is interested in working in an area, (indiscernible) Epidermolysis Bullosa, start putting together a registry, a natural history cohort, and start using all the measures that you would want to look at, the key clinical features of that disease, so that when it comes time to have an intervention and to

actually begin screening and enrolling subjects, you could look backwards at those subjects and see if they've actually had a change from what they had experience before they were enrolled in the trial.

In the same way, I'd like to look at natural history it's just another way to look at the controls that you have. And you can see whether or not the natural history that you match by either best match, best rematch, you know, so you can do any kind of virtual matching, many different ways as different activity measures. So, you look at the natural history controls and see how do they compare to your subjects who were randomized to the control arm; how do they compare to the ones who were randomized to the experimental arm.

So I think what you end up having, in my mind, is you actually have three different sources of information that will help you in the context of small trials determine how credible the findings are. The alternative world is just to rely upon your RCT, your randomized control trial. In that case, you have your results. And like I said, in rare diseases,

often you don't know all the prognostic variables that are really important for predicting who's going to deteriorate more rapidly.

So in that case you have a situation in which if you look at external controls, both patients as their own control, or a natural history control, you have other ways to be able to assess the reliability of the conclusions you're making from your trial results.

The other thing that has come along, and I know that Dr. Telba Irony at the NORD Summit just was explaining hybrid controls, and it's something that we've been talking about, which is to take people who are natural history controls and try to match them into your control arm.

So, for instance, if you have, again, a situation in which you have a very small number of subjects who are willing to participate in a trial, 20, instead of having them randomized 10 to 10, you might have them randomized 15 to 5. And then take the five who are randomized to control and augment that control arm by matching out of a natural history

database people who meet those same prognostic features.

And so in that way, you're able to expose more people to the investigational arm so that you have more safety data on what the investigational arm will do, as well as you then still have more information in the control arm by expanding it through your natural history control.

So my rule is always to have all three controls if you possibly can. A concurring control that's randomized, an external control that's a patient as their own control, and then also a natural history control. And a variant of the natural history control is having this hybrid control to expand.

And I put together a list of some of these natural histories, just over the last couple years. What the Agency -- if you look at this list, you'll see some examples of products that have been approved in the last five years using natural history controls. And I categorize them as patients as their own control, or prospective natural history, or retrospective natural history.

The Glaxo speaker mentioned the March 2019 guidance on rare diseases, I think that's excellent. It's a great start. Dr. Roman pointed out, well, what else do we need beyond that? I think it is a great start, there are more things that can be expanded on.

And I think that Brineura is an example that several senior FDA officials have used publicly to cite as an example of the good use of an external control.

Promoting intra-OND consistency, bridging commonalities, was a report that came out in May 2019. I think we don't always have to reinvent the wheel with rare diseases. Sometimes we can rely upon commonalities, and I see that being done.

At the NORD Summit last month, Dr. Woodcock described a new division of rare diseases and medical genetics as a virtual "center of excellence for rare diseases." She noted, though, that it would be the thought leader for rare diseases in most areas, but not for oncology or neurology. But that's one attempt to have some intra-OND consistency by having

an organization that's tabbed as being the thought leader within OND on rare diseases.

Another possibility is to look at the model that Rick Pazdur used in the Center for Excellence for Oncology, and that is he's for volunteers to fill novel posts within his Center for Excellence. So, you could ask for a dedicated medical officer in each OND review division to see if that person would be accountable to understand the science of small trials and to exercise the scientific judgment across OND divisions, so they understand that. You could even consider them as possibly an associate director for rare diseases within each review division.

Similar to that, you could have a designated reviewer who's the expert on the science of small trials. I had a meeting today that was outside. Everybody knows rare diseases are often in neurology and in the division of gastrointestinal or inborn errors of metabolism. But I had a meeting today that was in another division that was for a rare disease. I had a meeting on Tuesday that wasn't a

rare disease but was in a different division.

So if when we go into these other divisions within OND, if there was a person who was tabbed to be the person responsible for understanding the science of small trials, I think would lend some consistency, instead of each time going into a division and then having to work with new reviewers who aren't familiar with this because that division doesn't have to have the same workload in rare diseases that other divisions like neurology and DGIEP have.

The last topic -- and I'll go through this quickly -- Dr. Stein -- at the September 6th, the EveryLife Foundation's annual scientific meeting, Dr. Stein put up a slide that I think was really revelatory. And that was, he talked about the different ways that you could have a single trial, plus confirmatory evidence, which is the 1997 law. But it has seldom been articulated as clearly as Dr. Stein did in this slide, which I'm replicating for you.

In that slide, he talked about

different ways that you can have confirmatory evidence. And I think that this kind of articulation of the different ways you can have confirmatory evidence by looking at trials from related indications, which was in the May 1998 Clinical Evidence of Effectiveness Guidance document, but these others, like compelling mechanistic information, including from non-human, non-clinical trials, and looking at natural history, and then looking at the same pharmacological target. So these are all different ways to have confirmatory evidence.

And the last thing I wanted to say is that the FDA has evolved its articulation of how it expresses what is the quantum of efficacy information that's necessary to approve a rare disease therapy. Over time, it's involved. And it's improved as it's evolved over time. And I walked that through on the slide. I'm not going to talk it through, but I walked in through on the slide.

But even today, with the clearest articulation that we've ever had from FDA on what's necessary to approve a rare disease, we still don't

capture about one-third of all the rare disease therapies that FDA appropriately approves.

So, the FDA is making the right decisions according to science and making the right decision according to its regulatory authority. But its articulation, that is, when you write your meeting minutes from an end of phase 2 meeting, or even a pre-IND meeting, you say here's what you need to do. That articulation of what is the quantum of evidence that you need doesn't comport with the experience that FDA has approved therapies since 1983 for rare diseases. One-third of the time it doesn't meet that standard.

So I have two examples, option 1 and option 2. I'm not going to read through them because they'll be in the record when I submit it to the comment. But I have different ways of expressing it that would capture -- this is option 1 and option 2 -- that if this kind of language was adopted is boilerplate for these kind of communications to the rest of the stakeholders, I think it would significantly advance our ability to intoduce people into the space, because we dearly need to have more

people involved in developing therapies for rare diseases. And it would give the FDA comfort that your statement of what you're requiring is consistent with your practice.

Thank you.

KEITH FLANAGAN: Thank you. Dr. Chambers?

WILEY CHAMBERS: So you talked about the distinction between rare diseases and I guess non-rare diseases, but not about using endpoints that are subjective in rare diseases. Can you expand on how you would control bias if you have a subjective endpoint?

FRANK SASINOWSKI: Yeah. Subjective endpoint, I'll take, Dr. Chambers, that what you're talking about is instead of an objective, you look at how many lines on a chart. You know, that's an objective. Subjective would be, you know, the kind of thing like a patient's global impression of severity. You know, how bad was your disease at the baseline, and then six months later, how bad? That's subjective.

WILEY CHAMBERS: Actually, how well you see, even counting lines, is subjective.

FRANK SASINOWSKI: Oh, yeah.

WILEY CHAMBERS: And can be clearly influenced if you know what you're on.

FRANK SASINOWSKI: Yeah. Well, and six minute walk, although it appears to be objective, is certainly effort-dependent. So, there's subjectivity, even in some of those. I don't know, when you measure the speed of the electrical conductivity of nerve conduction, maybe that's pretty quantitative. But then what's the clinical meaningfulness?

So, your question, Dr. Chambers?

WILEY CHAMBERS: How do you control bias?

FRANK SASINOWSKI: Oh. Bias is everywhere. I mean, you know, we have bias, that's what we're dealing with. I mean, we have selection bias, we have disease bias. When I talk about patients as their own control, diseases change, you know, a person's thing. So, it's just comparing how

they were two years before the intervention and then two years after. Some of that might be due to the intervention, but some of it might be because their lives have changed and the disease, you know, has changed.

So bias is a tricky thing, and that's why I think a focus on the science of small trials within having a person who's really devoted time to think about these very daunting questions, very real questions, would be important to have within each division.

WILEY CHAMBERS: Thank you very much for your presentation today.

FRANK SASINOWSKI: Okay.

FREDERICK DEROSIER: Hi. I'm Fred Derosier. I'm here from Covance and our parent company, LabCorp. And I'm going to be following on to our last two presenters and present a tool or a technique that we've been exploring to understand patients a bit better, using an application of real world evidence. We think this has particular application in rare disease, but it certainly has, I

think, broader application outside of that particular arena.

And in following along to what has been said previously, natural history is a critical component to understanding patients, and again, particularly within rare diseases. However, the reality is, in rare diseases, that in many cases natural history is incomplete, or in some instances, not even available.

So the question then becomes, how can we go about generating evidence that we can leverage to understand the evolution of these patients and their diseases, and how can we apply that to medical research, to clinical trials, and drug development.

At LabCorp, we are privileged to have a database which is really the largest of its kind in the world. It now comprises well over 30 billion test results, comprising more than 5,000 assays that’s been accumulated over decades now. And we have literally roughly half of the U.S. population that's covered within this particular dataset.

To define the technique that we'd like

to use to create these longitudinal datasets out of this real world evidence, we start with the LabCorp data as a foundation. And what we do is we define a population of interest on the basis of laboratory testing and/or ICD codes and some combination thereof. And that gives us our starting point.

This database is something that once the individual is identified, we go back and we pull in all of the historic records from that point to the past that we have, and then from that point forward to the future.

The database is updated on a near real-time basis, and so it can be followed prospectively, once a population of interest has been identified.

It is also possible to pull in data from outside sources and supplement the LabCorp dataset, and these can include pharmacy data, payer data from insurers, institutions, registries, clinical trials, so forth and so on. Ultimately, that final dataset is created, it's anonymized, and then we can go ahead and take a look at it and begin to try to understand the population of interest.

This is a Spotfire snapshot of one of the results. This is information on an individual with transthyretin amyloidosis. This is a single genetic mutation here. It's a Val 122 isoleucine mutation, which is common in people of African descent. And what you're seeing in the middle box is the compilation of all of the different laboratory tests has had, and how they've changed over time.

The top bar shows you color-coded boxes, which represent the different ICD codes that were Present at the time these tests were ordered on the individual. Now, these ICD codes are particularly interesting because they give us insight as to what the condition of the patient was at the time that the diagnostic testing occurred. So it gives us insight into what the position is seeing and what the physician is thinking in terms of their patient.

Furthermore, we can see how things evolve over time. And if you look here, you can see that there's an off a lot of activity going on with this individual, lots of different ICD codes. As well as down below, you can see a corresponding level of

activity when it comes to the changes in laboratory testing.

There was also some activity a bit earlier, a couple years earlier, in this individual. But clearly, there's an event that's occurring for this particular person.

Now, we can go and examine the testing in these events in more detail. And in particular case, there was a phase 3 study that was conducted a few years back. And in that particular trial, unexpectedly a number of patients began to develop renal failure.

So, in this particular dataset, which was derived from a cardiomyopathy panel that included the TTR gene, we polled those individuals. We had 853 individuals that tested positive for mutation of the gene. And we asked the question, how many of them had problems with renal function? Was there a specific mutation that was associated with this particular problem, as an example of what can be done with this type of dataset.

In addition, if you'll see in the third

box from the top, this is EGFR here. This is examining the patient's renal function. And you can see that this individual certainly had a problem with their kidney function. And the box, or the bar down below, shows this blown up to get a better view of the timescale.

So here, roughly, we can see that at the end of 2012, beginning of 2013, this individual had normal renal function, and it declined over a period of time. Roughly, about a year later, this person had about half of their renal function present, and within a couple of years, clearly was someone who needed to be on dialysis or considering a transplant.

So now we have an example of how we can understand how a problem may evolve, its relative degree of severity, the time course and so forth, over which a problem may evolve.

Across the very top of the screen, you'll see different colored boxes. There's a blue box, which indicates the time point at which this person received their definitive diagnosis from genetic testing. So that's when TTR amyloidosis was

definitively identified in this particular individual.

What we did here as part of this exercise was to review all of the ICD codes associated with this dataset and assign them a color coding based upon their known association with the disease. So red indicated diagnostic codes or diagnoses that were very strongly, or highly associated, with this disease, such as cardiomyopathy.

The yellow represents diagnoses that are probably associated to green, possibly. And then those that were felt not to be associated with the disease were not given a color code.

What you can see is at the time that the genetic testing occurred, that this person had a number of ICD codes which were possibly and probably associated with this disease, and may potentially have been the things that allowed this person to then get the genetic testing for the definitive diagnosis.

Also, and perhaps not unexpectedly, you can see that there are number of ICD codes that then follow that genetic testing that indicate possible or probable association with TTR amyloid.

However, we can understand the patient journey a little better here by looking a little bit further. About three and half years earlier, there are two red boxes, which indicate diagnostic codes that are strongly associated with this disease. And we have to ask the question, was this potentially a signal that was missed by the physician. And consistent with what we see across rare diseases, there's often a lengthy time from symptom appearance until diagnosis. So, this becomes a mean of exploring practice patterns and how people are diagnosed at some certain degree.

We can take and then apply this same thing in terms of looking at associations between genotype and phenotype. And you can see this particular individual's gene in the second column with the colored bars, and you'll see midway through, heart failure is one of the most common associations. And this gene is known to be pathogenic for cardiac disease.

However, immediately next to it, there is a genetic variant, which is currently classified as

benign or as a variant of unknown significance. But yet when we look at the associated ICD codes and comorbidities represented there, we can see that roughly 40 percent of the people with this disease have an ICD code that indicates hereditary neuropathy, which is one of the other common symptoms for this disease.

And so, we have to ask ourselves the question then, does this type of dataset provide supplemental information that we should be potentially considering when we talk about the pathogenicity of particular genetic variants.

We can use this this point to fine-tune our protocols. We took and applied that Phase 3 study that I was referring to earlier and the inclusion-exclusion criteria to this dataset, and we can see how the inclusion-exclusion criteria filter down the population and reduce it by almost a quarter in this instance. So this is a way that we can model protocols, and we can also use this to assign geography to patient populations in clusters to help us plan where to put investigational sites.

This is a topic that's been touched upon by other speakers. It's a presentation in and of itself. And I'll say that, again, I think this information could be used to support synthetic controls in similar.

And so lastly, I'm just going to conclude that we think this real world evidence is something that is a tool that could be applied much more extensively to great benefit in medical research. It's unbiased by trial selection. It can leverage multiple sources. It can be compiled very rapidly and does not require years to acquire patients and information. We can use it to hypothesis test protocol model and potentially characterize other things about this population or any population.

And with that, I'll stop, in the interest of time. Thank you.

JIM SMITH: Thank you. I guess I would ask what do you see the greatest advantage is of using the types of data you're describing in drug development currently, and what are the biggest limitations and barriers to doing so at present?

FREDERICK DEROSIER: Well, I think looking back at various programs that I've been involved with over time, I think one of the biggest thing is the things that you don't know about the population. Again, particularly in rare diseases, there are a lot of unknown unknowns, if you will.

If you developed a type of dataset like this prior to going to first time in humans, or at the early stages of your clinical program, this gives you a means of surveying the patient population. If the folks conducting that Phase 3 transthyretin amyloid study had known that there was actually a propensity to develop renal failure and associated with specific genotypes, this in turn might have influenced the way they conducted the trial.

So these are things that we can do. We can, again, using the example of modeling protocols, we can adjust our inclusion-exclusion parameters in a very logical data-driven manner so that we can accommodate more individuals safely into the clinical trials. It's a means of also accelerating and removing time in many instances from the development

program. So I think there are a tremendous number of applications, frankly, that could be part of this type of data work.

JIM SMITH: Thank you very much.

FREDERICK DEROSIER: Thank you.

JIM SMITH: I appreciate your presentation today.

LUCY VERESHCHAGINA: Good afternoon, everyone. I'm Lucy Vereshchagina, Vice President of Science and Regulatory Advocacy of the Pharmaceutical Research and Manufacturers of America, or PhRMA.

PhRMA represents the countries leading in a way to biopharmaceutical research companies which are devoted to discovering and developing medicine that enable patients to live longer, healthier, and more productive lives.

Since 2000, PhRMA member countries have invested more than $900 billion in the research for new treatments and cures, including an estimated $79.6 billion in 2018 alone.

So our comments today will echo comments made by many speakers earlier today, including those made by PhRMA member companies. PhRMA and our member companies strongest support of these ongoing efforts to facilitate effective drug development by leveraging a rapidly evolving scientific and technological advances, including the important initiative to modernize the new drug regulatory program.

We're thankful to FDA for convening this meeting to provide the clinical and scientific leaders of the Office of New Drugs suggestions on where the Agency can provide regulatory clarity and consistency to promote innovative and effective drug development across multiple therapeutic areas.

PhRMA strongly supports a vision of a future new drug regulatory program paradigm that is optimized for early identification and the resolution of key issues, promoting efficiencies and effectiveness in drug development, and allows for highly productive and timely interactions between FDA and sponsors doing drug development. PhRMA believes

the tangible steps taken by FDA will help ensure greater predictability and consistency in the review of new drug applications and supplements.

PhRMA believes that the OND organization, including the establishment of the centralized Office of New Drug Policy Review will enhance the efficient (indiscernible) ways to review of new drugs and biologics, as well as prepare FDA for receiving and assessing emerging and future types of therapies.

Consistency and predictability across disease areas and between review centers and divisions is imperative to promote efficient drug development and timely access to known therapies, including those for mathematical needs.

PhRMA offers the full recommendation to help continue to build on the efforts already underway. And I would like to know that PhRMA will provide more detailed comments to the docket.

Many speakers before me today commented on the importance of interactions and communications between sponsors and FDA. And PhRMA applauds FDA for

its efforts to enhance timely communication between the Agency and sponsors during development of certain emergent technologies.

PhRMA recommends that the FDA apply these enhanced communication practices with emerging technologies more broadly, providing timelier and clearer guidance on regulatory expectations to further expedite drug development.

In general, improved interaction between FDA and sponsors would facilitate more iterative and timely feedback during drug development, and PhRMA believes that an informed iterative approach, rather than multiple rounds of meetings and feedbacks on critical regulatory elements, would help to better inform sponsoring of their decision-making on innovative development programs.

While certain therapeutic areas divisions have a broader experience with innovative approaches and are thus more willing to accept such innovative approaches, such as rare diseases and oncology, for example, there is a need to promote drug development in non-rare diseases and chronic diseases.

FDA should address variation of feedback from review staff and in consistent approaches to areas such as assignment of expedited pathways, review of supplemental indications that are reviewed across divisions, acceptance of extrapolation pediatrics, acceptance of external controls in clinical trials. As noted by many speakers before me, acceptance of innovative drug development tools and (indiscernible) points across deviations.

PhRMA believes that the FDA (indiscernible) pilots on model-informed drug development and complex innovated designs will further advance the consistency and predictability around the use of these tools in regulatory decision-making.

Importantly, PhRMA recommends that FDA develop and share best practices based on learning from those pilots. And in addition, again, as we have heard from many speakers today, PhRMA recommends that the FDA provide additional regulatory clarity on acceptability of (indiscernible) data sources, simulation and analysis, (indiscernible) clinical

trial designs, and (indiscernible) statistical (indiscernible), including (indiscernible) analytical tools.

Consistent input from review division and timely discussions between FDA and sponsors around post-marketing requirements and post-marketing commitments will help ensure that this (indiscernible) are consistently imposed, that they are feasible and scientifically justified.

Combination products and use of digital technologies are another area where increased consistency and additional clarity from the Agency would help to create efficiency and promote innovation. In this we see a proactive policy opportunity for cooperation within (indiscernible) and across FDA centers, to leverage expertise and help ensure timely access to new therapies for patients.

In conclusion, PhRMA would like to thank FDA for bringing all stakeholders together today, and we look forward to continuing working with the Agency as it continues to implement reorganization of the Office of New Drugs, and

encourage continuing efforts to drive more efficient and effective development of innovative drugs and biologics.

JIM SMITH: Thank you very much. Questions? I suppose I'll ask one. You stressed the desire for consistency, which we've heard a lot today. We've also heard the theme of flexibility. Do you have any thoughts -- sometimes those could be at odds with each other, right? If we're driving a consistent approach across divisions, they could be perceived as being inflexible to remain consistent. Do you have any thoughts about marrying those concepts from a policy perspective?

LUCY VERESHCHAGINA: I think from our point of view, it definitely goes back to consistent application of guidances across divisions. And PhRMA always advocates for flexible regulatory approaches. But guidances are helpful and important, so as long as you apply them consistently across divisions, I don't think that this concept is mutually exclusive.

JIM SMITH: Thank you. Okay.

Thank you for your presentation.

MARTIN ROESSNER: Good afternoon. I'm Martin Roessner. My background is in biostatistics. I worked for many years in the pharmaceutical industry, and meanwhile, I worked for about almost 10 years now in a CRO. Worked for many companies, and I want to share a couple of things with you to what I experience in terms of design. So I will focus a little bit more on design aspects.

But before we go there, I want to also share with you some thoughts on innovative approaches. Parexel has commissioned a research and a survey which tried to understand how innovations were used in clinical trials. This was done in cooperation with the Economist Intelligence Unit, and the methodology and report is available publicly.

The results were quite interesting. You can see four major innovations were looked at: adaptive trial designs, precision medicine -- so, genetics, biomarkers -- patient centricity, and last, not least, real world data.

You can see that from the impact, I

think it's not surprising, over a total of 24,000 studies were looked at in the timeframe of 2012 to 2017. The impact looks understandable, that if you use these innovations, you get faster enrollment. You'll have a better chance of getting the drugs to patients, so that's the likelihood of launch.

But depressingly, you can see the innovations were really in almost less than five percent applied in these trials. These were Phase 2, 3 trials. So, what's the cause of that? And we heard already today a little bit about the diversity of data, fragmented data, where do you find data. And a lot of institutions have their own source of data, and we all have some thoughts what the bias is of those data.

Small inadequate workforces, not knowing what we are doing, is another reason. Negative perceptions -- and I will come to a very concrete example of that -- and also cultural barriers. They all prevent us from using innovations.

I will say adaptive trial designs are around for about 30 years. In 2015, we had a

publication talking about 25 years of adaptive trial designs. And still today we talk about that this is innovation. When do we start to implement that? If it's not implementable, then maybe it's not really an innovation. But I'm convinced it is. We should use it and we should apply it.

I will talk about a couple of very concrete examples. I used the oncology as an example. We have rule-based, we have model-based designs, and it's very clear that, obviously, model-based designs are much better than rule-based. So we save time, the patients, but we detect the same rate of the same rate of DLTs there.

So my question is, why do I still see by consulting with many biotech companies today, maybe 70, 80 percent using a 3+3 design? We have a very new paper out there, which talks about an 3+3 design from this year. Why not use that, or use a model-based design? A consideration could be to reject an IND, which still proposes to do a 3 design.

We talk about seamless Phase 1, Phase 2 studies already in oncology. If the mechanism is

clear of a compound, we can use a dose escalation design and then really go seamlessly into a dose expansion study. And if we have a hypothesis that this drug can work in several tumor types, because the mechanism is there, we can do a basket design type and evaluate the compound for several different tumor types.

Now, this type of design, I would argue, you can replace the melanoma, the non-small cell lung cancer, head and neck, and gastric, with maybe other therapeutic area indications, you could include, for example, rheumatoid arthritis, psoriasis, Crohn's disease. If you look back, drugs which were approved in these indications, it took probably eight to 10 years to get through all these indications. If you do it this way, I think you get a much better idea early on where the drug works and what could be used.

Although we don't want to talk about real world data, it comes up every time. I want to use this opportunity not to talk too much about the real-word data, but the methodology of it.

So here we have a single arm study in

potentially a rare disease. And I would ask, why do we limit that to rare diseases? I think it's equally challenging to think about a mega trial where we have ten or twenty thousand patients and need a control for that and have to treat ten or twenty thousand patients with a control, which we know is potentially inferior than what we are doing. So, similar application should be allowed.

But the question is, if we do the natural history, the real world data collection, how close do these patients need to match? That is a question which I think is not decided. We heard today about AI and developing twin patients. So, how (indiscernible) does that patient need to be?

I still think the randomized clinical trial has some variation, some differences between the control arm and the test arm, even it's randomized. But in this setting, we still have the requirement to say how close does that control arm have to match the actual treatment arm?

So that is something I would say is probably an opportunity to bring statisticians and

regulators together to discuss that and find a way to really address the uncertainty which we have in that space.

So summarizing that, I would say we should apply the innovations that they don't stay innovations but become reality in daily practice. Very concrete. I believe we can use some of the newer designs developed in oncology to apply them also in non-oncology diseases.

And last, not least, the acceptability of the methodology we use for real world data (indiscernible) control arms needs to be defined and agreed upon. Thank you.

JIM SMITH: Thank you. Dr. Beaver?

JULIA BEAVER: Thank you. Regarding the adaptive trial designs for dose finding, do you think the reluctance from the companies you've spoken with to adopt those versus the 3+3 comes from their challenges with implementation, or from a perception that FDA -- rather a misperception that FDA will view those negatively? Because that's, you know, of course, something we could correct, where the other

is not.

JIM SMITH: Thank you.

MARTIN ROESSNER: I think it's more the perception of operational implementation. People have a concern, but some of them -- nobody wants to give up control and give it to a statistician to do a CRM, a continuous reassessment methodology, where you select the next dose. It's more the implementation, I believe, than the operational transparency, you see how to do that.

But some of these methods are very simple. They are transparent. You can really develop that in the beginning. Lay it out, how it's done, and use it.

JIM SMITH: I'd like to ask about the seamless trial design that you noted as there's been the most experience within oncology, but that you're advocating that it could potentially be used in non-oncology settings as well.

Are there certain types of either therapeutic areas or disease entities that you think that it might be particularly suited? Because I could

imagine that that design might not be appropriate everywhere. But have you given some thoughts to where it might be more or less useful in other areas outside oncology?

MARTIN ROESSNER: Yeah. As an example, what I mentioned, the autoimmune diseases are probably a good example. In my view, it depends primarily on the mode of action of that compound, whether you can address. And we may see more and more opportunities there when we go on with genetic testing and development of biomarkers, which are applicable to several different indications.

JIM SMITH: Thank you. Okay. Thank you for your presentation.

JAMES VALENTINE: Good afternoon. My name is James Valentine, and I'm from Hyman, Phelps and McNamara, where I work with both regulated industry, but also patient advocacy organizations on navigating issues related to new drug and biologic development.

My work crosses therapeutic areas, so I've had the pleasure to work with almost every one of

your offices and divisions, both from the sponsor perspective, as well as from the patient stakeholder perspective.

So, I appreciate this opportunity to share with you some of my thoughts, and I actually have four opportunities that I would like to share with you today.

First, as we heard from a number of our industry colleagues, the policies and practices of a review division, however informal, have considerable potential to influence industry interest in drug development in a therapeutic area.

We've heard from companies both large and small that are constantly reevaluating their pipelines, based off of the regulatory requirements that exist, and perhaps more importantly, how certain they are in how those requirements will be applied within that particular therapeutic area. This informs risk assessments of embarking on and continuing product development in one area over another, even.

So now we have an opportunity. Now we have more alignment of therapeutic areas, both at the

office and division level within OND, as part of the reorganization. And I think here we have an opportunity where office and division directors can engage further in thought leadership. This could be through purposeful participation in scientific and medical workshops, not only speaking, but also participating in the dialogue of emerging approaches.

This form of podium policy can allow the researchers, developers and other stakeholders within a disease community to feel supported by FDA and get insights into the Agency's the current thinking.

Of course, both general, such as across all rare diseases as well as specific disease area drug development guidances are effective at this. It's helpful for the divisions to engage with external stakeholders as a feedback group to help inform them in their understanding of the current science and medicine, as well as inform the development of guidance. This was something that, as an example, the Division of Neurology Products did in modifying and updating its draft guidance for ALS. So, commend

Neurology for that activity.

So this thought leadership by office and division directors will not only benefit individual programs, but has the potential to attract high quality and innovative drug development in therapeutic areas that will fall under the regulatory purview of these thought leaders.

Next, I have a new ideas that relate to the changing landscape of patient advocacy, and maybe patient advocacy in a way that is novel from what you might be thinking.

Patient organizations have moved beyond just providing public awareness and patient support, or even from just supporting basic science research. Patient organizations have recognized that they need to help translate advances in their understanding of the basic biology of their disorders in order to help further de-risk product development.

And this is particularly true in rare diseases, where patient organizations are often the largest funders of research in their disease, and they are the ones developing the network of interested

academic and clinical experts to help focus on clinical research and care.

In this new era, patient organizations are also taking on activities that would have traditionally been the purview of academic or industry sponsors. These are activities that they are constantly hearing from Dr. Woodcock and other CDER officials that they should be embarking on. Things like establishing research-enabling registries, running and funding natural history studies, and developing biomarkers and clinical outcome assessments.

However, current guidance seems to be written for a more experienced industry stakeholder. For example, in the guidance on natural history for rare disorders -- and we've heard this brought up a few times -- in this guidance, it speaks to the utility of collecting this information, but could provide more practical guidance for patient advocates on how to go about doing this. What are the approaches to design and collection that can really maximize the utility of natural history information?

Patient communities would love the opportunity to build non-proprietary platforms and tools, but without additional guidance, they will continue to default to supporting individual academic situations or companies in their more silent efforts.

Beyond guidance, there is a need for greater opportunities for patient organizations to engage in meetings to advance these more technical activities, which these go beyond the existing opportunities that exist at the Agency. So while industry can request a pre-IND meeting, or meetings under their INDs to get feedback from review divisions, there is no corollary for patient organizations. This contrasts with the great pathways that have been established throughout all of FDA for patient organizations to share patient experience, things like listening sessions and PFDD meetings.

So it has been my experience working with patient organizations that they are treated inconsistently when engaging on these more technical matters. Sometimes divisions are willing to grant a meeting. Other times these groups are passed around

between different program offices, whether that be the Critical Path Innovation meeting office, or one of the qualification program offices, only to find out that the specific questions that they had don't fit neatly into one of those programs.

So this, to me, appears to be a result of a lack of an internal and external facing policy on how to accommodate the emergence of this new type of stakeholder interaction.

Unfortunately, this stymies groups; abilities to take on these critical activities, as they're not able to meet timelines that they've set out in grant or funding requests to do them. And they can't provide assurance to academic and industry partners that they will even be able to get Agency input as they've proposed.

So I would encourage OND offices and divisions to consider expanding existing successful programs like the listening sections that provide a gateway into the Agency, but expand them to allow for patient organizations to have these conversations that are more technical in nature.

Finally, and still on the topic of patient engagement, there has been huge progress of incorporation of patient experiences and preferences into review. New drug approvals now include a statement of what patient experience data were available to review teams. We saw some of the outputs of an analysis of that earlier. And there's great experience and guidance for methods on eliciting patient input, such as the series of PFDD guidances that are coming out.

However, one area that's missing from all of this is guidance or good review practices on how review team should be utilizing this input. I have worked with dozens of patient organizations in putting together listening sessions. I've helped organize two-thirds of the externally-led PFDD meetings to date. And one thing that I can't help point these patient organizations to is anything that helps describe exactly when and how review staff will utilize this input.

I certainly have lots of great examples to share with them from my personal experience. One

being the issuance of the Epidermolysis Bullosa draft guidance just two months after that externally-led PFDD meeting. However, guidance for reviewers on how to assess and utilize this new type of information could help maximize impact.

And as I started out at the beginning of my presentation, talking about being thought leaders, it will also help signal to the outside world that PFDD activities are worth investing in.

So just to summarize, I want to commend you all on this discussion today, as well as for the flattening and therapeutic focusing that's occurred with the OND reorganization. I hope that office and division directors will take this opportunity to engage further in thought leadership, particularly with greater engagement with external stakeholders at meetings and workshops.

I also ask that OND consider ways to update its existing policy and engagement frameworks to keep pace with the emergence of patient organizations as stakeholders that are taking on traditional drug development activity, but in a non-

competitive, non-product-specific way. Thank you.

JIM SMITH: Thank you. Dr. Lemery?

STEVEN LEMERY: When you -- specifically for patient advocacy groups, you know, frequently more and more we're having the patient needs involve more than just the drugs. It involves maybe a device for either treatment or diagnosis and may involve cellular therapies. I think in oncology, you know, we have the OCE. Maybe perhaps mechanisms to sort of involve all of them.

But as far as -- what would you say to both FDA and advocates when the issues that are important to them really are cross-cutting across multiple centers within the Agency?

JAMES VALENTINE: Yeah, I would absolutely agree with that sentiment that, you know, patients, patient advocates, patient communities are interested in all of the different medical product areas that FDA regulates. And a lot of their activities would involve and include engagement with not just the Office of New Drugs, but perhaps the Office of Tissues and Advanced Therapies in

CBER, some of the different review groups in CDRH.

And that was why one of my thoughts of maybe low-hanging fruit for a way to allow patient groups that might want to discuss some of these technical areas, you know, natural history study they might be building, it would be useful across all of those medical product areas. It would be to utilize something like the listening sessions program, which is an Agency-wide program, to allow for getting some technical advice across the different centers.

JIM SMITH: Thank you very much for your presentation today.

JAMES VALENTINE: Mm hmm.

JIM SMITH: Appreciate you being here today.

CARTIER ESHAM: All right, next to the last. We're almost done, and I know we're overtime, so I'm going to try to be as efficient as possible.

So, I'm Cartier Esham. I am the Executive Vice President of Emerging Companies and

Senior Vice President of Science and Regulatory Affairs at BIO. For those that are not familiar with BIO, we are a policy and advocacy organization that represents the entire ecosystem of biotechnology companies, including those that don't yet have a product on the market, all up to the multinational companies.

So one, I just want to take a moment to really thank all of you in this room for taking the time to have this meeting today. I think just looking around the table, it's a true reflection of the commitment the Agency has to advanced shared learning, shared understandings amongst you all, as well as with stakeholders. So, again, really want to reflect our appreciation for that.

So along those lines, I think one of the things that -- we would like to see more of this. So I think in terms of looking about how to approach guidance on a more regular basis and opportunities to use stakeholders to maybe help identify areas of guidance where updating is needed, or where new guidance might be needed, we perhaps would propose a

similar approach to what CDRH does in terms of having an annual engagement, where we actually identify those types of issues.

I would say that for the rest of my presentation, I would view this as our initial outline as to what we're going to be developing in far more detail and submitting to the docket in January. So we're also open to if there are areas that are not presented in this outline that you would like to see details on, we would certainly like to hear that as well.

So again, words you'll see in these slides, clarity and coordination and consistency, I think we all agree that those are somewhat limiting into what we are actually talking about, and as was raised earlier, some would appear to be in conflict, but we don’t actually think that they are.

But in terms of new guidance that we think would benefit new guidance development include those areas on digital technologies, and hopefully with an effort that is coordinated across review divisions and centers to provide information about how

digital technologies can be utilized for siteless trials, digital endpoints, combination products that contain the digital component, and other such things.

In addition, we think guidance around use of alternative preclinical tools and non-animal methods would be quite beneficial. We know this is something that the Agency encourages, but guidance that provides specific criteria and evidence requirements for regulatory acceptance of new approach methodologies would be quite beneficial.

We also think it's very important that as soon as possible, we're able to see a final guidance on PREA about how to comply with the new pediatric oncology requirements. We understand there's probably very legitimate reasons, and understandable reasons, why that's been delayed. But it is our hope that that is published as soon as possible.

And likewise, we hope to see new guidance to replace the 2014 guidance that was withdrawn on Analgesics.

Continuing on to (indiscernible) in

pediatric, where we think some updated guidance would be quite beneficial. The 1999 guidance on BPCA: we do think that finalizing compliance with that would be helpful. Updating the 1977 Guidance on Clinical Evaluation of Drugs in Infants and Children: specifically looking to update content on terminology, such as "school-aged children", "special problems", and the addition of references to other pediatric guidance would be very helpful in this area.

The 1998 Guidance on Clinical Evidence of Effective for Human Drug and Biological Products: we think this could benefit updating that reflects current thinking on use of external controls, optimizing retrospective natural history, studies real-world evidence, patient focused drug development, and the totality of evidence. Understanding that these pieces, these additional elements are reflected elsewhere in specialized guidance, we still think it might be beneficial to review that guidance.

Looking at ways in which we stakeholders can further engage and better engage with the FDA in utilizing public opportunities to discuss

areas of evolving science and emerging approaches, we think we could all do a better job on that. And specifically, we think areas and discussions around evolving methods by statisticians to make benefit risk decisions, and perhaps use of artificial intelligence, sort of top the list of that engagement.

And I do think, you know, we often talk here and all of us have probably at one time or another participated in multiple public private partnerships between industry and the Agency, stakeholders, academia and others, but I think we could all probably do a better job in sort of (indiscernible) the conversation about where are we in our understanding of emerging science and technologies. And then use that to help us focus and clarify how to develop and implement a public private partnership with purpose, that hopefully walks us towards a greater understanding in terms of specificity and guidance.

We also would be very interested to work with FDA, as well as NIH, to try to better understand how the two organizations are working

together and tackling things like how we translate our understanding of basic science discoveries, and how that impacts regulatory approaches.

I think there's a lot of great work. An example there might be HEAL Initiative. I think that's a great -- there's a lot of exciting things happening in that space, and we certainly would look to continue improving upon that.

In terms of question 2, one thing we did want to highlight in things outside of non-targeted medicines, we did want to highlight that Highly Prevalent Chronic Diseases, we continue to see a lot of challenges in that space, particularly in the level of investment, and something that has a lot of factors. Some of that is science. Some of that is the reimbursement.

But the third leg of the stool, the regulatory approval pathway, we do think could benefit from concentrated thinking about how improvements to PMC/PMR, acceptance of innovative clinical trial designs, utilization of real-world evidence, novel endpoints, and digital technologies, including the

ability to conduct the siteless trials, would be highly beneficial.

I'm just going to highlight that we've had very productive conversations with the FDA on PMC, on post-market commitment and requirement reforms that are basically focused on having engagement earlier, and continuous. So, pre-submission of application, during application, and then ensuring that once the commitments are in place that they are reviewed to make sure that they still reflect current science and understanding and realities.

I have one minute left, so basically, I'm going to say yes, innovative clinical trial designs are highly beneficial for a lot of reasons that are in your packet. And we do think that specific guidance listed here on data integrity and evidence for decision-making, adequate interventional control arms, and adequate safety and monitoring are right for specific guidance development activities.

In terms of, again, the great question about consistency, I think today is a tremendous reflection on that. We do think that there's still a

lot of work to understand how to approach different review divisions and understanding rules of engagement to enable utilization of innovative clinic trial designs and novel endpoints. I think it's still something that many of our companies are struggling with. And again, we believe that's a two-way street.

And we also want to make sure that we kind of think through, are we really doing our best in talking about lessons learned with mandated pilot programs, as well as innovative approaches being tested within the Agency. Is there a way that we could better understand externally what those learnings are, what actions are going to be taken, and what, if any, actions are not going to be taken, why? And so, we can continue to try to be more helpful in advancing those type of activities for the ultimate advancement of regulatory science and application.

So, with that, again, I have 27 seconds. So, my team is going to be very disappointed that I didn't use all of the slides. But again, I think that today is a great example about how we can best work together and share learnings. We look

forward to providing much more detailed responses to the docket.

We know that under the OND reorganization efforts, a lot of the things that are highlighted in the slides that were submitted for the record are being undertaken right now. And so we do want to make sure we understand that. We're very appreciative of that, and we just want to try to determine how we can best support those activities that are creating shared learning, shared understandings within the Agency, across divisions, across centers, as well as with stakeholders.

So again, thank you for the opportunity, and we look forward to working with you in the coming months as we develop more specific recommendations and suggestions.

JIM SMITH: Thank you. Go ahead, Dr. Joffe.

HYLTON JOFFE: A theme that's come up a few times is this inconsistency across the divisions, which is another area that's somewhat fuzzy to me in terms of where exactly we're being

inconsistent, given differences in disease areas. So, I would encourage folks in the written document, in the public document, to the extent possible, to provide as much details as you can publicly.

And also, I was wondering if when a sponsor feels a division is being inconsistent, do they bring it up to the division in real time and say, hey, you know, Division B just told us something else. So, I'd like more details on these inconsistencies we keep hearing about.

CARTIER ESHAM: Yes. And we agree, more detail is -- we will be providing more detail on that to provide some additional clarity on what we mean by flexible consistency.

HYLTON JOFFE: And I encourage that not just for you, but for all the speakers who are here, and even folks who aren't here. I hope people do that.

JIM SMITH: Thank you for making that comment, Hylton, because that is one of the things that we are very much looking forward to and trying to get after with this meeting. I'll just ask

a question, and if it's beyond the scope of thoughts that you'd like to give, that's totally fine.

You flew by, for reasons that are totally understandable, innovative clinical trial designs, and just said you support them. But I think you might be one of the only ones who paired it with highly prevalent chronic disease. We often hear them encouraged in other areas of rare disease.

So do you have ideas in mind of particular types of innovative designs that would be particularly useful for highly prevalent chronic diseases?

CARTIER ESHAM: We are working on that, and that will be submitted as part of the record, some more specific examples on types of designs we think would be applicable to many of the highly prevalent diseases.

JIM SMITH: Thank you. Appreciate your presentation.

CARTIER ESHAM: Thank you.

LIZA O'DOWD: Good afternoon. My name is Liza O'Dowd. I'm from Janssen, which is part

of Johnson & Johnson. In the spirit of getting you out of here, because I see the energy fading, I'm going to try to be consistent and align with many of the comments we've heard today and say that we recognize and support many of the things that were raised. But I'm also going to try to be flexible and highlight things in response to some of your comments to give a little bit more granularity to some of the thoughts that we have.

As a company such as Janssen, we have the opportunity to work across multiple disease areas because we have products across many of the therapeutic areas. But being part of J&J, we also have the opportunity to talk to our colleagues and work with our colleagues who work in the device groups as well as the consumer groups. So as such, we are able to see some things across all parts of the FDA and try to share those learnings and help us understand the inconsistencies or consistencies and opportunities in a little bit of a different way.

One topic that we haven't touched much on today has been the topic of combination products.

And here, I'm specifically talking about drug device combination, but in the future I'm sure it will be drug -- digital solutions, et cetera.

We do see, to the question that was raised earlier, variable approaches to how, for example, the different divisions may look at risk management for some of our products. And we find that a little bit challenging at times to best predict what sorts of data in test may be necessary to satisfy the Agency's concern around residual risks with the use of the devices.

We specifically find this in the area of human factors studies, where there may be different assessments around critical task identification, assessment of residual risk. And we would like to understand a little bit more deeply from the FDA's perspective why we may see those differences, based on what we understand around good risk management principles.

We also find that there is a little bit of a stylistic difference as to when that engagement may happen in terms of the feedback. When we get

feedback from the human factors group of the FDA, sometimes it comes early in design, but sometimes it comes quite late in the review cycle. And that creates a little bit of a challenge (indiscernible) for both for us in generating new data, but also for the FDA in having to assimilate that data late in the review cycle so we don't delay access of medicines for patients.

There was a lot of conversation earlier around the opportunity for informal communications. And for our perspective, we like to highlight in this case what we are talking about when we say informal communications is actually the opportunity to provide clarification.

Sometimes we find, particularly on the device side, that the FDA may not be sure what we are talking about when we refer to something. And at the same time, we may not be sure what the FDA is asking for. And oftentimes we spent a lot of time stressing about Type C meetings and setting this up, and we go 120 days down the road, and it turns out we really just didn't understand something quite simple. It

might be that, oh, we didn't realize that that study report you were looking for was actually submitted as part of a 510k sponsor's submission, and it was already there all the time.

So, very simple things. So, clarification as opposed to perhaps giving us detailed advice on development programs. So if there was a mechanization to do that that was rational, we would be most welcome to that.

We spent a lot of time today talking about perhaps some inconsistencies in applying statistical approaches. We may suggest that we see this like Andrew does. Perhaps he does a little bit more formally. It's (indiscernible) with the tools. We do kind of track the kind of advice we get because we like to learn from each interaction that we have with the Agency and see how we can apply best practices to the next development program that comes on.

So, I would see that we see some variation from example and preferences for how we might control Type 1 error and secondary endpoints,

as an example. We may see difference acceptance in thinking about adaptive designs. There may be a couple of places where consistently when we submit an adaptive design, we say, that's great, but maybe you should've thought about a group sequential design instead. And we think that we see that kind of consistently. We'd like to understand why that might be.

We also note, as others have, that there is some variability in accepting pediatric extrapolation, even when we, to the best of our understanding, believe that the disease is similar between kids and adults in the MOA for the drugs that we are (indiscernible) should have the same effect in both children and adults. So, we'd like to understand a little bit more why we see those differences.

And finally, there is variation in the tolerance for Bayesian statistics as well. So, for us, we accept that there is going to be variation, but we would like to understand more clearly whether or not these variations are really due to true scientific and statistical reasons, or rather it's due to

preferences for people who may have a strong sort of rooting in Bayesian statistics or (indiscernible) for example. And if it's the latter, then we think there might be opportunity for better cross-training and sharing across the statistical (indiscernible) of the FDA to perhaps at least share a little bit of the thinking, and maybe help some of these approaches become a little bit more acceptable.

We heard a lot about modelling and simulation today. I'd like to put a postulate out there as more futuristic thinking, that there may be opportunity for us to use all the data that exists in the world, along with deep data collection early in clinical trials for particular subpopulations of interest, to perhaps streamline drug development for chronic diseases. If we could understand a little bit more deeply around particular subpopulations, perhaps we would not have to include the subsets in large clinical trials for cardiovascular disease, for example. Perhaps we could accept that we might not have huge numbers of patients, but still can find ways to appropriately label it. We'll give you our comments

about this in our written comments, but we think there's opportunities to apply the totality of data science and modelling and simulation to more chronic diseases, rather than perhaps the rare diseases that we were focusing more on today.

And then finally, I'd like just to conclude with a couple of observations. We heard a little earlier today that there was a time when the HIV epidemic hit, and we found ways to move drug development forward in a quick way.

We at Johnson & Johnson, particularly going through recently trying to come up with the Ebola vaccine and our experiences with, obviously, the oncology area, we see what happens when everyone is united toward a common goal and a sense of urgency of trying to make a difference for patients who have unmet need.

Those success stories are really based in a different way of working. It's iterative, it's collaborative, it's mutual problem-solving, it's enhanced communication. And we like to believe that if we apply some of those best practices that we can

glean from those experiences to thinking about chronic disease, we may be able to move the ball a little bit forward toward improving drug development.

So, with that, I'd like to thank everyone for their patience. Long day. But I wanted to thank the FDA for the opportunity to hear from us and for us to make the comments.

JIM SMITH: Thank you very much. Dr. Marzella?

LOUIS MARZELLA: Yes. I wonder if you could elaborate more on the issue of human factor studies. These are particularly important in the context of imaging drugs. And so we encourage submission of actual protocols and we comment on the actual protocols before they are carried out. So I wonder if you could comment, and what are the issues that you are experiencing with the process?

LIZA O'DOWD: So we do acknowledge that there is that opportunity to submitted get comments back on the human factor protocols, and we do appreciate that greatly. What we see is some differences, is you know, when we get back the initial

results and we are deciding on how to further that, we see differences in interpretation of the balance of the assessment of probability of risk occurrence, along with severity of potential harm.

So, some of the divisions seem a little bit more balanced in taking the two into account, where others perhaps are more concerned with the possibility of harm. We want that fully elucidated down, even though the possibility of occurrence is quite low. So, that's the main one.

And then we also find that the timing of feedback sometimes doesn't come quite as early in that cycle that we would like, so it can come quite late.

JIM SMITH: Thank you. Dr. Chambers?

WILEY CHAMBERS: So, sometimes differences in things like how combinations are handled are because of devices and regulations. The (indiscernible) products, for example, are treated -- have a regulation that exempts them from a number of the combinations. Is there reluctance in asking why

it's being treated, or do you not get answers if you ask?

LIZA O'DOWD: It is a little bit of reluctance. There's a little bit of who's on first procedurally. So, sometimes were getting guidance, for example, in one meeting from the division, and sometimes the advice is obviously coming from the device reviewers. And how we get there sometimes is a little bit awkward. So, we don't perceive a consistent way to engage in the process. You know, sometimes we think it's just faster to go to the human factors expert and say, what were you asking, could we clarify that? But it ends up being a little bit more complicated than getting that clarity of response.

We're very happy to ask questions. It's just the process to get there is sometimes not always clear for us. We have some specifics. We'll be happy to outline those for you.

WILEY CHAMBERS: Thank you. Any other questions for the panel? Okay.

KEITH FLANAGAN: Thank you. This concludes today’s presentations. Than you to all of

our presenters for providing your input today. OND's clinical leadership will take your comments, in addition to the comments submitted to the docket, under careful consideration. Thank you to everyone who attended today and to others who were watching remotely. Thanks to all the division directors and their designees for taking a full day.

The docket will remain open through January 7th, 2020. The Federal Register Notice announcing this meeting has instructions for how to submit electronic comments. We will consider these electronic comments along with the views presented here today. It will take us some time to digest all the input we have received and will continue to receive through January 7th, but I can assure you we have been listening carefully and will leverage your insights wherever possible.

Thank you again for joining us here today. This meeting is adjourned.

(Whereupon, at 4:45 p.m., the proceeding was concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of 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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