FDA'S RARE DISEASE DAY 2022

SHARING EXPERIENCES IN RARE DISEASES TOGETHER

VIRTUAL PUBLIC MEETING

Conducted by Food & Drug Administration

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R E C O R D I N G

DR. RETZKY: Thank you for joining us today for FDA's Rare Disease Day 2022. My name is Sandy Retzky. I'm the Director of the Office of Orphan Products Development. Today we are very fortunate to have Dr. Robert Califf, our new FDA Commissioner joining us for opening remarks. Thank you, Dr. Califf.

DR. CALIFF: Thanks, Sandy. It's really great to be back at the FDA. This is my second run, as most of you know, so it wasn't a whole new thing. Thank goodness, because there's so much going on at the FDA and there's so many priorities that we have, especially with the pandemic having been such a big issue. But we're all aware that development of treatments for rare diseases is really critical to our public health.

There are special issues that we have to pay attention to and it -- I think today will be a really interesting day.

DR. RETZKY: I agree. You know, our workforce, our FDA workforce is so important and in planning this event which has the theme of sharing

experiences in rare diseases together, we wanted to emphasize some of the personal experiences of the FDA reviewers of products to treat rare diseases.

Now, reviewers are the teams of FDA scientists, clinicians, biostatisticians. There's a whole host of multidisciplinary, very talented people that review the files for rare diseases and, you know, the whole process, it's a gating process of getting a product to the marketplace and with each phase of clinical development, our FDA reviewers have to ensure that all of the studies are well designed both for efficacy as well as for safety and that the proper protections are in place for human subjects.

From the outside, it may not be so apparent how much work is done at FDA to try to get products for unmet needs to patients as quickly as possible. There are special challenges in developing products for rare diseases and I know you're very well aware of that. And so we wanted to share our own narratives on what we do every day and why it's so meaningful. The amount of activity and the breadth of expertise on products for rare diseases is just amazing.

DR. CALIFF: Well, I'm pretty excited about the makeup of today and, you know, I think it's very hard for the public to grasp how much work there is involved as you just pointed out. You know, scientists think of great ideas, patients and families hope for the best, but in the end, it's a back and forth between the FDA reviewers and those developing the therapies over the course of sometimes many years because, you know, sometimes things don't work and you have to make adjustments.

And so this interaction between the reviewers and the increasing attention to the needs of patients is something, I think today will be great but I hope we can expand this and make the public more aware of how critical this is.

DR. RETZKY: Yeah, I couldn't agree more, Dr. Califf. And along those lines, you know, I was a medical reviewer in CBER for a number of years and I worked on lots of rare disease files and I can easily say that my most meaningful experiences at FDA have been as a reviewer interacting with patients, caregivers, and advocates who sponsor meetings.

It really helped me to know what they think and what will be meaningful and what's important in their lives. You can't get this information from reading articles and books or even talking to experts and I can't tell you how much those interactions meant to me personally as well as professionally and they inspire me every day in my work at FDA.

DR. CALIFF: Well, you know, I've spent over 30 years as a busy cardiologist and spent a lot of time with patients and families and know how difficult this can be. I also have a daughter with congenital heart disease, and so I know what it's like as a parent to be anxious and worried, appropriately, about the wellbeing of a child who has a disease which is not so common. So I'm very confident that today's discussions will give us some really good examples of how things have worked and probably, and I certainly hope this is true, will lead to even better ideas. The importance of this interaction just can't be underestimated.

DR. RETZKY: I completely agree. So thank you so much for joining us today, Dr. Califf. I'm so

happy that you could come today. And to kick things off for this meeting, I am going to turn things over to Dr. Lewis Fermaglich who will be stewarding today's events. Lewis.

DR. FERMAGLICH: Thank you, Drs. Retzky and Califf. I'm honored to once again act as your Master of Ceremonies for this special day, FDA Rare Disease Day 2022. My name is Lewis Fermaglich and I'm a medical officer in the Office of Orphan Products Development. I've been at FDA for five years now after practicing as a General Pediatrician for ten years.

As a primary care doctor, I figured FDA was a faceless black box of government workers poring over labels and making decisions about which drugs I could or couldn't prescribe to my patients. Since I've started working here, I've been struck by how diverse, talented, thoughtful, compassionate and dedicated the workforce at FDA really is. We're physicians, pharmacists, chemists, lawyers, social scientists, statisticians, biologists, toxicologists, and engineers as well as parents, children, patients,

siblings and friends who truly care about the public health of our country.

We hope today's meeting gives you a better idea of who FDA really is and what we do every day to improve the availability of medical products to treat rare diseases.

Today you'll hear from FDA's reviewers, the ones evaluating the data, analyzing the applications submitted by sponsors, listening to patients and their advocates and spending countless hours laying the groundwork for the decisions made by FDA. Reviewers are the frontline workers for the Agency. You'll hear what they actually do and think about when they review an application for a new drug, biologic product or medical device to treat a rare disease and what it means to them.

FDA's Rare Disease Day will focus on how these reviewers evaluate products for patients with rare diseases. FDA's dedicated to helping these patients and one small way we're demonstrating that support is by participating in the National Organization for Rare Disorders campaign "Light Up for

Rare".

Every day this week from dusk to dawn, we're illuminating Building 1 at FDA's White Oak Campus with the colors of Rare Disease Day to raise awareness about rare diseases and their impact on the lives of patients and their families.

As you can see from the photo, the beautifully lit building used to be a Naval Ordinance Laboratory and just like some rare disease treatments, has been repurposed as the FDA's headquarters. It's uplifting to know that a building that was once used to manufacture weapons of war is now used to ensure medical products are safe and effective.

The theme of today's meeting is "Sharing Experiences in Rare Diseases Together". This morning's panels are unscripted conversations with reviewers from each of FDA's medical product Centers. Each panel will tell their own narratives of what it's like to review rare disease files. The stories they'll tell are uniquely their own.

The Oncology Center for Excellence will talk about the review processes that led to the approvals

of two drugs to treat rare tumors. The Center for Biologics Evaluation and Research will discuss the collaborative process involved in reviewing gene therapies for rare neurocognitive and neurodevelopmental disorders in children with a team consisting of more than just physicians. They'll include scientists with manufacturing expertise and consultants from across FDA to advise on appropriate endpoints.

The Center for Drug Evaluation and Research will talk about how FDA is involved in a public-private partnership to help develop endpoints for a rare disease, amyloidosis. And, finally, the Center for Devices and Radiological Health will describe how their team uses patient input and benefit-risk assessments toward the approval of devices for patients with rare orthopedic conditions.

After lunch, we're honored to have remarks from the Principal Deputy Commissioner of FDA, Dr. Janet Woodcock. Afterwards, our first afternoon panel will shine the spotlight on the most important aspect of the review process and the reason FDA does the work

it does, the patients.

We'll hear directly from patients who've been diagnosed with rare diseases about their interactions with FDA. For our final panel of the day, we'll hear from each of the Centers about exciting initiatives being developed to continue to improve FDA's work to address rare diseases. We call it "Our Future Journey".

After the last panel, we'll have an open public comment period. Participants registered for this prior to the meeting. Participation is on a first come, first served basis and speakers will each have two minutes to speak. After the open public comment period, Dr. Retzky will provide closing remarks.

This year we're using an interactive platform called CrowdCompass by Cvent which will create a virtual meeting space that will give you access to the agenda and speaker bios and allow you to network with other FDA Rare Disease Day attendees. Just go to the link on the screen now or use your smartphone's camera to scan the QR code on the slide here.

A few comments about meeting etiquette. We

encourage all individuals to contribute to the dialogue and we appreciate the opportunity to hear your perspectives. The views expressed are personal opinions. You can ask a question by clicking the "ask a question" icon or by emailing oopdorphanevents@fda.hhs.gov and we'll try to respond to as many of them as time permits.

For transparency purposes, when you're sharing a comment, we ask that you please disclose if you're affiliated with an organization or if you have any significant financial interest in rare disease medical product development.

A public docket will be open until April 8th to submit comments. We highly encourage you to do so. A webcast recording and a transcription of the meeting will be available on the FDA meeting website following the conference and will be available for one year after the event. Evaluation forms will be emailed to you following the meeting.

After the meeting ends today there will be additional opportunities to interact with FDA. The Office of Orphan Products Development and the Office

of Patient Affairs are here and want to stay in contact with you, whether it's helping you stay connected with other activities at FDA or addressing any future questions you might have.

This slide contains our contact information. For media inquiries, please contact our Press Officer, April Grant. Also, if you choose to tweet about today's meeting, please use #fdarare2022. Let's start the program. First up we have a panel of reviewers from the Oncology Center for Excellence at FDA moderated by Dr. Martha Donoghue, the acting Associate Director for Pediatric and Rare Cancer Drug Development. They'll be discussing their experiences with development programs leading to approval of two new drugs to treat rare tumors. Dr. Donoghue.

DR. DONOGHUE: Thank you so much and good morning, everyone. My name is Martha Donoghue and as mentioned, I'm a pediatric oncologist. I'm also a mother of four sons and I've worked at the FDA in the Office of Oncologic Diseases for about 12 years now which is hard for me to believe. I currently help oversee the work done by the division that oversees

development of new drugs to treat patients with a variety of types of cancers including lung cancers, brain cancers, pediatric solid tumors, all of which are rare, and other rare cancers such as thyroid or neuroendocrine cancers.

Thank you so much for taking the time to join us bright and early on this Friday morning. Over the next 45 minutes or so, my colleagues and I will try to give you an inside glimpse into what many have called the "black box of the FDA". Specifically we'll talk a bit about our work leading up to recent approvals of two drugs to treat rare tumors. The first is selumetinib for the treatment of pediatric patients with plexiform neurofibromas and the other is called tebentafusp tebentafusp, or KIMMTRAK which is easier to pronounce, which was a very recent approval this year for the treatment of patients with ocular melanoma.

The paths leading to approval for these two drugs are very different, just like all rare diseases are different, and you know, I think our discussion will reflect the fact that successful development of drugs to treat rare cancers really have to be context-

specific and tailored to the needs of patients with that disease as well as the disease rarity and also that collaboration and strong communication between all parties, both within FDA and outside of the FDA is vital.

In a minute, I'll ask my colleagues to introduce themselves but first I'd like to give you a general idea of the flow of this panel discussion. First, my colleagues Dr. Diana Bradford and Dr. Denise Casey will discuss the development of selumetinib and then Drs. Jamie Brewer and Elizabeth Spehalski will discuss KIMMTRAK for the treatment of ocular melanoma and I hope to reserve the last ten minutes or so so that we can address any questions you might have for the panelists, so please do submit questions if you have any.

And now I'd like to ask my colleagues to introduce themselves briefly, and if you will, just please describe your background a bit and what brought you here to FDA. And I think we'll start off with Dr. Diana Bradford.

DR. BRADFORD: Good morning, everyone. It's

nice to be here. I'm Diana Bradford. I'm a Pediatric Oncologist. I've been at FDA for about five years and what drove me to come to FDA is my interest in development of new therapies for children with cancer and I saw that working at FDA is now continuing to work on that on a broad scale. Happy to be here today. Thank you.

DR. DONOGHUE: Next I'll move to Dr. Denise Casey.

DR. CASEY: Hi, good morning, everyone. My name is Denise Casey. I, too, am a pediatric hematologist oncologist by training. I, too, am a mother of four. Prior to being at FDA, I was in clinical practice in upstate New York at Golisano Children's Hospital in pediatric hematology oncology for about four years. After that, we moved down to the DC area where I joined FDA and I was at FDA for about 7.5 years working with Martha and Diana on the pediatric rare tumors, brain tumors and neuro-oncologic tumors team as well as some about a year on the sarcoma and melanoma team.

I love working at FDA. It was a truly

positive and educational experience for me, so I am so pleased to be here today. Thank you. Thank you for organizing the event and inviting me.

DR. DONOGHUE: Thanks, Denise, much appreciated. I'll move on to Dr. Jamie Brewer.

DR. BREWER: Good morning, everyone. My name is Jamie Brewer. I am a medical oncologist by training and I've been at FDA for about four years now. I'm currently working as a clinical team lead in the Division of Oncology III where we, my team in particular, focuses on development of drugs for the treatment of GI cancers, gastrointestinal cancers, colon, liver, et cetera, and then also melanomas. In regards to what brought me to FDA, you know, I think everyone on the panel you'll find is curious and inquisitive and loves research. What I think really brought me here is the ability to work so closely with people of so many different specialties and everyone is so interested in really working together and collaborating and teaching and learning. So it's a great environment to be in, it's a great place to learn and to really have an impact. So thank you all.

DR. DONOGHUE: Thank you so much, Jamie. And last but not least, I'd like to have Dr. Elizabeth Spehalski introduce herself.

DR. SPEHALSKI: Hi, good morning. My name is Liz Spehalski and unlike my colleagues, I am a nonclinical reviewer at the FDA. I work in the Division of Hematology Oncology Toxicology and we support the nonclinical part of the clinical division. So like Jamie, I work on cancers that are gastrointestinal, melanoma, sarcomas, cutaneous cancers. I've been at the FDA about five years now. My background is a PhD Scientist and Cancer Biologist and I was attracted to working at the FDA because the FDA has a strong public health-minded mission and working at the FDA allows me the chance to see how the basic research that I've worked on for 15 plus years now immediately can translate into patient care. So thank you for having me today.

DR. DONOGHUE: Thank you so much, Liz. So next we'll kick off just level set a little bit on the approval of selumetinib for the treatment of pediatric patients with plexiform neurofibroma. Dr. Bradford,

Diana, will provide a very brief presentation just to describe what selumetinib is, what plexiform neurofibroma is and after that we'll talk informally about our experiences during the review. So Diana, I'll turn things to you. And if we could have our slides up, that'd be great.

DR. BRADFORD: Can you see the slides? Oh, yes, I'm sorry. I see now. Okay. Wonderful. Thank you. So my friend and former colleague and I, Denise Casey, will be discussing our experience with the program that led to the approval of the drug selumetinib which is in a class called a MEK inhibitor for children and adolescents with neurofibromatosis type I and plexiform neurofibromas -- more on what that is in just a minute. This application was approved on April 10, 2020. If we could go to the next slide, please?

So briefly, what is neurofibromatosis? Neurofibromatosis is a genetic disorder that affects about one in 3,000 people. The most common type is NF1. It can affect many parts of the body but not all people with NF1 will have all aspects of the disease.

I've listed some of these here. Affected areas can include the skin, including spots or bumps, bone issues like scoliosis, impacts on height, learning issues, and high blood pressure among other things.

People with NF1 are also more likely to develop tumors, both benign and cancerous tumors, and what we're going to be talking about today is plexiform neurofibromas. So somewhere between 30 and 50 percent of people with NF1 have a plexiform neurofibroma, a benign tumor that can occur anywhere in the body and depending upon where the tumors are, they can cause symptoms like pain, difficulty with range of motion and even have life-threatening consequences if they're located near important structures like the airway, they can be very difficult to remove by surgery.

So this is an area very near and dear to my heart. Before I came to FDA, I was working at the National Cancer Institute and the research team there treated many patients with rare diseases including patients with NF1. My mentor at the NCI, Dr. Birgitta Weideman has led many trials to find a treatment for

patients with plexiform neurofibromas and when I joined, the team had already evaluated a small number of pediatric patients with the drug selumetinib and seen some exciting prospective benefit and they were starting to enroll more patients on a trial to further evaluate how the drug worked in these patients. One of my projects there was to develop and start a trial in young adult patients to see if these patients would benefit.

It was very exciting to be a part of a team evaluating this promising therapy because at this time there were no effective therapies for these patients and as a physician and researcher, I saw how patients were affected in terms of mobility, pain and also the need for regular monitoring as malignant tumors can develop within plexiform neurofibromas or in other parts of the body.

So in addition to trials of drugs for the treatment of plexiform neurofibromas, the team at NCI had been conducting a natural history study for patients with neurofibromatosis. That is, they were following patients over time including with MRI scans

to see how their disease changed over time and tried to better understand the course of the disease. This turned out to be important to showing how selumetinib was changing the course of the disease and the benefit that patients were experiencing, as my colleague Denise will be explaining. If we can go to the next slide?

I'll briefly show you one example, and this is from a publication by my former colleague Andrea Gross in the New England Journal of Medicine. This is a young boy who was treated with this drug. You can see on the left photo that he has a bump on the side of his neck which is his plexiform neurofibroma. This is his picture before he started taking selumetinib and in the middle you see the photo after about a year of receiving selumetinib and the tumor is visibly smaller. The chart on the right shows how the size of this tumor had been growing before the drug was started. The red arrow shows when selumetinib was started and how the tumor started shrinking on treatment. We can go to the next slide.

And I'll show you one more example, also from

the same paper by Andrea Gross. Panel A is an MRI showing a cross section of the patient's body. You can see the bright white plexiform neurofibroma has a very complex shape, is very large and extends from the neck, chest, and upper arm. Again, panel B in the middle shows the tumor growing until selumetinib was started and then panel C, see how the research measured pain, strength and range of motion which improved on treatment. I know there are a lot of details on this right side but just to give you a sense of what the researchers were measuring.

At this point, I'll turn it over to my colleague Denise Casey who is the reviewer for this program to describe her experience. Thank you.

DR. DONOGHUE: Thanks so much, Dr. Bradford. Denise, it's on to you now. I guess could you just first describe just a very high level why we decided to approve selumetinib? Like, what was the evidence that was provided that, you know, led to us deciding that we thought this drug was effective for patients?

DR. CASEY: Okay. Yeah. So absolutely. The, you know, selumetinib is a MEK inhibitor. It is

a drug that was being developed in this indication and a number of other indications at the same time and this was going to be the first approval for the drug. So, you know, we had to come up with or the sponsor and the NCI came up with a number of ways to look at the safety and the efficacy of this drug and the intended use in patients with neurofibromatosis type I and plexiform neurofibromas that were causing symptoms.

You know, one of the challenges with this was how to measure the effectiveness of selumetinib in this tumor type because of the -- because this is a benign tumor. Right? And since the tumor is benign, we weren't always thinking about tumor shrinkage in the same way you would think about shrinking a tumor in a patient with cancer. And so it was really important to look at how the decrease in tumor size during the treatment correlated with the patient's symptoms and their ability to do things that they weren't able to do when they first entered the trial.

So, for example, you know, if a patient enrolled in the trial with a large amount of pain, and

you just saw Diana's slides, some of these tumors are very large. They grow along the nerves. As the patient was treated during the trial, they would get routine MRIs to look at how the tumor was shrinking. If the tumor was shown to be shrinking on the MRI, the investigators at NCI and the other centers running the trial were assessing whether the patient's pain was also decreasing or improving during treatment.

Another example, you know, patients some of the patients had tumors that were pressing on their lower spines in an area that serves us with bladder control and so some of these patients had urinary incontinence when they entered the trial. Over time if the tumors shrunk on the MRI, were these patients able to have better bladder control. So, you know, looking at these MRI scans in parallel with these and other similar clinical outcomes or patient experience aspects was really key during our review because, you know, we wanted to get a sense of whether selumetinib was shrinking the tumor, but more so, you know, whether this tumor shrinkage was actually affecting how the patients were, you know, their daily lives and

their function and Diana showed some nice images, particularly that last image with the patient with the large neck tumor, you know, there were lots information submitted in this application but you know, interviews of the patients and their families and even having better range of motion of the neck can improve the patient's daily function in school, in play. It's, you know, it was a great application to review from that standpoint to, you know, read about these patients as individuals and their experience during treatment.

So it was certainly a drug for a debilitating and chronic disease that, you know, had -- it was an unmet need, there were no other systemic therapies, so it was important that, you know, we review this application and I think it was a successful review in the end with all the parties.

DR. DONOGHUE: Thanks, Denise. And so just to kind of provide everyone with a bit of a framework or an understanding, so this data package was for just a small number of patients, about 50 patients I think and the percentage of patients whose tumors shrunk was

about 66 percent, 70 percent range. So the drug was shown to be able to be successful with shrinking the tumors for quite a few patients. And also equally important I think to the review team was not just the percentage of patients that responded with their tumor shrinkage but also how long they responded, which is particularly important I think for disease such as plexiform neurofibroma that is associated with potentially lifelong sequalae and so I think that was also a very important part of the review process as well.

Denise, I know there was a long road that people traveled to reach the point of even receiving an application or submitting an application to FDA and I think it was a labor of love for many parties including Dr. Bradford as she described. Other researchers led by Dr. Weideman at the NCI, but also many, many other stakeholders including patient groups who dedicated their time to describe -- to be part of that natural history protocol and go through interviews to help people better understand what the primary symptoms were that were causing them problems

with the disease or for their children.

So very unique, at least in terms of oncology, as you eluded to in that this isn't a disease that tends to cause people to die quickly, thankfully, but it is a disease that can cause a lot of problems, very, very severe problems for patients and decreasing their quality of life. Can you speak a little bit more about the involvement of multiple stakeholders during the development program and how we interacted with them a bit during this process?

DR. CASEY: Sure, sure, Martha. You're right. I mean, this was a huge collaborative effort, the success of this development program and when I first came to FDA, I came to FDA in 2013 and I think it was early 2014 when the NCI investigators who were seeing this, studying this drug in very early phase in the clinic came and presented to our office to the oncology office and showed us some of the very early safety and efficacy data they were seeing in patients and just a handful of patients early phase data. But they detected that there was an effect and there was a potential benefit they were seeing in these patients

and they -- we actually had a small roundtable discussion after that meeting to discuss next steps and then I guess it was a few months later NCI investigators came again to FDA with the commercial sponsor of selumetinib to discuss a -- I would call it an innovative trial design. How were they going to show in a registration-enabling trial like a trial to support the marketing application that this drug truly was effective and beneficial to these children.

And so they met with us to discuss that trial design and to discuss how they were going to measure the effect and it was from that meeting on there were several guidances, certainly some challenges as we see with rare development tumors, pediatric development tumors, but NCI investigators and the commercial sponsor came to every meeting with FDA from that meeting to the pre submission meeting when we were discussing the results that would be included in the marketing application and I can't tell you how important and useful it was to have the three parties at the table, the NCI investigators treating these patients, talking to families, understanding the

effects of the treatment and some of the even side effects of the treatment firsthand and then speaking with us as regulators and with the commercial sponsor who was going to be manufacturing this drug in a formulation that was to be suitable for very young children over the long term.

So I think the success of the program was all about that collaboration. And then as you mentioned, Martha, we -- NCI invited FDA reviewers and FDA medical officers to attend some of their conferences and workshops that they had on NF1-related tumors, how to measure them, patient engagement with these groups and so for us as reviewers, we had the ability to meet patients and to meet advocates and families firsthand and the scientists who were coming up with ways to measure this tumor and ways to think about how to measure benefit in these tumors. So, again, all stakeholders led to the success of this application and this approval.

DR. DONOGHUE: Thank you so much. I think you encapsulated it really well. I was involved when I was a primary reviewer very early on in this process

and I got to see firsthand a lot of sort of the problem solving attitude that all parties brought to bear when trying to figure out how could we possibly figure out a way to show that this drug is effective given the constraints in terms of patient numbers, given the issues relating to how to even measure a neurofibroma that spreads out in many different ways very different than our typical cancer lesions, how do we define benefit to patients by through patient reported outcomes measures, et cetera.

So I do think that that as really crucial, as you said, having people come to the table together, being open to maybe different types of solutions, not just going with the "tried and true" approach to drug development which we often use for refractory cancers just looking at tumor shrinkage alone in a very typical way. So I think it was definitely a great experience for us.

And there were also issues, just because this is a bit of a different development program for us because it's directed against a tumor that's benign. And we say benign which means essentially that it

doesn't tend to directly cause death to patients, it doesn't tend to metastasize or spread beyond the area of the tumor. So it's benign in that sense, but not benign at all to patients because of how large these tumors can grow, but because of the fact that this wasn't cancer per se, we also had to look a little bit differently at safety because we knew that people, particularly vulnerable patients, pediatric, young patients might be taking this drug for many years.

So I know we don't have a ton of time left, but just quickly, would you mind describing a little bit about how we thought about safety in this population and how we assessed that we thought it was safe to be approved?

DR. CASEY: Right. Sure. Safety was a big piece of the application. Like Martha said, we only had the 50 patients in the registration trial, so it was important to sort of collect safety data from other sources for us to review, and so NCI again was able to put forth some early phase data from their phase I studies and the sponsor was able to obtain safety information from ongoing trials that were in

different pediatric indication.

So of course there had been MEK inhibitors approved for cancer indications in adults, but we really had to be careful here because this was a pediatric indication and as Martha and Diana have already mentioned, really the anticipation of these children using the drug chronically, it's a benign tumor. We did know from the early phase data that with -- for long drug interruptions or holidays, the tumor in some patients did grow again, so it was best that they stay on the drug long term to maintain the effect.

And so it was really we had to be careful and think about the pediatric population, young children, we had to think about the short-term side effects and then of course the long-term side effects of using a MEK inhibitor and then balance that out with the benefits the patients were having with the drug. And so we always think about growth, development, and there are some -- the company's continuing to do some studies in looking at the long-term use and long term side effects of the drug in patients with the disease.

DR. DONOGHUE: Thank you so much, Denise. And Diana, I'll get back to you at the end of the panel discussion because I did want to get some last thoughts from you on this as well. But I think we should move on at this point and we'll talk about the development of KIMMTRAK for the treatment of ocular melanoma. And so Dr. Brewer and Dr. Spehalski.

DR. BREWER: All right. Thank you. Yes, so my colleague Elizabeth and I are going to be talking about this approval for really about uveal melanoma and the treatment of it with tebentafusp. The patient population for this study was a population of patients who had unresected or metastatic uveal melanoma that hadn't previously been treated with a systemic treatment or a treatment that goes throughout the entire body.

This is an exciting approval for us which we'll talk about in the next couple of slides and we just recently approved this drug in January of this year. So next slide, please.

Before we get into a little bit more detail about tebentafusp itself, I wanted to give some

background on ocular uveal melanoma. And so uveal melanoma is a type of cancer that affects the eye, specifically it affects the middle part of the eye which is called the uvea. The uvea is made of three main parts which are circled on the left end of the slide diagram.

Like melanoma that affects the skin, uveal melanoma begins in cells that make pigment and our coloring called melanin and the cells that make this melanin are called melanocytes. And although uveal melanoma is the most common type of cancer that develops or affects the eye in adults, it’s still very rare and only makes up about three to five percent of all melanomas.

It's expected that in this year, 2022, there will be about 3300 new cases of uveal melanoma. Some of the symptoms of uveal melanoma can include problems with your vision, a growing dark spot in the colored part of the eye which you can see on the screen in the middle picture. There can also be changes to the shape of the pupil or the center portion of the eye which you can also see.

Other changes may include changes in the position of the eye or the way that the eye moves. Unfortunately, even with treatment, about 50 percent of patients with uveal melanoma will develop metastatic disease or disease that spreads from the eye to other places in the body and the liver is most commonly a source of spread when patients develop metastatic uveal melanoma.

Prior to the approval of tebentafusp, patients with uveal melanoma that was advanced or uveal melanoma that had spread outside the eye, they would receive the same therapies that were approved for melanoma of the skin. However, these therapies tended not to work as well in patients with uveal melanoma. And so that’s why this approval of tebentafusp has been really exciting because it’s the first drug that has been approved specifically for uveal melanoma.

Tebentafusp was studied in patients, as I stated before, with metastatic uveal melanoma who had not received any prior treatment for their metastatic disease. And patients on the trial were assigned to receive treatment with either tebentafusp or treatment

with what's considered a standard of care therapy which is what they would usually get if they were not on a clinical trial. And what we saw with this trial was that the patients that were treated with tebentafusp had an improvement in their survival compared to patients that received the standard of care therapy.

There are some additional interesting characteristics about tebentafusp, so I'm going to actually have us advance to the next slide and I'll turn it over to my colleague Elizabeth to discuss.

DR. SPEHALSKI: Thanks, Jamie. As Jamie outlined, the approval of tebentafusp was exciting for us because it provided an approved treatment specifically for patients with uveal melanoma who prior to this approval had no treatment made specifically for them. But from the standpoint of a biologist, tebentafusp is also a very interesting product. So this is the first product that the FDA has approved that involves a T-cell receptor.

I just want to talk a little bit about how this drug works. So tebentafusp is what we call a

bispecific fusion protein. On one side of this product, which is the left here, where I have the melanoma cell labeled is an engineered T-cell receptor. So a T-cell receptor is a protein that's naturally found on the surface of your T-cells which are the white blood cells of your body that are primarily responsible for the adaptive immune response.

And so in your body, these T-cell receptors assigned to these cell surface proteins which are these known as MHC molecules or HLA molecules which are these blue balls here. And so in your body, all of your cells, they have these MHC molecules and their job is to present little pieces of proteins. And so they can either be from your cells themselves or from diseases, little peptides from either diseases or cancer cells.

And so the T-cell receptor recognized these complexes of these MHC molecules bound to a protein and they'll say "Okay, this is your cell and we won't attack it" or "This is a disease and we can attack that." And so how this drug was designed is this particular

MHC molecule called HLA0201 presents GP100 and GP100 is a little protein that is specifically enriched in melanomas. And so the drug, tebentafusp, will recognize this MHC on a melanoma cell specifically. On the other side of this is an antibody fragment that basically identifies T-cells.

And so this drug was engineered to bring your T-cells close to the melanoma cell and then they can release factors that will kill the melanoma cell itself. And so this is exciting because it's allowing your immune system to attack the melanoma cell specifically.

And so for us, besides providing a treatment specifically for patients that have nothing before this, it's kind of a new exciting mechanism that we can see the possibility of expanding to other types of cancer.

DR. DONOGHUE: Thanks so much, Liz. Much appreciated and it's a very exciting drug, both in terms of the patient population that it is able to treat as well as the way it works which is also very unique and exciting. I know that before I started at

FDA, I didn't really understand how different people who are not physicians get involved in drug development and what their role was in shepherding a drug from the very beginning when it's -- before it's even going into patients in clinical trials up to the point where it gets approved. So I was wondering if you could just describe at a very high level what your role is as part of the FDA review team?

DR. SPEHALSKI: Sure. So as a non-clinical reviewer or a pharmacologist, my job is to look at drugs before they go into people and decide whether or not the data that a company or a sponsor has provided for us in cells and in animals, if it's enough to provide a safety net to put in people.

So the FDA requires that when anyone comes in with a new drug that they show us that it works the way that they say it works. So for example, for selumetinib that it does target MEK, for tebentafusp that it targets these specific tumor cells that present this GP100 protein and that it also can, in the case of tebentafusp, activate your T-cells to attack the tumor cells.

On top of that, my job is to look at the toxicities of the drug before they go into people. That allows us to anticipate what might happen in the clinic. So the FDA requires that drugs are tested in animals before they're tested in people. The primary reason for this is safety. Two or more animal species are typically tested because the drug may have effects in different animals that both may apply to the clinic and so my primary job is to look at drugs before they go into people and see if we can anticipate problems that may arise once it's in the clinic.

DR. DONOGHUE: Thanks, Liz. I've also found you as members, you and other members of the nonclinical review staff very, very helpful in helping us to understand as you did here hopefully for all of us how drugs work or how drugs might potentially work when we're making that kind of risk/benefit assessment throughout the drug development process to determine does this study make sense, does this patient population make sense to kind of expose this drug to that you may not know all of the safety risks for and also really helping to guide us with what is the

appropriate starting dose to give, how quickly should we go up on that dose, what's safe for patients, how do we even figure out how to monitor patients. What should we be looking for in potential toxicities because we don't want to subject patients to too many tests too often but we also want to make sure that we're evaluating their labwork appropriately to be sure that we're not causing problems that we're not aware of and also so that if we detect problems we can detect them early enough to mitigate them so that they don't become life-threatening or dangerous or impede their quality of life to the extent that we can.

Could you speak a little bit as well to just at a high level to the philosophy and sort of the -- I look at nonclinical reviewers as also shepherds and protectors in many ways of animals as well because while the animal studies are important, we recognize that they have to be treated humanely and we don't want to have unnecessary studies either. Could you just speak a tiny bit to that? Because that was something I hadn't thought of before coming to FDA.

DR. SPEHALSKI: Sure. Absolutely. I

understand that animal testing can be sort of a contentious topic but the FDA does require that drugs are tested in animals before they're tested in people. I touched a little bit on the primary reason for this which is safety and toxicities but there's other reasons. Efficacy, we want to see that a drug can have some effect on killing tumors in a living animal before we put it in people. We don't want to give people a drug that we don't think will work, especially given that some of them do -- especially cancer drugs -- do have a lot of toxicity. We also want to find out what the body does to the drug, so we talk about things like absorption of drugs, how the drug is metabolized, how long it will stay in your blood and that will ultimately affect how drugs are dosed in people and so we need to know all of that in living systems.

However, the FDA does support the development of the use of alternative to whole animal testing. Tebentafusp is a great example of this actually because of the very specific nature of what it recognizes, the HLA on people and the T-cell receptors and then also

CD3 on a T-cell, it doesn't actually bind in animals. So tebentafusp was not used in any animal experiments before it was put in people and so this was a great way for us to see what other tests can we do to make sure that this drug will be safe before we put it in people. A lot of these tests include looking at cells, looking at human tissues and putting the drug (Inaudible) tissues, seeing where it would bind and really just starting at a really low dose in the clinic.

So the FDA does continue to be an advocate for methodologies that reduce or replace animal testing as well even though we do require it at this time.

DR. DONOGHUE: Thanks so much, Liz. I think we have about four minutes left and there was one question that came in in the chat. Just I think it was from Rhett who asked, "Is the interaction that we were describing between the FDA and NCI stakeholders unique to oncology?" And I think the short answer to that is no. I don't think it's unique to oncology. There is quite a bit of infrastructure in place at the

FDA for every disease type to kind of foster these collaborative interactions. And I am pretty sure that as the day progresses there will be additional information from other disease experts on that, but I do think it is -- I don't think from my own personal viewpoint, I don't think we're there and I don't think we have the perfect formula for this interaction yet and I think that's something that we all need to work together as a community on to figure out how best to foster this collaborative approach that I think selumetinib exemplified. So that's my take on that very excellent question, so thank you for that.

But I wanted to just take the last few minutes just to ask the panelists to reflect a bit upon their experiences with their approval of the drugs that they worked on and just whether their -- what they took away from that experience as a reviewer and how you think you could apply any lessons learned to the future. So you can take all or part of that question as you see fit. Jamie, I'll start with you.

DR. BREWER: Thank you. I think the one thing that I thought was interesting with the

tebentafusp program was the fact that they were able to do this randomized trial and they enrolled a pretty significant number of patients to the study. What we tend to see in other melanoma studies that focus on melanoma of the skin is that they don't have slots and openings for patients with uveal melanoma or other rare types of melanoma.

And so it definitely answers the question that if you build it, they will come. The patients are out there, we can enroll, we've done it with tebentafusp and maybe we should be opening more slots on other studies and other development programs to enroll more of these rare melanomas into clinical trials so that we can improve our knowledge base.

DR. DONOGHUE: Thank you. I think that's an excellent takeaway. Much appreciated. Maybe we'll move on next to Diana, Dr. Bradford. And I know you did not, you were not a primary reviewer of this application, but I think we all followed this closely and certainly there were some experiences that I think we shared.

DR. BRADFORD: Yes. I wasn't a direct member

of the review team, but very exciting to see it unfolding and sort of from both sides. I think what Denise spoke about earlier, the importance of collaboration with investigators with sponsors was the real takeaway for me and how critical that can be, especially when we're dealing with rare diseases to enhance really our understanding of the disease, how the drug is working, what the clinical benefit is to patients to really all work together. That's my biggest takeaway and that I think about often.

DR. DONOGHUE: Thanks so much, Diana. Liz, I'll have you go next and then last but not least we'll have Denise.

DR. SPEHALSKI: Sure. As I touched on earlier, I think the approval of tebentafusp was a really great blueprint of how we can cut down on animal use and other ways that we can look at human tissues and pharmacology data to cut down on the use of animals. Additionally, I think tebentafusp was an interesting new technology that we can move forward with and it can hopefully allow us to target maybe other rare cancers in a way that's safe and effective.

DR. DONOGHUE: Thank you so much, Liz. And lastly I'll go with Denise before we close.

DR. CASEY: Yeah, so really I would echo what Diana said and I think the only thing I could add for me, I think we're all pediatricians but just being thoughtful about and learning about how to think about pediatric data a little bit differently and to think about patients practically and how they're practically going to be taking a drug or families administering a drug to children. I learned a lot from the other FDA teams in addition to the other stakeholders but for example our clinical pharmacology team, how can we practically give this to young children and how can we expect families to be giving this to their young children every day for a long-term period around eating or fasting conditions, things like that. So I think I learned a lot from the other disciplines at FDA and again, like I mentioned, just meeting with the actual patients and families at those workshops when we were covering the IND or the development of this drug and it was just this parallel very inspiring experience for me to be hearing what it was like for

them to be living and functioning as best they could with their tumors and to think about okay, well, maybe we're going to be part of a team that can make things a little bit better.

DR. DONOGHUE: Thanks so much, Denise. I think you summarized it very, very nicely. I just want to thank the panelists for their time. Thank you to the Office of Orphan Drug Products for having us for this panel and thank you so much to everyone who joined us for this session. We have a couple of questions very late that we unfortunately don't have time to address, but I will try to get those addressed through the chat mechanism so we can address those. So thank you very much and I'll turn things over to the next panel.

DR. FERMAGLICH: Thanks, Dr. Donoghue. Up next we have our second panel from the Center for Biologics Evaluation and Research, or CBER. They'll be talking about how collaboration, in this case with another center at FDA, helped inform and guide their reviews of gene therapies for neurocognitive disorders in children. Their panel will be moderated by Dr. Vic

Baum, a Medical Officer in the Division of Blood Components and Devices in CBER. Dr. Baum.

DR. BAUM: Good morning and on behalf of the Center for Biologics Evaluation and Research, welcome to FDA's Rare Disease Day. Now, it may be that some of you are more familiar with other FDA centers such as the Center for Drugs, so what we'd like to do first is just give you a very brief 30,000 foot view of our Center which is known widely by its acronym CBER.

Now, CBER had a very atypical gestation. It was originally part of the Public Health Service then was transferred to NIH where it remained for quite a few years before being transferred to FDA and then finally becoming CBER.

The Center has three offices with product review divisions, the Officer of Blood Research and Review, or OBRR, the Office of Vaccines Research and Review, or OVRR, and the Office of Tissues and Advanced Therapies, or OTAT. But as we're going to stress all day today, it really requires critical input and cooperation from multiple offices, not just within CBER, but across the Agency.

I think it's tempting, it certainly is for me, when hearing the term rare disease to think about it sort of in the genetic and metabolic disease context. But what we'd like to do is show you that there are other types of rare diseases that CBER deals with and these are just some very brief selected examples, but there are many others.

The Office of Blood Research and Review regulates, among other things, modified blood products for use when conventional blood isn't available. Now, it turns out the FDA has to approve and facilitate importation of unavailable rare blood from overseas and as I recall this four-year-old girl required importation of extraordinarily rare blood type from the Middle East. OBRR's Division of Emerging and Transfusion Transmitted Diseases regulates test use for screening blood donors to prevent relevant transfusion transmitted infections such as when ZIKA threatened several years ago. So in that context, CBER works to help keep rare diseases rare.

The Office of Vaccines regulates a lot of products including phage therapy which can be tailored

to a population as small as N-of-1. And finally OTAT regulates quite a few proteins, gene and cell therapies but one that you might not be aware of is that OTAT regulates poisonous snake antivenoms.

But as I said, we don't act alone and today we're going to present OTAT's experience in the review of gene therapies for neurocognitive disorders in children.

We're pleased to have as our panelists Dr. Elizabeth Hart who is the Chief of General Medicines Branch I in OTAT, Dr. Naomi Knoble who is a reviewer in CDER's Division of Clinical Outcome Assessment and Dr. Andrew Byrnes who is the Chief of the Gene Transfer at Immunogenicity Branch at OTAT. And before I turn it over to Andrew, let me just remind you that we'd like this to be as interactive as possible, so please enter your questions in the "ask a question" feature. And with that, why don't you take it over, Andrew.

DR. BYRNES: All right. Thank you, Dr. Baum, and good morning, everybody. It's a pleasure to be here. My role at the FDA is a little bit different

than some of the other panelists you'll be hearing about today. So my job is to review how drugs are manufactured to ensure that the drugs have appropriate quality and purity. And I'm a specialist in reviewing gene therapy vectors, so gene therapy is the subject of this panel here. And I also run a gene therapy research laboratory here at the FDA, so we study gene therapy in animal models.

So I can tell you a little bit about how we review gene therapy manufacturing and quality including the outstanding scientists we have here who are experts on gene therapy vectors and how we collaborate as a team with other reviewers from all across the FDA really and how we provide advice to gene therapy developers and I'll note that many of the developers that we have are small companies and investigators at universities trying to treat rare diseases.

So really this is such an exciting and promising time for developing gene therapies to treat diseases that affect the brains and my colleagues and I are all very highly motivated to help ensure that

these gene therapies are safe and effective and to ensure that patients can count on the quality of these drugs that they receive. These gene therapies can be lifechanging and can potentially treat genetic diseases or other types of diseases that have no other treatment available.

So one of the most versatile classes of gene therapies are known as AAV vectors and I'll mostly be using those an example today. There's two FDA approved AAV gene therapy vectors. One is for a rare form of blindness called Leber's Congenital Amaurosis, and that was approved in 2017. And the other is for fatal form of motor neuron degeneration called spinal muscular atrophy, and that was approved in 2019 and I was the chair of the review panel for that particular drug.

So there's many more AAV vectors in ongoing clinical trials for treating neurological diseases and other diseases and this includes many rare diseases that may only have a few hundred patients in the entire world. And one of the things that make AAV vectors so special are that they're very good at

delivering genes to neurons and other cells in the brain and you can even get them to deliver their genes to the brain if you inject the AAV vector intravenously, it's a very special property of this class of gene therapy vectors.

However, AAV vectors also sometimes have very serious side effects and that's why we're so motivated to make sure that gene therapies are well manufactured and rigorously tested before they go into patients.

So let me give you a little bit of an overview about how we review the quality of these gene therapy products. These gene therapies are still quite new. Manufacturing processes are not standardized for the most part and not straightforward and the vectors are quite challenging and very expensive to make often.

They're some of the most complex drugs ever manufactured and one of the reasons they're so expensive is that a manufacturing run may produce enough of the vector that's only enough to treat a handful of patients, so you need a large number of batches, especially if it's a common disease.

So our staff here, our reviewers like myself give extra attention and hand holding to less experienced manufacturers and particularly academic institutions or nonprofits who may need more advice about manufacturing and we also have special programs so you may have heard of the breakthrough designation and RMAT designation and those programs allow us to provide extra advice and interaction for drugs that show evidence of being promising.

I want to speak a little bit about good manufacturing practices, so as quality reviewers, this is one of the things that we look at. This is a set of rules for how to manufacture drugs consistently, how to document everything, how to make sure that the quality is consistent and it's important to note that there's some flexibility in good manufacturing procedures, so phase one clinical trials, the drugs do not need to be manufactured following GMPs. However, we still think it's very important to manufacture these drugs with a high level of quality. For many gene therapies, patient only gets one chance at gene therapy can't be readministered because of the immune

system, so it's important that the products are relatively pure and they have full activity and that they have the correct dose and taking shortcuts in manufacturing can make it quicker and reduce costs but there's also considerable risk in things we've seen and these are rare but they do occur.

Cross-contamination can happen during manufacturing that can be quite harmful if it's not detected. Gene therapy products may not work at all if they're not rigorously checked before administration to patients and then sometimes the quality or the stability of the gene therapy vectors is poor and as a result of that, sometimes the clinical trial results can be inconclusive or uninterpretable.

So when there is adverse events in clinical trials as there sometimes are, we reviewers all come together as a team, the quality reviewer, the nonclinical reviewer, the clinical reviewer, and try to figure out what happened and how to prevent it from happening again. And sometimes the problem is the quality of the vector, so we look closely at the

quality to see whether it needs to be improved.

So a little bit about when a new clinical trial application arrives, this is called an IND and we have 30 days to review it. This is a very team approach. We have, as I mentioned, quality reviewers, nonclinical reviewers, clinical reviewers and sometimes others as well.

So an example of other types of reviews that we may need, expertise that we may need, we bring in from other parts of the FDA. So many gene therapy trials in the brain or the eye or the ear or the spinal cord, they may use novel unapproved delivery devices to administer the gene therapy products, so we collaborate with reviewers in FDA's Center for Devices and Radiological Health to make sure that these delivery devices are safe for patients and also that the delivery devices themselves don't inactivate or harm the quality of the gene therapy vector.

And another example, so we collaborate with reviewers in FDA's Center for Drugs if an investigational drug is used in the clinical trial along with the gene therapy vector. So, for example,

some clinical trials use immunosuppressive drugs to try to decrease the immune mediated side effects of gene therapy vectors. And, of course, we work closely with other members of our FDA review team within our office to review the quality of the gene therapy vectors that are used in the clinical trial as well as the quality of the vectors that are used before the clinical trial and the nonclinical animal studies.

So the expertise we have at the FDA, I've been working here for over 20 years and I've been in the gene therapy field for 30 years. Many of us are active laboratory scientists and we perform research on cell and gene therapy and on animal models. So we have a very high level of expertise overall and familiarity with the challenges in this field and we ground our approach to regulating these novel drugs in science.

So in addition to our internal review, we also have external activities. As I mentioned, we regularly meet with sponsors, drug developers to provide them with advice about their products and about their manufacturing facilities. This includes

meeting with them at the very earliest stages in development when they're still thinking about starting a clinical trial. And then usually at multiple times as drug development proceeds or when they encounter challenges.

For example, one challenge in the gene therapy field right now is shortage of manufacturing space at manufacturing facilities because of the large increase in gene therapy activities and also all of the COVID vaccines being manufactured, many of those use the same facilities. So I'll stop there and you'll hear a little bit more about CBER's outreach activities in Celia Witten's talk later on this afternoon and I'd like to turn it over now to Elizabeth Hart who is a medical officer here in OTAT. Thank you.

DR. HART: Thank you, Andrew. So as you all just heard from Andrew, there are a lot of complexities with cell and gene therapy products and although there are a lot of challenges from a clinical perspective, we believe that many of these products offer great promise, especially for rare disease.

Overall as an Agency, we are committed to advancing the public health by helping to speed innovations that make medical products more effective and safer. There is nowhere that this is more true than when we're dealing with rare diseases, especially for serious conditions that have no available therapies.

On a personal note, it was this desire to make a difference, especially in the lives of children with serious rare diseases, that inspired me to become a physician and then to join the FDA and it has been incredibly rewarding to be part of the development of novel therapies for rare diseases.

Developing cell and gene therapies for rare diseases is definitely not a "one size fits all" approach. We know that the clinical development programs need to be individualized. We know that the development process can be challenging and it requires a lot of advanced planning.

As this audience knows, we are committed and our ultimate goal is the approval and availability of safe and effective therapies. Throughout the Agency,

we use the same definitions so you heard about this in the prior panel, but by effective, I mean products that have appropriately demonstrated an improvement in survival or another clinically meaningful benefit in the way patients feel or function.

Each approved product needs to have a favorable benefit-risk profile for the specific patient population that is being treated. We recognize that each medical condition is different and that there are differences in what are acceptable risks and side effect profiles for each condition. So instead of continuing to speak in a lot of generalizations, I want to focus on some of our experience with the development of gene therapy for several inborn errors of metabolism.

The inborn errors of metabolism that I'm going to focus on and that Naomi is going to subsequently focus on have to do with those that primarily affect young children. For these conditions, children often are asymptomatic when they're born and then in early childhood, their developmental trajectory changes. We know that ordinarily children develop new milestones.

These children develop those new milestones more slowly and then they stop developing them. And then they lose those milestones that they previously had and often these conditions are also associated with premature death.

Each of these inborn errors of metabolism, while they share several commonalities, they're each different and even within a single disease, patients' courses are different. This obviously poses unique challenges and requires careful consideration as we determine the best ways to study and evaluate therapies for these conditions. And most importantly, this requires a lot of collaboration.

So as you heard from Andrew, we work collaboratively with sponsors who are developing these therapies beginning really in very early in product development. So while they are still refining their product and before they have conducted extensive preclinical testing all the way through to the post-marketing period and we really work a lot to try and ensure that there is a smooth and effective development program in which patients are really being

thought about and we are ensuring that we're getting the maximal information while still minimizing the burdens on patients, their families, and most importantly, minimizing their risks.

The other area where there is incredibly important collaboration is that with the patient community. So the FDA has hosted listening sessions and patient-focused drug development. These interactions are really, really, really important for us to understand what is truly clinically meaningful to patients. What are the risks that they are willing to accept in the context of the disease, really trying to understand these tradeoffs because as we've talked about with rare diseases, there is often only one chance and we really want to ensure that each product that has a potential to help a patient is developed in the best way possible and that patient safety is protected. So we really appreciate the time that patients spend talking to us and sharing their experiences because we really are able to incorporate that into the clinical development program.

Then you have heard a lot as far as

collaboration amongst the CBER team and it really is essential to understand the risks from both the CMC as well as the pharm/tox perspective.

Additionally, when a disease only affects children, we need to ensure that we have information on prospect of direct benefit from appropriate nonclinical studies before initiating research in children and so we work very closely with the pharm/tox team to understand these issues and to help them to advise sponsors on how these studies should be conducted.

Then when it comes time for developing the clinical development program, it's very helpful if there is appropriate natural history data given the rarity of some of these diseases so that we can understand the trajectory so that we can appropriately design a study that is maximally informative.

And so we collaborate with people outside of just CBER and one of the areas that we tend to collaborate a lot on is in clinical outcomes assessment and that's especially true for these

neurodevelopmental diseases. And so with that, I'd like to turn it over to Naomi from the Clinical Outcome Assessment Team in CDER to discuss this further.

DR. KNOBLE: Thanks so much, Elizabeth, and thanks to all of you for being here today as well. It's a privilege to be part of this Rare Disease Day and to celebrate and bring attention to patients living with a rare disease and their families and caregivers.

So I wanted to just in my little chat here give you a little bit of insight into what it is that I do in my little corner of FDA here and then highlight some of the really critical work that I think FDA is doing to advance rare disease measurement. But to start with, my name is Naomi Knoble and I work as a reviewer in the Division of Clinical Outcome Assessments and I work within CDER, the Center for Drug Evaluation and Research. But I work closely really with CDER the most but with CBER as well and certainly Elizabeth and I have worked together on a number of reviews. Every once in a

while I work with our Device Center, CDRH, and like many of us at FDA, I have two parallel tracks in my career: I'm clinically focused and then also research focused. And so clinically I'm a pediatric neuropsychologist and in layterms it means I used to give IQ tests to kids. The kids that bounce off the walls a little are really my favorites and near and dear to my heart. But I worked in autism and then other chronic illnesses like cancer and kids with kidney and other renal diseases and I really enjoy the work.

And interestingly, many of the tests that I used in my clinical career I often see proposed for neurodevelopmental disorders in the rare disease space as well. And then I also have this part of my career where I specialize in measurements, the measurement science for clinical trials. And so within FDA, I exclusively work on pediatric rare disease applications, within CDER and CBER.

And so as both of my colleagues Andrew and Elizabeth highlighted the work that we do here is highly collaborative, I'd say intensively collaborative, and we really can't do I think any

review without one another. So just to give you a little more insight into what this world of clinical outcome assessments is, some but not all rare diseases have clear indicators of biological processes that we can call biomarkers. Some diseases have these, but not all. And so when we don't have biomarkers, sometimes we can use a clinical outcome assessment, we call it a COA, and it measures how individual patients feel, function or survive and we can use these for clinical trials to evaluate how patients are responding to new treatments.

And so at the heart of clinical outcome assessment measurements are patients. And so like patients and caregivers might not be clinical experts or necessary experts in clinical trial design, but patients and caregivers are experts at what it's like to live with a rare disease and to bring some nuanced insight into what that looks like that no one else has.

And so it's understanding how people who are living with a rare disease experience symptoms or impacts or what treatment priorities are and that

needs to be at the heart of clinical trial measurement and also clinical trial design.

So it's part of my job as a reviewer to see how sponsors have included patient insights both into the measurements of their trial but then also to the trial design, too. Sometimes trials are designed in a way that's maybe not feasible for patients to complete necessary and there are just some modifications that need to be made to make it a little more patient-friendly.

And so at FDA we're often asked sort of how we use patient perspectives in our work and for my review in clinical outcome assessments, patient input is essential. The -- it was actually the patient-focused drug development initiative that FDA began I think circa 2011, 2012 and that's part of what inspired me to bring my career to FDA knowing that we really do make patients the center of the work that we do. Patients are the primary stakeholder in any medical product development.

And so when I start a review, like ideally, the sponsor submitted a summary of evidence from

patients or caregivers, maybe patient advocacy groups as well, to explain symptoms and impacts that patients are experiencing and then also treatment outcomes that are important to patients.

I think especially in the rare disease space, and certainly the pediatric rare disease space, having insights directly from patients and caregivers are essential because there can be a lot of heterogeneity, a lot of diversity and difference from one patient to another even though they're all under the same umbrella of the same disease label.

And so sometimes I get this information from sponsors and sometimes I don't and so when I don't, I turn to a number of resources, all of which Elizabeth touched on in her talk. So first I'll check to see if there is a "Voice of the Patient" report and this is an initiative that started at FDA in about 2012 and it continues importantly through patient advocacy groups largely and those "Voice of the Patient" reports typically summarize what patients and caregivers are saying about the impacts and experience of a disease and what treatment priorities might be.

Sometimes we have that and sometimes we don't, especially in the rare disease space. So I'll take a look to see if we've done a patient listening session with the rare disease community and that will give me at least some insights from patient and caregiver perspective about a condition. I'll also look for published qualitative interview-based studies or survey studies with patients or patient advocacy groups because that can also be just really helpful, again, to systematically and collectively summarize patient experiences.

And then when sometimes last but not least I'll go to patient advocacy websites and then also social media just to see if I can get a little bit of insight or understand sort of even what it looks like to have this condition. So patient perspectives are essential for trial measurement and then also other aspects of clinical trials. And so one example of measurement, especially in the pediatric rare disease space, clinical experts or publications on the disease will indicate that motor functioning is clinically important but when you ask patients and caregivers,

especially caregivers of patients who can't report for themselves, folks might say, well, you know, it's actually that my muscles get so fatigued that I can't walk across the room or whatever the activity might be.

And so it's that important aspect, that nuance of motor functioning of muscle fatigue that's likely most critical to focus on from the patient perspective and might also give us the best chance of detecting treatment effect if one exists.

Certainly in the neurodevelopmental/ neurocognitive space -- so many of the IQ tests that I used to use in my clinical career are proposed for use in clinical trials. Kids don't always like to do them, but they're not the end of the world. Sometimes it's just it looks like playing with blocks or toys, but clinical experts might say well, you know, change in cognitive functioning is the most important thing, but when you ask parents and caregivers of kids with rare diseases, especially that impact other developmental functioning, parents and caregivers might say well it's language or communication. If my

kid could just have a couple of more words in their vocabulary, I might have a better chance of knowing what they want and they might be less frustrated with trying to get what they need.

And so instead of looking at necessarily cognitive processes or reasoning, we want to look instead at language and communication and so I think these are the insights that are so critical, especially in the rare disease space and the pediatric rare disease space and it can make all the difference both for the success of the trial but then also making sure that outcomes are meaningful for families.

One last point I want to touch on for bringing patient perspectives to bear on clinical trials just from my clinical knowledge of kids and also my knowledge as a parent, I can appreciate, I think many of us can, that going to the doctor's office and doing a clinic visit can be a little stressful and so sometimes I'll look at clinical trial schedule of assessments and I'll ask myself if I think it's patient-friendly and I'll see if the sponsors indicated whether or not patients and patient

advocates have been consulted. Every once in a while that happens but I wouldn't say it's the norm. And sometimes tests are required of a patient in the afternoon on a clinic visit where I know that kid might have problems because of their disease, they might have problems with behavioral functioning and they might be more inclined to refuse after lunch if they're tired and they're already stressed out from a morning of blood draws and other things.

And so sometimes flipflopping the timing of assessments can really increase the patient's experience of being part of the clinic visit but then also improve data quality.

And so as both of my colleagues have mentioned already, both Elizabeth and Andrew touched on, is collaboration is critical to our work here at FDA and if you can't collaborate, this definitely isn't the place to work, but every single review that I do requires that I work very closely, especially with my clinical colleagues and my statistical reviewing colleagues and so I'll meet with my clinical colleagues often multiple times in the course of the

review to understand the disease process, the mechanism of action of the novel treatment to give me additional insights into looking at what the sponsor's rationale might be for how they've designed their measurement approach.

Also, depending on the disease that I'm reviewing, if I'm working with CBER on a review, I'll often reach out to other clinical colleagues over in CDER to bring their insights to bear on whatever it is that we're taking a look at. And then, of course, my statistical colleagues, while I have a background in psychometrics, which is a niche area of statistics for designing clinical outcome assessments, I have colleagues who uniquely focus on the nuances of those types of statistics as well and I leverage their insights, too.

So the last thing I just want to highlight here are some I think really important FDA funded external collaborations for advancing rare disease measurements. The first that I want to mention is C-Path's Rare Disease Clinical Outcome Assessment Consortium and this only just formally launched this

January but it's a project that’s been underway for a few years now and the mission is to enable precompetitive collaboration to advance measurement science for rare disease clinical trials.

Often even just trying to find a starting point for measurement can be really burdensome for sponsors, especially some of maybe smaller companies as well. And so part of the larger consortium initiative is to be able to give sponsors a leg up to identify some potentially suitable clinical outcome assessments for use but then also in sort of a broader vision, to be able to advance measurement science so we can do the best job for patients and make the most of their data. It’s my true privilege to serve as FDA’s liaison through CDER to this particular consortium.

There’s also a Rare Disease Cures Accelerator and Data Analytics Platform, also through the C-Path organization and the function of that initiative is to accelerate our understanding of rare diseases and advance biomarker and also COA measurement research and facilitate innovative trial designs and

mathematical modeling and the development of that. And so the Rare Disease Cures Accelerator and Data Analytics Platform is an exciting new opportunity and there are some current projects underway in some rare diseases that I'm really excited to see what's happening next there.

And then finally, through CDER we have a pilot grant program called a Standard Core COAs and Related Endpoints and the purpose of this is to make publicly-available COAs for use in clinical trials. Sometimes the clinical outcome assessment might be under copyright and it's not publicly available and so this sort of open access copyright approach would be critical I think to help advance clinical trial design and it includes rare disease measurement as well. So with that, Vic, I'll turn it over to you and maybe we'll take some questions.

DR. BAUM: Thank you. Actually, we have several questions. Maybe I can send this one to Andrew. Can you -- actually, I'll start off with everybody. Can you tell us about how CBER and others collaborate to bring forward an N-of-1 or N of very

few patient treatments? What other parts of FDA are involved in N-of-1 therapy approval? I might just add, I believe that the FDA issued a guidance just over the past few months about N-of-1 trials, so that should be available. Anybody want to talk about N-of-1 trials? Or not?

DR. KNOBLE: Well, I can't speak specifically to N-of-1 trials, but I am aware that there is a precompetitive, I think largely academic consortium, that's recently launched regarding N-of-1 research and I think it's a really interesting methodology for us to keep watching this space and see what methodological advancements can happen that we could bring to bear on clinical trials.

DR. BAUM: Okay. We have another one about would newborn screening be beneficial to us? Elizabeth.

DR. HART: Sure. So absolutely newborn screening has a lot of potential as far as earlier identification of patients and accessing standard-of-care therapy. So there is absolutely a role for newborn screening. From a clinical trial perspective,

one of the issues that we face is when is it appropriate to begin treating an asymptomatic patient with gene therapy? Typically, and as you'll see in our guidance, we recommend that early therapies begin in symptomatic patients because again we're looking for a favorable benefit risk and as you've heard discussed by Andrew, there are a lot of risks associated with gene therapy. A lot of promise, but there's also a lot of risk. And so typically we think that that initial favorable benefit risk in general applies to patients who are symptomatic and then once we start to see early promise, it's possible that a therapy could be expanded to go into an asymptomatic population.

DR. BAUM: All right. There's a question here about what's the typical time to expect a response from FDA if we're asked about a pre-IND meeting and does the investigator participate in pre-IND meetings? Pre-IND meetings, remember, are meetings that are held relatively early in the clinical development process before filing -- in order to develop a fully formed IND. Anybody?

DR. BYRNES: I can take that. So pre-IND meetings, our goal is to respond within 21 days to the request for a pre-IND meeting and to schedule it within 60 days of the request. And due to the COVID pandemic and shortages of staff, unfortunately we're not always able to meet those goals within 60 days, but we try very hard about that. The investigators do participate in those meetings and sometimes we have patients or patient advocates participating in those meetings as well and that gives us a very important perspective. Those representatives are invited by the sponsor.

DR. BAUM: All right. Here's another one which actually has to do with a specific metabolic disease, but I'll generalize it. Can you please provide more information on gene therapy opportunities, specifically how can patients participate? You know, similarly, the FDA does not have a role in enrolling patients in studies, but certainly clinical -- if you look at clinicaltrials.gov, it's very easily searchable and you can see what's going on nationally if not

internationally in the field.

How can the FDA make patient input sessions more widely known and available to rare disease patients themselves working to broaden the pool of essential patient perspectives into consideration?

DR. KNOBLE: Yeah, Vic, I can take a stab at that one. I think it's -- disseminating these things is never direct necessarily or easy but we have here at FDA the Patient Affairs staff who are under the Office of the Commissioner and their whole mission is to engage with patient communities and lead patient engagement activities through public-private collaborations and partnerships and also expanding public awareness and so I think it's been my observation that our Patient Affairs team works very closely with other external organizations like NORD, the National Organization of Rare Disease, and who are just an amazing resource I think for things like gene therapy trials and other initiatives or ways to help patients who are in rare disease communities connect with one another and other resources, too. So staying connected and staying aware of what opportunities are

available I think in some ways can be its own full time job, but thankfully we have Patient Affairs teams to lead that for us.

DR. BAUM: I have a question for Elizabeth which is that, you know, some trials are established as randomized controlled trials where some patients get the drug, some get a placebo or another drug or no treatment depending. Well, for serious pediatric diseases, why can't everybody or all the children in the trial receive the treatment? Why are some companies required to do a randomized controlled trial?

DR. HART: Thank you. This is a very good question and basically in the end it comes down to the fact that our goal is to help to get answers and to find out if a therapy works and to move that towards approval if that's possible and so often a randomized controlled trial is the best way to adjust for other factors that could basically impact our ability to interpret results and so it can often be the most expeditious pathway to getting answers.

One of the challenges with the external

control natural history is if the disease is very heterogenous or not able to distinguish what might be a treatment effect versus natural variation and so especially in small populations that can be very challenging and so it's often needed to demonstrate a much larger treatment effect to overcome some of those challenges and so these are things that are really figured out on a individual product and condition basis, but know that when we recommend a randomized controlled trial, it is because we think that that is the most expeditious way to get answers. And so I think that there is definitely a role and it does benefit the patient community.

DR. BAUM: All right. We have a few more questions. I'm just going to try and perhaps answer them very briefly because we're just about out of time. Any breakthroughs in a certain disease? Somebody asked. The answer is, actually, FDA is not allowed to comment on any INDs that are in house. We can't tell you -- actually, we can't even acknowledge that they're in house, so what we can tell you is limited about things coming along.

Does the FDA have any collaboration with the European Medicines Agency or other health authorities? The answer is yes, there is a I want to say monthly or maybe bimonthly meeting, a pediatric cluster meeting with EMA and other regulatory agencies and there is also an International Counsel Harmonization which has several guidelines, for example, on pediatric clinical trials. So those exist, but we don't have time to talk about them at any length. So with that, thank you very much for listening.

(BREAK)

DR. FERMAGLICH: Welcome back to FDA Rare Disease Day 2022. Our next panel organized by the Center for Drug Evaluation and Research, or CDER, and moderated by Cardiologist and former FDA Clinical Team Leader, Dr. Preston Dunnmon, will focus on the lessons learned and outcomes of a public-private partnership among diverse stakeholders to address a devastating rare disease, amyloidosis.

Before the panel starts their discussion, Dr. Kerry Jo Lee, Associate Director for Rare Diseases in the Division of Rare Diseases and Medical Genetics in

the Office of New Drugs in CDER will start off with a little background on CDER and their work in the rare disease space. Dr. Lee.

DR. LEE: Thank you so much. I'm so happy to be here. I'm Dr. Kerry Jo Lee. I am a pediatric gastroenterologist/hepatologist who worked for many years taking care of children with some of our rarest conditions before coming to the FDA where I've been for the past eight years. I currently am the Associate Director for Rare Diseases at CDER in the Office of New Drugs' Division of Rare Diseases and Medical Genetics and I lead the Rare Diseases Team.

That's a multidisciplinary team that works to coordinate rare disease policy and programmatic functions across the center such as developing guidances, educational training and engaging with multiple stakeholders both internal and external to the FDA in order to achieve our mission which is to facilitate, support, and accelerate the development of drug and biologic products for the benefit of patients with rare diseases.

Drug development in rare diseases can be

complex for many reasons. They have challenges using well-established trial designs in small populations, selecting endpoints -- the outcome measures to demonstrate benefits that are both robust and clinically meaningful -- and we have challenges when there is limited understanding of the natural history of disease.

In order to overcome these challenges and really move the needle in rare disease drug development, it takes collaboration and communication and we need to hear from patients and their caregivers about what matters most to them. On the slide that you have in front of you, I just wanted to highlight a few of the many ways for patients to engage with us here at CDER. So we have Patient Listening Sessions and these helped provide insight and understanding of the patient experience and this informs our perspective on what is most important to patients.

We have Patient-Focused Drug Development meetings. These are more systematic approaches to help ensure patients experiences, perspectives, needs and priorities are captured and meaningfully

incorporated into the drug development and evaluation of drugs.

We have workshops or conferences and these might be public meetings or more focused and targeted workshops to solve specific challenges for development in a condition and then we also have public-private partnerships, one of which you will hear about today, or consortia, and this is when you form collaborations with other government agencies, industry, patient groups, academia, and other stakeholders to really promote the development of new tools and methods and approaches to foster innovation and bring efficiency into the FDA-regulated product development.

And finally, we have Critical Path Innovation meetings and these are used generally as a forum for FDA and stakeholders to discuss potential scientific advancements in drug development, so biomarkers, clinical outcome assessments, natural history studies, emerging technologies, or other innovative conceptual approaches.

I'm very happy to be here today to highlight just one of the many efforts CDER review staff

undertake and introduce Dr. Preston Dunnmon who is a cardiologist and former FDA clinical team lead from the Division of Cardiology and Nephrology who really exemplified the collaboration and communication that we talk about during his time here at the FDA and his work to advance drug development for amyloidosis, a rare disease. Dr. Dunnmon, I'm happy to turn it over to you to further share this work.

DR. DUNNMON: Kerry Jo, thank you so much. Good morning, good afternoon, good evening, depending on where on the planet you are, to everyone. My name is Preston Dunnmon and I'm a cardiologist and want to start today's session with a heartfelt thank you to FDA for welcoming me back to participate in today's proceedings.

The Center of Drug Evaluation and Research or CDER and specifically the Division of Cardiology and Nephrology was my professional home for the past 11 years during which time the public-private partnership between FDA and the amyloidosis research consortium was created. I'd like to pay special tributed to Dr. Norman Stockbridge, my former boss and mentor at FDA

for his unwavering support of our efforts and encouragement when the road was occasionally difficult. His leadership was a critical enabler of much of what you're going to hear about today.

So to start, amyloidosis is actually a group of diseases, all of them profoundly serious, all of them can be fatal, and all of them either rare or ultra-rare or orphan and they affect different people in different ways. These different manifestations of these diseases make drug development really challenging and until recently there were no treatments.

About four years ago, The Center for Drug Evaluation and Research entered into a public-private partnership with the Amyloidosis Research Consortium, specifically to tackle these barriers to developing medicines for the various forms of amyloidosis. I often get asked how did this public-private partnership come into being and why? In short, it was born from the combination of profound unmet medical need, fascinating science, and the frustrated energy of multiple stakeholders. What am I referring to here?

There was the frustration of the patients with no approved drugs to treat these debilitating and often fatal conditions. There was the frustration of regulators and at the time it was me, who by mandate of law, must have substantial evidence of both safety and effectiveness in order to approve drugs. There was the frustration of the academics whose voices on subjects like biomarkers seem to go unheeded. And there were the frustrations of industry trying to understand how to engage the seven different divisions at FDA that might become involved in reviewing an application for a drug to treat the multiple different organ systems that can be affected by amyloidosis.

So it was with this incredible unharnessed energy that FDA and ARC, the Amyloidosis Research Consortium, began a series of communications that led to the formation of the Amyloidosis Forum where all stakeholders could meet, hear the needs of the others, understand what the hurdles would be to surmounting these barriers that we faced as well. At our first meeting, CDER made available senior staff from all of the involved divisions including cardiology,

nephrology, neurology, gastroenterology, hematology, clinical outcomes assessments and statistics. Subsequently, the MHRA, which is the UK counterpart of the FDA, joined our effort. Patients came to these forums and told their stories and industry asked questions about possible regulatory pathways to drug approvals.

Along the way, ARC, with its focus on supporting patients that critically to the sciences behind drug development, applied for and received NIH funding. Specialists in imaging joined our meetings, papers were published, and I think more importantly, CDER continued to engage in the support discussions about these barriers to the approval of drugs in this precompetitive environment.

Have no doubt, this work was hard. No one got recognition rewards, no one got bonuses and no one got consulting fees. Instead, the work of this group arose from the commitment of patients, regulators, industry and academics to move this field forward with the goal of developing medicines for patients with amyloidosis. We were fortunate to have four of these

experts with us here today on this panel.

So to start us off, it is my pleasure to introduce our first speaker, Dr. Matthew Maurer, who is going to talk about what amyloidosis is and how it affects patients. Dr. Maurer is a Professor of Medicine and Cardiology at Columbia University Medical Center where he is also Director of the Cardiac Amyloidosis Program. Importantly, he was the co-chair of the steering committee of the ATTR-ACT trial showing that tafamidis was safe and effective therapy for transthyretin amyloid cardiomyopathy.

As many of you know, or may know, ATTR-ACT was the study that was pivotal to the approval of tafamidis in the United States. So Dr. Maurer, thank you for being with us and I'll turn this over to you.

DR. MAURER: Thank you, Dr. Dunnmon, and I want to thank ARC and the FDA and I don't think there is an activity I've been more engaged in in the last few years than the efforts of this public-private partnership and it really all starts with being a bedside clinician and having the privilege to care for individuals who suffer from this disorder and I can

tell you they're wonderful people and they're lovely and they deserve all the efforts of everyone that's put into this in trying to accelerate on the development of new therapies to address this condition. So I'll briefly give an overview of the disorder and particularly with regard cardiac disease.

These are my relevant disclosures and support I have both from the government and from various sponsors. So for those of you who are unaware, systemic amyloidosis is a disorder in which there is an extra-cellular deposit of a fibrillar protein and that protein interferes with the structure and function of numerous organs throughout the body, the heart, the kidney, the liver, and so forth.

While there are dozens of proteins in the body that can form amyloid in vivo in the heart which is my focus there are really mainly two types and that is AL, a disorder of the light chain which I'll highlight in a minute and transthyretin, a disorder of a protein produced by the liver that can either be in a variant form with a mutation or exist as we say in the wild, we used to call that senile cardiac amyloid

because it disproportionately afflicts older adults.

AL amyloid is really an amyloid in general is a rare, but multisystemic, disorder which makes it difficult for clinicians to diagnose and often leads to delayed diagnoses and I briefly highlighted here both with AL and TTR of the multifaceted different organs and manifestations that a particular patient can have that really lead to reduction in their functional capacity and their quality of life, recurrent hospitalizations and unfortunately early demise.

These multisystemic nature really requires a bunch of experts and obviously requires multiple aspects of FDA to engage in trying to develop drugs that can forestall any of the consequences.

In the world of amyloid and especially obviously in cardiology being no exception, it's imperative to distinguish what is the precursor protein, if you will, that's causing the amyloidosis and we spend an inordinate amount of time trying to do this. We've gotten much better at it and that's because the biology of these diseases, AL amyloid and

TTR are very different as is their natural history and prognosis. The genetics are highlighted, there's a genetic role in TTR, not in AL, and obviously treatment is markedly different. One treated with anti-plasma cell therapy, that is for light chain amyloid, and quite distinct for TTR.

So over a very brief period of time, I would say ten to 15 years, transthyretin has gone from a very rare disease, still rare, but one that was underdiagnosed and untreatable, to one that's increasingly recognized and certainly treatable and that's because we've now moved from needing an invasive technique as shown in the middle there, a biopsy of the heart to one in which we leverage a nuclear scintigraphy to diagnose amyloid. This is an approach that's available in almost every cardiology practice in the United States of which there are almost 10,000, and that has led to a marked increase in our ability to diagnose patients with this condition and more importantly diagnose them earlier in the course of the illness and then I'll highlight some of the emerging treatments that have been shown

both for AL and TTR.

So as I highlighted, this is one of the seminal events in the field and now to FDA's credit , we are able to enroll patients in clinical trials and no longer requiring an endomyocardial biopsy as we did in the original ATTR-ACT trial that I had the privilege of leading but now can enroll patients in clinical trials using these noninvasive techniques that rely on pictures of the heart and you can easily see in the bottom here panel a patient who has a marked cardiac uptake of the tracer indicating the disease.

In the world of light chain amyloidosis, a really devastating form of cardiac amyloidosis, we had really no, if you will, FDA-approved therapies. Everything was borrowed from the space of a multiple myeloma and I'm proud to say colleagues throughout the world collaborated and this agent daratumumab which is a monoclonal antibody against CD38 has been shown, on top of standard therapy, to result in a much better hematological response and better outcomes in patients. These data were featured in the New England Journal in part of the ANDROMEDA trial and led to the

approval by the FDA of daratumumab, a real seminal event for patients with light chain amyloidosis.

And transthyretin amyloidosis and our emerging therapies have been born out of incredible work done by basic science researchers. For those of you who don't know, transthyretin or prealbumin is a tetrameric protein composed of four individual monomers that are shown in this cartoon here in red, yellow, green and blue and in the setting of either aging or with variants in the protein, they dissociate into monomers and those monomers can fold and agglutinate forming amyloid fibrils that can either deposit in the heart causing amyloid cardiomyopathy or in the nerves causing amyloid polyneuropathy, and notably most patients have a really a mixed phenotype with deposits in both organ systems.

And from this emerging biology, production of the protein by the liver with dissociation of the protein as I said into legemers (ph.), a deposit in the various organs. We've been able to now have emerging strategies, some of which have been borne fruit, if you will, and have approved therapies. One

is a TTR silencing or knockdown. That is, reducing the production of transthyretin by the liver using either small interfering RNA or antisense or maybe even CRISPR-based therapy. TTR stabilizers, we heard of tafamidis and its success and others are on the path hopefully and emerging is the concept of anti-amyloid therapies that may address preformed amyloid fibrils in various organs including the heart and so with all this excitement, it's really a privilege to work with multiple stakeholders in advancing the care of patients through this partnership with ARC and the FDA. Thank you for your time.

DR. DUNNMON: Matt, thank you so much. Next we will proceed on to our second speaker and then we'll go through all the speakers and take questions here at the end because I want to make sure that everybody has a chance to describe to you their work. Our next speaker here is Kristen Hsu. Kristen is the Executive Director of Clinical Research at our partner in this partnership, the Amyloidosis Research Consortium, and Kristen is going to take you through how the partnership actually works and how it produces

the outputs that it produces to help support the development of medicines in this space. So, Kristen, take it away.

DR. HSU: Thank you, Dr. Dunnmon. Hi, everyone. My name is Kristen Hsu and I'm the Executive Director of Research here at ARC. My background is actually in drug development. Before joining ARC five years ago, my career had been focused on planning and executing clinical trials across a number of different disease spaces: from Alzheimer's studies with thousands of patients to rare and ultra-rare disease studies with maybe dozens or less.

Now, I had worked in Alzheimer's Disease for a number of years. During that time, I never had the opportunity to actually sit down and meet an Alzheimer's patient, to speak with them or their caregiver, or hear directly from them about what living with Alzheimer's was really like. Rare disease gives you that opportunity. It demands it, that you learn directly from patients in order to design your research and so that's really what prompted me to move from industry to a patient nonprofit organization, the

chance to put my skills to use in a more patient-centric environment.

So a little bit about the Amyloidosis Research Consortium, or ARC. ARC is a patient-led nonprofit organization. We were founded in 2015 by Isabel Lousada, a patient with AL amyloidosis who had the vision of making a material and significant impact to the curability of amyloidosis.

ARC was founded during a time when the amyloidosis landscape was rapidly changing. For the first time, there were multiple companies interested in the disease and a number of new promising therapies in development but selecting the right patients and endpoints within clinical trials was proving to be very challenging. A promising drug for TTR amyloidosis failed to meet its endpoint in phase three clinical trials and was rejected by the FDA.

There was a huge risk of additional failures and a need to develop a new model that would support the potential and shift the changing landscape. And so ARC's model is to work with and across all stakeholders within the community, harnessing the

power of collaboration and innovation to advance science and both improve and extend the lives of those with amyloidosis. We pride ourselves on being a science-based patient organization working to de-risk drug development by strategically implementing programs that we believe are critical to better care for patients and facilitate and accelerate drug development in these rare diseases.

Now, from our formation, we've been strategic and stepwise in the way we've worked and have built the programs at ARC. Our strategy has been driven by our engagement with a broader research community to identify the unmet needs and barriers that are standing in the way of progress, bringing together the best minds in amyloidosis across the patient community, academia, regulators, industry, and other related research fields.

Now, this slide shows some the key initiatives from our formation that were instrumental and led to the development of our public-private partnership. We've been grateful to have always found enthusiasm and willingness from FDA to both engage,

give thoughtful input and participate in our different activities. Some of these engagements have been quite successful while others have naturally been more challenging.

In 2015, shortly after launching ARC, we held our inaugural research meeting with experts including representatives from the cardiorenal division of CDER and representatives from the Office of Rare Disease. We went on to hold one of the first externally-led Patient Focused Drug Development meetings later that year with 12 members of FDA in attendance representing the Divisions of Cardiorenal, Hematology, Neurology, The Rare Disease Program, and the Office of Orphan Products Development.

Now, given the number of treatments that were under development at that time, FDA was very eager to understand the perspectives of patients with amyloidosis. One of the standouts of that meeting were comments from FDA that what they heard patients voice as the most significant and impactful symptoms of their disease were not actually being measured as endpoints or even collective within the clinical

trials.

This shows the disconnect between the patient experience and drug development and highlights the need to incorporate patient involvement and prospectives throughout research. From this meeting, we subsequently submitted a "Voice of the Patient" report to the FDA which has informed the benefit/risk assessment made during multiple product reviews since.

Now, it was phenomenal that we heard the perspectives and the unmet needs from patients through this effort, but clinical and regulatory fields don't necessarily always align when it comes to the endpoints and measures that can or should be used in clinical trials. As an organization, we've worked really hard to figure out how to address those types of challenges and some of them, like the work we're doing around specific biomarkers, we're continuing to refine and progress further.

In 2018, we held a research strategy roundtable convening the leading experts across all stakeholder groups to identify and align around the most important priorities across the amyloidosis

research and development continuum. The consensus went on to be published as a white paper and has served as a roadmap for the research community within amyloidosis. We were fortunate to have Dr. Dunnmon attend and participate in this meeting on behalf of FDA. It was following this meeting and across stakeholder discussions around the complexities of cardiac AL amyloidosis that promoted FDA to invite ARC to establish a public-private partnership which was called the Amyloidosis Forum.

And so what is a public-private partnership? A public-private partnership, or PPP, is a collaboration between multiple stakeholder organizations including at least one nonprofit, or 501C3 organization, to achieve a shared goal that’s beyond the capability of any one stakeholder. What the forum allows us to do is bring together the entire amyloidosis community to partner on key initiatives that are designed to bridge gaps in regulatory science and ultimately help improve and speed up how quickly we can bring new, safe, and efficacious drugs to the hands of patients with amyloidosis.

We engage with researchers, clinicians, patients, industry, FDA and MHRA and we're actively working to include EMA as well. As Dr. Dunnmon mentioned, our inaugural meeting in 2019 focused on AL amyloidosis and the challenges facing designing clinical trials for that population. As part of that meeting, we identified a number of priority topics to explore through the forum and those topics have defined our activities to date. We're excited to expand the focus of the forum to include TTR amyloidosis and other rarer types of amyloidosis later this year. We have an established steering committee comprised of ARC, FDA and a number of the world's leading hematology and cardiology experts in amyloidosis.

The forum convenes regular public meetings and has defined workstreams that focus on priority areas. There is a high level of rigor that goes into these workstreams and the resulting meetings.

Now, we heard from Dr. Dunnmon and Dr. Maurer that amyloidosis is a complex, multisystemic disease and that patients experience very different levels of

organ involvement. On top of that, the drugs that are being developed to treat the disease are designed to do different things in some cases, whether it be stopping the production of the toxic protein, preventing it from misfolding or removing the existing deposits altogether. All of this makes it really challenging to design trials that are meaningful to a broad range of patients and achievable from both a clinical and regulatory standpoint.

To tackle these challenges and address the multisystemic nature of the disease, we established organ specific working groups comprised of not only various stakeholders within the community, but in a number of cases even different specialties within each stakeholder group. Addressing a multisystemic disease like amyloidosis requires working both within and across stakeholders and specialties. We've been extremely fortunate to have had the remarkable engagement with the community which you can see here between 20 different regulators, 55 amyloidosis clinician experts, 16 industry representatives and so on.

Now, before I wrap up, I just want to give an example of some of the work that we're currently doing within the forum. I'll quickly walk through one of these efforts designing a multidomain endpoint for AL amyloidosis. Now, an endpoint, I've mentioned a few times but an endpoint is an event or something that can be measured objectively to determine whether a treatment that's being studied in a trial is beneficial. It's usually something that measures whether patients feel better, function better, or live longer. In many cases, endpoints are directly related to a single organ affected by a disease.

Now, a multidomain endpoint is an endpoint that considers changes a treatment may have on several different affected organs like your heart, kidney or liver. The goal behind this type of endpoint is to better take into account each AL amyloidosis patient's unique experience with the disease and hopefully speed up drug development. A multidomain endpoint could allow for enrollment of a broader patient population, earlier detection of treatment affects and allow for shorter follow up

within clinical trials.

Now, we've set about this goal by bringing the community together to learn from other rare diseases, establish organ-specific working groups that I mentioned earlier with the goal of identifying and prioritizing potential components to a multidomain endpoint, and we're now working through the process of evaluating those components through collaborations and analysis of data collected across the community.

We're also focusing on how we can bring together data from different clinical trials and analyzing those data together to answer specific questions that might help speed up drug development. This is a process called federated data analytics. It's something that James is leading on through the forum and will talk a bit more about next. By analyzing prioritized biomarkers across multiple clinical trials through federated data analytics, we hope to be able to evaluate whether they could be used as endpoints in AL amyloidosis and potentially speed up how quickly these clinical trials can be conducted.

All of this work requires tremendous

participation across the community and we're so grateful to have had the involvement of so many regulators, clinicians, researchers and patients to date. Just to close, I'd like to thank FDA for the opportunity to highlight the forum as one approach of how to enhance product development within a rare disease. Like many rare diseases, amyloidosis is complex and multisystemic, and making meaningful progress in clinical trials and drug development requires cross stakeholder collaborations.

We're very eager to continue the important work of the amyloidosis forum and to see it expand to include additional types of amyloidosis later this year. Thank you.

DR. DUNNMON: Kristen, thank you so much. That was just a wonderful review of the activities of our partnership and a nice segue into this issue of endpoints and statistical tools with which those endpoints might be measured. And for that, I'd like to introduce our next speaker, Dr. James Signorovitch who is Managing Principal of The Analysis Group in Boston and formerly a research fellow at the Harvard MIT

Program in Health and Sciences and Technology. Dr. Signorovitch advises life sciences organizations on research strategies, regulatory strategies and economic appraisals and real world monitoring of outcomes. It is indeed our good fortune that he also happens to chair the Statistical Working Group of the Amyloidosis Research Forum. James.

DR. SIGNOROVITCH: Thank you, Preston. So as Preston said, my expertise is in data analytics and I really got into the rare disease space about 15 years ago through the cystic fibrosis community. I was a researcher doing research, presenting it at conferences, and I still remember just the energy at a cystic fibrosis conference and particularly the fact that patients and family members attended and came to the presentations and had really pointed questions about the meaning of the research and how it would have value for themselves or their family members and that really had an impression on me and ever since then I've tried to work in the rare disease space as much as possible.

So what I'm going to talk about today is how

rare disease research isn't always smooth, there's often challenges that arise and one of the special things about the forum is how the collaboration and the expertise involved and the structure really helps us address those challenges in a timely way and accelerate the important research that we're doing.

So like many initiatives in the rare disease space, one of our main goals within the forum for AL amyloidosis is to learn from clinical data to inform smarter trial design. So how can we make trials faster, how can we make sure they don't fail for the wrong reasons, not because the drug doesn't work but because the trial was poorly designed. How can we reduce the need for unnecessary exposure to placebo and do all this while still ensuring that we've learned as much as we need about benefits and risks.

So, of course, if we can do this, that can make trials more favorable for patients and it also lowers barriers and can increase the throughput for clinical development and by evaluating more therapies rigorously and in a more timely way we can more quickly find the ones that work. So this all sounds

great and the world of health data analytics is making tremendous advances these days and in particular there is very valuable guidance coming out from FDA and others on how to make the most use of real world data and other sources in these types of efforts.

But as those of us engaged in research know, especially in the rare disease space, research doesn't always follow a linear path and sometimes success towards our end goal comes not just from our original plan, but how we can be nimble and innovative and responsive to what we learn and how we address challenges along the way.

So we're going to focus here on two challenges that are quite common in rare disease research if you're involved in the space, you've probably run into these. I certainly have on many occasions across many different rare diseases. So one of our specific goals in the Forum, as Kristen mentioned, was to develop better endpoints for drug development in AL amyloidosis. And a first hurdle that was run into is for the particular goal on the table at the time, which was developing a surrogate

biomarker. There just wasn't enough evidence out there to meet the important standards that FDA has set for surrogate biomarkers. And it wasn't just that the evidence wasn't there, but the data wasn't available. For this goal we really needed data from multiple randomized controlled trials to be able to establish a surrogate.

And so that -- if you go back five years ago, there really wasn't any data, but even as that data has accrued, it's not always immediately accessible. And so advancing along this path, we have this end goal in mind, we want to come up with better end points, we have an initial plan we're going to develop a surrogate biomarker. We run into these very, very common challenges.

So because data weren't available to support a surrogate, within the Forum we prioritized this parallel path that Kristen mentioned of developing a multidomain endpoint which is particularly well-suited as she described and as Dr. Maurer described for a multisystem disease such as amyloidosis. And this is -- this goal of developing a multidomain

endpoint is really something that could not have happened as quickly without the Forum since it cuts across many different medical specialties and also ties into cutting edge and innovative thinking from FDA and other regulators about how to design and validate these types of multidomain endpoints. They are not easy and a lot needs to come together to make sure that they're going to give us crisp answers on whether a drug works or not and not cloud the results of a clinical trial.

So a second challenge going back to our original path of validating a surrogate biomarker is that now after some years more data has come available, so Dr. Maurer highlighted one of the trials for daratumumab that's read out. There's been others that have read out but not resulted in approvals but we're now in a world where there is enough clinical trial data out there to validate a surrogate, but the challenge is that data is not readily accessible.

In particular, the data is spread out across the world in different data silos. Some of these are in academic centers in Europe and China, others of

these data are held by different pharmaceutical manufacturers and for a number of very understandable reasons these data cannot be pooled all in one place anytime soon for analyses. Even when investigators would wish to be able to share these data and pool them, there are significant issues around patient privacy at the national level that can really prevent data sharing.

So as researchers that are looking to accelerate research and answer important questions for drug development, this can be quite frustrating. So within the Forum, we're taking an innovative approach to federated analytics that allows us to learn from all of these data across the world in a harmonized, rigorous, and coordinated way but without requiring that the data leave institutions or cross international borders. Essentially, we can take the analytics that we wish to do and break them up statistically into pieces that each center can run themselves and then we can assemble all the results centrally later without sharing that patient-level data.

So this allows us to learn from the data faster and reach important conclusions for drug development sooner. One of the really important things about the Forum that's enabled this kind of research is with so many different groups across the world, it was critically important that we have the Forum in place and structured to develop a research plan that we're sure was going to be valuable from a regulatory perspective and to generate the kind of momentum and engagement that would be needed to have so many groups across the world put effort into this type of databased collaboration.

So this is recapping what Kristen had shared about the goals of the Forum and I hope what I've shown by zooming in is that these goals are not always easy, these roadblocks and hurdles are very common and it really takes the right type of collaboration and the right structure to address them and as someone who's engaged in data-driven research, I'm truly grateful to the ARC and FDA and all the clinical collaborators for the dedication they've brought to making this type of research possible. Thank you.

DR. DRUNNMON: James, thank you so much. That really encapsulated the fact that what seems simple is not and the devil is really in the details. Our last speaker I'd like to introduce to you is Dr. Rosalyn Adigun. Dr. Adigun is actually now CDER's liaison to the public-private partnership. Dr. Adigun completed her fellowship recently at Mayo Clinic where she was recipient of the Barbara Bush Distinguished Fellowship Award for outstanding clinical performance, scholarly activity and humanitarianism. ARC and FDA's public-private partnership is indeed fortunate that it moves forward with Dr. Adigun as its liaison from CDER. And with that, Rosalyn, I turn this over to you.

DR. ADIGUN: Thank you, Dr. Dunnmon. Good morning. It's my pleasure to be here today to give my perspectives on public-private partnerships and I also want to thank Dr. Stonebridge who is the Director of the Division of Cardiology and Nephrology Products for the opportunity for me to continue in this manner and for his mentorship concerning this -- today's program.

So I would like to start with this image here

which shows the different stakeholders relevant and important in public-private partnerships. We've seen some variations of this in the earlier talks but I think it goes to show that for this public-private partnership to be successful, it takes a lot of work by different stakeholders who have the shared common interest of helping to advance the science and also to bring relevant perspectives to the table to answer critical questions and if I were a patient who was watching this today, when we see what the Amyloidosis Forum has accomplished, very commendable, but it might be overwhelming because it's been years and tireless efforts and commitments to establishing what is today known as the Amyloidosis Forum but I want to encourage you because I think the most important thing is to get involved, especially in the rare disease space because getting involved, even at your local community, over a period of time can have significant impact.

So what are the benefits of a public-private partnership? Through public-private partnerships, and more specifically the one that I am involved with the Amyloidosis Forum, CDER and the various stakeholders, some of

which you have heard from this morning, have been able to leverage expertise in your various areas and resources for mutual beneficial science activities in the precompetitive space. These aims have targeted finding innovative ways to advance drug discovery and development and will also be able to get the stakeholders to the table to discuss innovative ways to promote collaboration across different spheres of involvement with the ultimate goal of making the results of these efforts available to the public and to benefit public health which aligns with the mission of the FDA.

And one thing I want to spend a few minutes discussing are some of the limitations of CDER's involvement with public-private partnerships. Our involvement is limited to providing general perspective from regulatory standards, scientific issues, and scientific gaps related to precompetitive drug developments and to that effect, we are not able to comment on specific regulatory applications on nonpublic information. We provide specific opinions on the quality and quantity. We are not able to

provide specific opinions on the quality and quantity of scientific evidence or regulatory decision making and we do not provide opinions on what conclusion a regulatory review might reach based on scientific evidence. We do not provide recommendations on specific applications intended for FDA review and we don't give advice on specific proprietary drug development programs.

So a lot has been said about public-private partnerships, how the Amyloidosis Forum came to be, especially with the work and the tireless efforts of Dr. Dunnmon and the Amyloidosis Forum in the early days to be able to fashion what is now what we're seeing today and has done a lot over the last few years. But I want to spend a few minutes giving some personal thoughts, drawing on my experiences as a clinician and a medical officer who recently joined the FDA.

We all know, will know, or have known someone with a rare disease and I think this is the passion that drives us to do the work that we do and try to get everyone to the table to collaborate on ways to

bridge gaps in our knowledge and find innovative ways to create endpoints meaningful across the sphere of sciences to the patients through patient advocacy groups and also one that could support the regulatory approval of products. One of the things that is very motivating for me are the words of Marie Curie. "Nothing in life is to be feared, it's only to be understood."

Now is the time for us to understand so we may fear less. I think when we get together across different groups and get to the table to discuss what is meaningful to a patient and ways to get drugs to the market that are safe and effective that benefits the patient and protects the public health, that is the true victory. And through programs like public-private partnerships, which is one out of many ways to engage the FDA, these can be fulfilled.

I want to thank you for the opportunity to be able to share my thoughts today and I look forward to answering any questions specific to public-private partnerships. Thank you.

DR. DUNNMON: Rosalyn, thank you so much. I

know that we're at the end of our time. There are several questions that I will commit to answering offline, but I just wanted you all to hear one question that I just received.

"To what degree was the creation of the Forum due to industry interest and work being done that allowed everyone to get together on the same page and particularly FDA's interest in engaging? I ask because I wonder if in other situations, the lack of clarity around pathology, a clinical path forward and endpoints becomes an impediment to having pharma initiate development work."

Bingo. This is it in a nutshell. And what I can say is, we all have critical roles to play in this, but when those doing the development work see no path forward because there are 13,500 people at White Oak and it's not quite clear whose door to knock on, that in and of itself gets to be a barrier to moving forward because people don't know where to go to ask their questions. And so that's where this commitment that CDER has made to this process is just so incredibly critical from my perspective and my

experience and I certainly look forward to, Rosalyn, it continuing under your auspices at FDA. With that, I'm going to turn this back to Kerry Jo and the organizers and if we have further time later on to address questions, we will certainly do so.

DR. LEE: Thanks so much. I think we are out of time, and so we'd just like to thank everyone so much and I hope this session was informative and really showed the commitment of collaboration. It really does take us all. We are stronger together to move the needle forward in rare disease drug development, so thank you.

DR. FERMAGLICH: Thanks, Dr. Lee. Our last Center panel of the morning from the Center for Devices and Radiological Health, or CDRH will focus on their approach to patient input, how reviewers consider benefit/risk for rare conditions and how CDRH works to make devices available to patients with rare conditions. It'll be moderated by Dr. Michelle Tarver, Deputy Director, Office of Strategic Partnerships and Technology Innovation in CDRH. Dr. Tarver.

DR. TARVER: Good morning, good afternoon, good evening. I am Michelle Tarver, I'm the Deputy Director of the Office of Strategic Partnerships and Technology Innovation at the US FDA Center for Devices and Radiological Health. Our office provides leadership in advancing partnerships with patient organizations, healthcare professional organizations, industry, scientific and any other external organization to help support broad national, and international patient-focused and regulatory science programs and activities. I also am clinically an ophthalmologist and I specialize in the care of people living with uveitis, a rare eye condition.

I continue to clinically care for patients and in this work, I consistently am reminded of the impact that the work my colleagues at FDA do and how they can really transform people's lives. Well, I have the great pleasure of welcoming you to panel four. During this panel, we will share with you how we incorporate the perspectives of patients and all the work we do and then focus on the journey of reviewers in the evaluation of devices designed to

treat people living with rare diseases affecting their bones.

I'd like to introduce you to our reviewers from the Office of Health Technology 6, Dr. David Scott who is an orthopedic surgeon and Commander Michel Janda, a Biomedical Engineer. They're going to share with you their experience evaluating a device for bone tumors. Following their presentation, Dr. Eileen Cadel, another Biomedical Engineer and Dr. Caroline Moazzam, an orthopedic surgeon will share their experiences reviewing the device for a condition that many of us may have heard about or been screened for as children, adolescent idiopathic scoliosis, a condition where there is a curve in the spine.

Following their presentations, we're going to have a panel discussion and we really welcome your questions at that time, so as you think of your questions, please go ahead and put them in the chat because we're happy to address them.

So I'd like to first share with you the work we are doing in patient science and engagement at our Center. Patients are at the heart of all we do, as

you probably have heard us say that many times in the past. In fact, we are inspired by patients and driven by science. And this inspiration plays in the work that we do in reviewing medical devices. Now, you've heard a lot about different medical products. Medical devices encompass a wide array of different products from implantable pacemakers as well as diagnostic devices that screen for elevated blood sugars or evaluate the blood sugars in patients living with diabetes.

We also have devices that people use at home like contact lenses and lastly I want to mention that we have devices that are involved in the diagnosis of conditions such as blood tests that are used in COVID-19 as well as genetic tests and markers and imaging devices.

Regardless of what medical device we're talking about, we look at the impact of the perspective that patients can lend across that total product lifecycle of the medical device, whether it's how the device is being conceptualized, what areas they're going to develop the device in, how that device is

designed in a way that's user friendly as well as how is it studied, evaluated, and then monitored once it's in use in the general population, patients can bring perspectives that really can be helpful as we're looking at all those different steps.

We see the impact that the patients' perspectives on the work that we do. In fact, we have had a number of different studies that have been done looking at how patients weigh the benefits and risks associated with their therapies and treatment alternatives and those are called patient preference studies. We've seen 25 of those so far to date and they've had direct impacts on our decision making. In fact, they've expanded our labeled indication for certain devices so that more patients can have access to certain devices. They've also helped to inform how we might design a clinical trial when we don't really know what an effective endpoint might look like for patients. We take that input into consideration when we define and design those trials.

We also see 50 percent of the clinical studies that are done at our center include patient

reported outcomes, measures of how patients feel and function. So I want to start first with a little bit of definition because you've heard my colleagues all morning talk about engaging patients and patient reported outcomes and all these different things. Patient engagement for us is defined as these intentional interactions we have with patients that allow us opportunities to have mutual learnings, shared decision making and effective collaborations really across a total product lifecycle as I eluded to before.

This is bedrock, it's foundational for how we develop the science of patient input and the scientific contribution of patient input is ones that are collected in a structured, well-defined way and that could be a measure of how patients feel and function which you've heard all about this morning as well as the perspectives that patients bring in terms of how they make a decision about how much they value the benefits and the risks associated with a particular medical product and that's patient preference information.

So we've talked about a number of different ways in which patients can scientifically impact our regulatory decision making. I just didn't talk about one of them which is patient generated health data and that's kind of the new kid on the block. This is the data that we're collecting every day. A lot of us have watches or smart phones or other technologies that are collecting data on how we're functioning all day long and that data is increasingly being analyzed and looked at as an opportunity to better understand the patient's experience as they interface with medical products.

I want to spend a little time sharing with you some of the mechanisms that we have at our Center for engaging with patients. One of them is the Patient and Caregiver Connection. This particular mechanism allows us to hear from patients at the time, particularly the reviewers, at the time when they may be trying to make some regulatory decisions or kick off a regulatory effort. This allows us to hear from patients about what it's like for them to live with their condition as well as their experience

interfacing with medical devices that are used in the diagnosis, management and treatment of their condition. It also is a forum where patients can share with us concerns they may have that are facing their particular patient community.

We currently have 19 organizations in which we -- that are part of this connection, many of which are rare disease organizations and we reach out to these organizations in many different ways to get insights on what their experience may be. I'd like to also share with you one other opportunity that we have to formally get recommendations from patients and that is the Patient Engagement Advisory Committee.

It's the only committee like it at the Agency in that it is comprised solely of diverse patients, caregivers, and patient advocates. The committee is solely patients and that committee provides us formal recommendations on general matters related to medical devices. In fact, they weigh in on a number of different topics and some of those topics include the engagement of patients in the design, conduct of clinical trials.

We've talked about patient-generated health data and the ways in which you can give us insights into how patients are interfacing with their medical products once it's on the US marketplace. We've talked about cybersecurity and many of us are hearing about that every day and the threats that cybersecurity potentially pose to medical devices, so how can we communicate about cybersecurity vulnerabilities more effectively to patients.

We had another advisory committee meeting that touched on artificial intelligence and machine learning. We increasingly are seeing this technology in all aspects of our lives, including medical devices, so what do we need to study, look at in order for patients to feel comfortable with this technology in their care as well as providers?

Our most recent meeting focused on medical device recalls. Recalls are when there is a challenge with a particular medical device and it may need to be either remediated or come off the US market. In those situations, how do we communicate more effectively about those recalls and what information do patients

want to know about recalls and how can we make it more transparent? These are topics that we discussed at our last advisory committee meeting.

These conversations are not just discussions but they result in deliverables, actionable outputs from the Agency. In fact, from our first meeting that I talked about where patients are involved in design and conduct of clinical trials, we put forward a guidance document that spoke to ways in which patients can be engaged in the design process of a trial or a clinical study as well as the benefits that industry may gain from including patients in those processes and then what FDA's considerations are with respect to those particular types of activities.

We understand it's important to include patients but it's also important to include patients with diverse perspectives across age, race, ethnicity as well as in rare disease populations. And so we worked with our office at Minority Health and Health Equity put forward a video encouraging underrepresented populations to participate in clinical trials related to medical devices.

The inclusion of patient perspective is also important as I noted across medical product lifecycle in our decision making and so we have communicated back to industry through our guidance documents. In fact, we have said that there's opportunities in every kind of submission that you interface with at the device Center to include the patient's perspective and we will take that into account in our benefit/risk decision making.

I had mentioned to you early at the outset of my remarks about patient preference information and this is kind of a new area where we are looking at structured ways of collecting how patients are weighing the risks and the benefits associated with a medical device. We have issued guidance in 2016 and it lays out a couple of overarching principles. The first is that it's all about patients and so we need to measure things in a very patient-centered way and then the last two points are good research principles in general. It should be designed well, conducted and analyzed in a manner that is robust and can support valid scientific evidence.

You've heard the mention of patient reported outcome measures and you know that there's a guidance document that is enforced by the entire Agency. In fact, all product Centers put it out to clarify what the expectations are around the development of patient reported outcome measures.

CDRH also had a requirement to put forward a guidance that clarified some of the least burdensome principles in which we may develop patient reported outcome measures, how industry may develop these measures and this is -- Center for Devices is slightly different from other medical products because we do have in law a provision of using the least burdensome pathway available. In our guidance, though, we ran out some best practices, some efficiencies, ways to include the patient's voice and do it using as many pathways as possible because we want to minimize the barriers to including patients in the medical device evaluation process.

So as we journey from conceptualization of a medical device to it being used in the care of patients, I wanted to summarize a couple of points.

The first is that we at the Agency have really had a paradigm shift where we are increasingly bringing the patient's voice into the work that we do as part of our daily business. It's not an exceptional event, it is an everyday event.

The other thing that we are doing is that we are looking at ways that we can proactively bring that voice to bear in multiple aspects, so not just at the time of the trial but are there other opportunities where we can understand patients' perspectives and bring them into play.

And then lastly, I want to emphasize the importance of collaboration. You've heard that already mentioned on the meeting today, but it really is an important element because we can't do it alone. We really do need all of the stakeholders in the ecosystem and this collaborative approach really creates solutions that works across the ecosystem.

And this was really the impetus behind our most recent strategical priority of collaborative communities. That particular initiative is a continuing forum for public and private sector members

to work together to solve shared challenges, leverage collective opportunities in order to achieve common outcomes and objectives.

We currently are participating in 12 collaborative communities and you can see some of them listed on the slide. One of the very beautiful things about these collaborative communities is that they include patients at the table as equal stakeholders with other contributors and there are a number of different collaborative communities that are tackling some of the topics that are relevant to the rare disease patient population.

So with that, I will conclude my remarks and I will turn it over to Dr. Scott to present on osteoid osteoma. Dr. Scott.

DR. SCOTT: Thank you, Dr. Tarver. Greetings. Welcome to the FDA and to the Center for Devices and Radiological Health, CDRH. My colleague Commander Michel Janda and I have the privilege of presenting to you a device approved as part of a very important and special program tailored to improve the welfare of patients with rare disease or conditions.

Unfortunately, only a small portion of the 7,000 known rare diseases have approved treatments. Developing and marketing a novel device or technology for a small group of patients may be slowed by cost considerations and the scarcity of suitable patients for clinical trials.

CDRH responded to this humanitarian aid by developing an innovative pathway, the Humanitarian Device Exemption or HDE program to encourage the development of medical devices for rare diseases or conditions that affect or manifested in not more than 8,000 individuals in the United States per year. After being designated as a humanitarian use device based on census data or population estimates, devices eligible for inclusion in HDE program, the pathway allows for the approval of novel devices by using a lower threshold for demonstration effectiveness, namely probable benefit. However, the threshold for device safety remains unchanged.

Images of three devices approved through the HDE program are shown on this slide, all of which have the potential for dramatically improving the welfare

of patients with indicated rare disease or condition. Commander Janda and I will review the regulatory journey in the Sonalleve Magnetic Resonance Guided High Intensity Focused Ultrasound, or MR-HIFU System while our colleagues Dr. Cadel and Dr. Moazzam will discuss recently approved vertebral body tethering systems.

Our journey begins with a brief overview of osteoid osteoma, a benign bone tumor that qualifies as a rare disease. I will discuss biology, natural history, and standard of care treatments with particular focus on the disproportionate impact that even a nonmalignant disease can have on patient welfare. After defining the limitations established, therapies, the helm will be turned over to Commander Janda who will introduce the technology underlying this HDE and guide you through the review process.

Osteoid osteoma is a relatively rare, biologically benign bone tumor that typically occurs in the cortex or outer layers of long bones such as the tibia or femur, primarily in children and young adults. The tumor core nidus is highly vascularized

boosting prostaglandins and other inflammatory mediators. Osteoid osteoma is often referred to as the "great mimicker" because the pain which characteristically worsens at night disrupting sleep is often dismissed as resulting from local trauma or as nonspecific growing pains.

Traditional radiographs maybe nondiagnostic, but particularly in advanced cases, classically demonstrate cortical thickening surrounding the area of central clearing. Although an osteoid osteoma remains small, typically one to two centimeters in diameter and does not metastasize or spread, its impact on patients is often disproportionate to its size. Delays in diagnosis and treatment can result in significant mental and emotional suffering, physical disability and missed social and sporting opportunities for young children and adolescents. Osteoid osteomas are less commonly associated with bony deformities, growth disturbances, joint damage shown as in case one on the left or painful scoliosis potentially requiring spinal fusion as shown in case two on the right.

Nonsteroidal anti-inflammatory medications,

such as ibuprofen, may be exquisitely potent in reducing tumor-related pain. However, some patients may require stronger analgesics such as opioids or narcotics to comfortably function. Both types of medications pose long-term risks and toxicities. Surgical removal of the tumor, specifically the nidus, remains a well-documented and effective treatment. Interoperative localization of the lesions may however be difficult leading to significant bone resection and damage to surrounding tissue.

Young patients such as these with large defects in weightbearing bones will not return to normal play in sports for some time.

Radiofrequency ablation, commonly referred to as RFA, is less invasive than surgical resection. Under CT guidance, a needle and a hollow bored tube is advanced into the tumor core. The needle is then exchanged for radiofrequency probe which ablates or destroys the tumor by briefly heating it to a 90 degree Centigrade, or if you prefer, 194 degrees Fahrenheit. Cryotherapy is a similar treatment that substitutes cycles of extreme cold for

heat. Although RFA is generally successful and may quickly eliminate tumor-related pain, complications such as skin burns, nerve damage, infection and fracture are possible.

Established osteoma treatments are effective but associated with significant risks. Although the adverse events and complications associated with invasive procedures such as surgery and RFA are generally well understood, the long-term effects ionizing radiation, particularly for children, are less well defined. A relatively new ablation technology, high intensity focus ultrasound, or HIFU, is noninvasive and is guided by MRI. Imaging that offers high precision but unlike a CT scanner does not produce ionizing radiation. Commander Janda.

COMMANDER JANDA: Thank you, Dr. Scott. The Sonalleve MR-HIFU system proposed an alternative noninvasive treatment for osteoid osteoma that did not require the use of ionizing radiation. The Sonalleve system includes the patient table assembly that is put in an existing MRI scanner, a generator cabinet that is used for power resolution and controls electronics of

the ultrasound transducer and finally a therapy planning consult with software used for treatment planning, monitoring, and review.

The first step in the review process was to assemble a multidisciplinary review team. CDRH is uniquely positioned to draw on expertise from multiple specialties to evaluate new technologies. This HDE brought together a diverse and exceptionally strong team of engineers, scientists, and clinicians.

MR-guided HIFU treatment combines both therapeutic focused ultrasound with real time monitoring of local temperature changes. This means that the ultrasound transducer located external to the patient's body generates a focused acoustic beam that can heat and destroy an internal target. This is combined with an MRI console that displays temperature maps, also known as thermograms, to improve the procedure's safety and effectiveness. During step two of the review process, our team thoroughly evaluated the electronics, hardware, software, and preclinical testing.

Step three of the review process focused on clinical data. Studies of a similar device, the ExAblate MR HIFU system, previously approved by the FDA for the treatment of uterine fibroids and for the palliation of metastases-related bone pain provided useful real world data and evidence. However, the clinical review focused mainly upon a recently completed clinical study. This study was an FDA-approved investigational device exemption, or IDE, that evaluated the effectiveness of the Sonalleve MR HIFU system for treating osteoid osteoma in patients under 25 years of age with an accessible tumor.

This single arm study that enrolled nine patients and followed their post-treatment progress for at least a year. The patients for this study were typically diagnosed based on symptoms, usually localized pain combined with imaging. The left three panels of this slide demonstrate characteristic bone scans, plain x-ray, CT scan on the top middle and an MRI scan on the bottom. The locations of the osteoma core, or nidus, is circled in each of these images. The top right half of the slide shows pre- and post- MRI

maps that are colored according to blood flow from least in blue to most in red. Comparison of the two maps show an obvious post-procedure decrease in tumor hypervascularity and bone marrow edema.

Although the changes in the imaging were impressive, study success was determined by patient reported outcomes such as pain relief and function. Measures such as pain visual and analog scale, the symptom distress scale, the PROMIS pediatric pain interference and the PSQL scale give patients and their parents an opportunity to shape and guide their treatments. In this case, MR-HIFU therapy resulted in dramatic pain reduction, improved functioning, and a reduction in sleep disruption and a reduction in medication use.

These clinical benefits were not associated with any serious complications or adverse events. The most common complaint from patients was localized leg, foot, or muscle discomfort. This was anticipated given the nature of the procedure. The discomfort was rated by patients as mild to moderate and rapidly resolved.

This HDE was ultimately approved after meticulous review of the demonstrated benefits and risks. Two rounds of review were needed with each round completed in about two months. Frequent interactions between the review team and the device manufacturer expedited the approval process. The review team did accept some uncertainty given the limited clinical data. However, the HDE pathway allows the FDA to accept greater uncertainty which ultimately allows patients earlier access to an innovative treatment option.

CDRH continues to monitor real world experience with this technology including published studies, literature reviews, and ongoing clinical trials. Post-approval feedback for this technology remains strongly positive. We thank you for your time and for this opportunity to showcase some of the merits of the CDRH's HDE program. Our next CDRH presenter is Dr. Caroline Moazzam.

DR. MOAZZAM: Hello and welcome to the FDA. I am Dr. Caroline Moazzam. Today my colleague Dr. Eileen Cadel and I will talk to you about our

experience with orthopedic HDEs for pediatric scoliosis devices.

As our colleagues just described, FDA has a two-step process for approving devices intended to treat or diagnose rare or orphan diseases. That sounds very formal but means that a group of experts at FDA decides if a device is meant to identify or treat a disease that affects less than 8,000 people a year. Then a different group of experts at FDA decides if the device is safe and probably beneficial for the less than 8,000 affected people.

Scoliosis can be broadly defined as an abnormal curvature of the spine. Many folks with scoliosis are diagnosed between the ages of ten and 15, but the condition also affects infants and adults. Subsets of scoliosis can be defined in many ways such as by patient age or curve severity. Scoliosis in children has a variety of causes. All of these different subsets of scoliosis have treatments that are tailored to individual patients in collaboration with their doctor, their families, and then entirety of their care team.

Today we'll be focusing on children whose scoliosis doesn't have a known cause. The medical name for this condition is idiopathic scoliosis and the most common type is adolescent idiopathic scoliosis or AIS.

So is scoliosis a rare or orphan disease? An estimated 7 million people in the United States have scoliosis. That number includes all the types we just talked about and more. When we consider the adolescent idiopathic scoliosis patients and we think about the ones whose curves are getting worse and who are not done growing, we start to define a patient population that is estimated at about 6,000 patients a year in the US.

Now we have a so-called rare or orphan subset of scoliosis which allows FDA to utilize the regulatory flexibility of HUDs and HDEs. Having regulatory flexibility promotes innovation and development of devices for rare subset populations.

There are general treatment guidelines which include observation, bracing and surgery. Observation may be appropriate for patients with curves that will

never progress past 25 or 30 degrees. Observations may continue for years with x-rays to reassess the spinal curve and determine whether it is causing problems for the patient.

Bracing may be recommended to stop a spinal curve from getting worse. The 2013 study in the New England Journal of Medicine found that braces work, but work best when worn 18 hours daily. Now, that sounds simple enough but anyone with personal experience with braces will be happy to give you an earful about how awkward, uncomfortable and cumbersome they are for preteens, teens and their families.

We at the FDA hear AIS patients and their families. We are listening when they tell us that it is very difficult to keep up with these braces for anything close to 18 hours a day. We also know that bracing can help prevent curve progression but braces do not correct, improve, or reduce a spinal curve.

The gold standard surgical option for scoliosis is spinal fusion. Surgery results in immediate correction of the spinal curve. However, it results in permanently fusing the instrumented levels

of the spine. This means no motion, no flexibility, and no growth in the area fused.

Here at the FDA, we understand that patients don't always fit nicely into the three treatment categories. There is a newer treatment for AIS, broadly called growth friendly or non-fusion surgery. Non-fusion surgeries internally direct growth to help modulate or correct curves. Because they direct growth, they are only options for patients who are not done growing. To date, two devices have been approved by the FDA under the regulatory flexibility of HDEs as growth friendly or non-fusion devices to treat idiopathic scoliosis in skeletally immature patients. I will now hand off to my colleague, Dr. Cadel, who will share more. Dr. Cadel.

DR. CADEL: Thank you so much, Dr. Moazzam. The tether from Zimmer Biomet Spine was approved as an HDE, or humanitarian device exemption, in August of 2019. The tether is for skeletally immature patients with progressive idiopathic scoliosis. The device functions by placing screws in the spine on the convex side of the spinal curve. A tensioning cord, similar

to a shoelace, is secured to each screw to connect each spinal level to one another creating a link system. The tether provides tension on the convex side of the curve that increases as a patient grows. As the tension in the cord increases, it stops the spinal curvature from progressing or with enough tension and growth can correct the spinal curvature altogether.

The minimally invasive deformity correction or MID-C system from ApiFix was approved as an HDE also in August of 2019. The MID-C system is for skeletally immature patients also with adolescent idiopathic scoliosis. The device acts as an internal brace to achieve spinal curve correction and stabilization. It is a ratchet-based expandable rod that attaches to the spine using two screws on the concave side of the spinal curve.

As the device expands, the rod that attaches to the spine using two screws on the concave side of the spinal curve. As the device expands during activities such as physical therapy, the spinal curve is corrected incrementally until the device is fully

extended.

Following HDE approval, the tether and MID-C system are currently available in the US as humanitarian use devices, or HUDs. For both devices, post-approval registries were established to see if outcomes were the same once more patients had the device implanted for a longer period of time. The Office of Orthopedic Devices is always working to advance development of novel devices for patients with rare diseases. This work requires partnerships with patients and their families, patient advocacy groups, and stakeholders from all sectors of the medical industry.

We also participate in various activities to make sure the work to develop devices for patients with rare diseases is constantly progressing. In addition, we encourage patients, caregivers, consumers and healthcare professionals to submit voluntary reports of significant adverse events or product problems with Med Watch, the FDA's Safety Information and Adverse Event Reporting program. This allows FDA to ensure that the experiences of patients,

caregivers, and patient advocates play an essential role in the development of medical devices.

The two HDE-approved devices, the tether and MID-C system are examples of orthopedic devices that have taken advantage of the regulatory flexibility that is available for devices for rare patient populations. By listening to patient preferences and capturing these in patient reported outcomes, HUDs and approved HDEs allow patients with rare diseases to have access to alternative treatments tailored to their specific condition.

But the work doesn't stop at HDE approval. CDRH is continually looking for direct patient engagement opportunities, whether it be through engagement with patients and caregivers, patient advocacy groups and patient engagement events.

In summary, both Dr. Moazzam and I want to make sure that you are aware of how seriously we take our mission here at the FDA, which is to protect and promote public health. Today's event is just to show you a few of the very, very many ways that we work to make certain that we are protecting and promoting the

health of patients with rare or orphan conditions while promoting innovation and bringing it into clinical application. We are only two of thousands of people here at the FDA that are working each and every day for you. Thank you for allowing us to share our experiences with reviewing devices for adolescent idiopathic scoliosis and we truly are honored to be with you here today. And with that, I will turn it back over to Dr. Tarver.

DR. TARVER: I wanted to thank all of our panelists and presenters because they've put flesh on the bones of what I described in terms of our patient involvement efforts, our patient engagement and patient science efforts. I'd like to first -- I think we received one question that I'd like to direct you to CrowdCompass to see the response to. Somebody asked, "How do we get involved in the Patient Engagement Advisory Committee?" And the way that you can apply, if you're interested in participating, is by visiting that link and getting additional details. But always stay posted for notices of when those meetings are occurring. You can always listen in. They are open

to the public.

I'd like to ask a specific question to Dr. Scott. We talked about osteoid osteoma and scoliosis and what are the questions that you think that parents or patients should really ask their healthcare providers when they're considering medical devices in the treatment of their health conditions?

DR. SCOTT: That's a wonderful question, Dr. Tarver. Thank you for asking that. Ensuring patient access to medical information is often an overlooked issue. We could spend the rest of the afternoon really talking about that. Unfortunately, time is brief, so I'll try to condense it down to my four rules, or golden rules, if you will.

First of all, patients should be sure that the healthcare providers that at they are talking to are the correct ones. Again, these are highly specialized fields for both the osteoid osteomas as well as for idiopathic scoliosis and so you want to make sure that your healthcare providers are not only know about these things but actually are the people that treat patients, are actually providers.

Referrals to academic medical centers or specialized hospitals are great and in the era of telehealth, it's a worthwhile investment that can be done very easily.

Rule number two, if you have a question, ask it. This is not a period where you should be bashful. I always encourage patients to bring a written list of questions with you. Have them written out, make sure your questions get answered while you're there with the healthcare provider. Also, take notes. It's very difficult in a short period of time sometimes to ingest all of the information that your healthcare provider is going to give to you. Take notes so that you can go home and look at them.

Rule number three is, make sure you get the answers to your questions so that you can make an informed decision. Options are particularly important. Know what your alternatives are for the in case of rare diseases, clinical trials often are an excellent source of medical care. Know what the effectiveness and safety of each option is. It's the same thing that we do here at the FDA. So you need to

know that for each of the options.

Know about recovery. Two very similar treatments in terms of effectiveness and safety may have very different recovery periods. Certainly that's a very important consideration. Know about complications. One thing that we don't talk to patients about or we're not very good about is costs. What are the financial costs of the different options? That's something that your healthcare provider may not necessarily know but they should be able to refer you to the appropriate person.

One of the best things to do when you've gone through all the questions and you're sure that at the end of your meeting with healthcare provider, ask the healthcare provider "What questions haven't I asked that I should have?" and that way it gives the healthcare provider the chance to fill in some things.

And then finally, benefit/risk ratio. You really need to tailor that with regards to your particular child, your values with what's important to you. Make sure that's included. As part of that, I always think it's great for patients to meet with

patients who have previously had a treatment, either directly or indirectly, patients provide a very valuable perspective that you may not get from your healthcare provider. The healthcare provider also can help you with referring you to other sources of good information. Be very careful about Dr. Google and Dr. Yahoo!

Finally, rule number four, if in doubt, if you're not absolutely sure, ask for a follow up appointment. Those are great, it gives you a chance and time to digest things and come back with new questions. Also, I'm a big fan of referrals, getting a second opinion. That's also going to be very helpful. The good news for osteoid osteoma and scoliosis, they're not emergent conditions. You have time to make a very good, informed decision.

DR. TARVER: Thank you very much, Dr. Scott. Very helpful. I want to end with one question about the regulation. The Orphan Drug Act currently defines rare diseases as those with an incidence of less than 8,000 cases per year or prevalence of less than 200,000. Can the HDE program be applied to diseases

or conditions with more than 8,000 people being diagnosed each year? And I'd like to Dr. Cadel to answer that question, please.

DR. CADEL: Thanks so much, Dr. Tarver. So that's a really great question and the HDE program can really only be applied to devices that have been designated as humanitarian use devices, or HUDs, and this is actually defined by an act of Congress and the HDE program can only be used for devices that are intended to treat or diagnose conditions that affect no more than 8,000 patients per year in the US, so our hands are a little bit tied from that perspective. But I will say that the HDE program is just one program within CDRH that's aimed to reduce some of these regulatory hurdles to get devices on the US market to help patients with rare diseases.

There are some other programs and these include the Orphan Drug Program and rare pediatric disease and designation voucher programs that are really beneficial for these rare orphan patient populations. But I did also want to emphasize that, as Dr. Moazzam talked about in our presentation, a

medical device company can get an HUD designation for a subset of conditions that really divides that broader 200,000 patient population into smaller subsets. And so this way, medical device companies can take advantage of the HDE program and get their devices to the patients who really need it in the best way possible.

DR. TARVER: Thank you very much. I believe we are out of time, but I really want to thank my fellow panelists, the Office of Orphan Products Development, and the audience for their rich questions and I really want to say we thank you, the patients. You all provide insights and learning that really do transform the work we do. So thank you and I will turn it back over to the organizers.

DR. FERMAGLICH: Thank you, Dr. Tarver. We'll now take a 40-minute break for lunch. Over lunch, please enjoy some recorded stories of rare disease patients and caregivers in their own voices. Please rejoin us for afternoon remarks from the Principal Deputy Commissioner of FDA, Dr. Janet Woodcock.

(BREAK)

DR. FERMAGLICH: Welcome back. I now have the great honor of introducing our next speaker, Dr. Janet Woodcock, the newly appointed Principal Deputy Commissioner of FDA. Dr. Woodcock began her long and distinguished FDA career in 1986 with CBER as Director of the Division of Biological Investigational New Drugs. She also served as CBER's acting Deputy Director and later as Director of the Office of Therapeutics Research and Review.

In 1994, Dr. Woodcock was named Director of CDER, overseeing the center's work that's the world's gold standard for drug approval and safety. In that position, she's led many of the FDA's groundbreaking drug initiatives. She's also served in other leadership roles at FDA including as Deputy Commissioner, Chief Medical Officer, and most recently, acting Commissioner of Food and Drugs. Without further ado, Dr. Woodcock.

DR. WOODCOCK: I'm delighted to join with you today to mark the FDA's Rare Disease Day, part of the global recognition of Rare Disease Week. This event

brings together patients, families, caregivers and advocates along with many other stakeholders including drug and product developers, clinicians, researchers, representative of industry and healthcare organizations. So, clearly takes a village. Each of these groups in different ways contribute to speeding the development of medical products to diagnose and treat rare diseases and to increase the quality of life for those living with these diseases.

At the center of this work are the voices and experience of patients, but as this broad-based gathering reaffirms, we achieve our greatest success in these goals by sharing information through collaboration and teamwork, listening to and learning from each other and supporting each other's work, resources and areas of expertise. The FDA plays an important role in these kind of partnerships, not just in the work that we do to support your efforts, but within the agency itself through collaboration between our Centers and across the entire FDA, whether through efforts to encourage scientific and medical innovation, by providing grants to support research

and development of new treatments or through careful review of product applications to make sure they're safe and effective.

We take this work and our responsibilities very seriously. That's why I'm especially pleased by the focus and format of this year's event. The theme, "Sharing Experiences in Rare Diseases Together" gives us a chance to recognize the important work and essential collaboration of the many different stakeholders in this area. It also provides an opportunity for you to learn more about some of the important work FDA staff are engaged in as well as about the deep commitment that these public health professionals bring to their work in rare diseases.

It's a field that involves a broad range of activities and challenges across many scientific disciplines and it's one that comes with substantial hurdles, as you all well know, for the development of treatments in this area as well as significant costs. The very nature of a rare disease that affects only a relatively small group of individuals means that the field faces unique logistic, scientific, and economic

obstacles. That's where the FDA can and does play an important role. Those who work at the FDA look at these challenges actually as opportunities. Indeed, the goal of finding new and better ways of approaching the challenge of rare diseases and to help us facilitate the development of new treatments and cures is central to our mission to promote and protect the health of all Americans.

So today you'll have the opportunity to hear directly from FDA's scientists, regulators and others about their experience working on products submitted for rare diseases. They will explain the importance of their work to help ensure that everyone in the country with an illness has access to the safe and effective medicines and treatments they need and they will discuss why this work has such personal meaning for them.

As I mentioned, at the center of this work is the patient's voice and perspective. It informs and inspires everything they do, every stage of the process, keeping that voice front and center helps reinforce and remind us who we're working on behalf of

every day.

Additionally, by examining and asking whether a drug or device improves how a person feels, functions, or survives, we can strengthen and support the many different aspects of the development and review process. It provides insight for the risk/benefit assessments that FDA staff conduct for products under review. It helps us identify areas of unmet need and it supports the work of developers of medical products to identify, create, or improve appropriate clinical outcome assessment tools which in fact have been rather sorely lacking in this space.

In short, from providing feedback on health and quality of life factors to critiques of clinical trial design from the participant perspective, patient voices provide essential data that FDA uses to achieve its public health mission.

You know, I've had the opportunity to see this impact firsthand in my own career. When I was working as a consulting internist, I actually decided to go into rheumatology to a great extent because of my experience in rare diseases and diagnosing them. I

diagnosed people who were referred who had been sort of wandering around in the wilderness for a long time seeking a diagnosis for their rare disease. They had diseases that had a lot of people's names in them like Churg-Strauss Disease or Adult Still's Disease and so forth. I saw people with all sorts of rare diseases who had really been striving sometimes for years to find out what was wrong and to seek effective treatment.

After that, as a rheumatologist, I of course saw many patients with rare diseases and it was very striking how little was known about the disease and how few treatments were available. I actually once had an experience I tried to get Thalidomide for a patient who had a very serious rare disease that was not responding to available therapy, it was a young patient. I was not successful in that because I couldn't find, of course, a manufacturer who would allow me to have an IND for a young woman with Thalidomide. But the patient did not do well and I always remembered the fact that there might have been a therapy that could have helped her and it was out of

reach.

Since that time, of course, after I came to the FDA, I have had many, many experiences with rare diseases and have really worked with the community and the folks inside FDA to try and improve the patient's voice, bring that in, understand the natural history of the disease and get better outcome measures so that we really could efficiently test interventions and see if they would be helpful for people. So I've had a long history of working with the community and there have been some really spectacular successes. But of course there is such a tremendous way to go yet.

So just as remarkable as the specific achievements that I've seen and the privilege to be a part of, it's been the transformation in the way rare diseases are approached in part due to the extraordinary advances in the power of science and technology. These developments have allowed us to make enormous strides in some areas, particularly genetically-based diseases, and provided enormous promises in areas previously thought to be unapproachable or inaccessible such as

neurodegenerative diseases.

A key aspect of this development in FDA has been a focus on strengthening the acquisition, review, evaluation, and application of data. At FDA, good science and rigorous data will always be priorities but they're particularly important in the rare disease space where nearly every aspect of the work we do relies on the need for strong data. That's why we're working to expand the sources and types of data we use, including real world data, sensor data and supply chain-related data so we can better address complex and challenging questions including understanding, diagnosing, and treating rare diseases.

Moving forward, we'll continue to modernize how we collect data and stay ahead of the science so that we have increasing capability to take on the challenges posed by rare diseases. Today's final panel discussion focuses on this figure journey and will offer an exploration of some of the ways we can build on our current efforts to promote the development of products for rare diseases and make a real difference in the treatment of patients, which of

course, that's our mission. Thank you very much.

DR. FERMAGLICH: Thank you so much, Dr. Woodcock. Our next panel, moderated by Wendy Slavit, Health Programs Coordinator of the Office of Patient Affairs, will focus on rare disease patients' and caregivers' experiences interacting with FDA. Wendy.

MS. SLAVIT: Thank you. As Lewis mentioned, this panel will be about how FDA involves patients and advocates in the work that we do. You heard a little bit earlier about some of the ways that patients get involved and you're going to hear a little bit more today and then also hear from a few patients themselves that have involved themselves with the work that we do and they're going to be talking a little bit about their experiences. So I just want to give you a brief overview and then I will turn the rest of the panel over to the panelists, to the patients, so that they can share with you their experiences.

This has been mentioned several times, but patients and patient voices are very important to the FDA. They give us insights into the needs and priorities that are important to patients and

caregivers. We know that not every disease or condition experience is the same for everyone, so we really want to hear diverse opinions and experiences. We also hear from patients about risk tolerance and potential benefits and patients are the ones living with the diseases and have the real world experience.

So I know this slide has a lot of information here, but I just wanted to highlight that patient involvement and patient engagement at the FDA really started in the 1980s with the ACT UP movement and the Office of AIDS Coordination. So it's grown exponentially throughout the years and we continued to carry on the importance of patient engagement.

So who are the Patient Affairs staff? This is the group that I work with. It's a small team within the Office of the Commissioner. It's a fairly new office. We were established in 2017 by the Commissioner at the time because he wanted to find a way to have all of the patients feel like they can connect to all of the different parts of FDA. So it was pretty -- it was a little bit all over. So we wanted to make sure that it was a way for all of the

patients to be able to incorporate everything into what we're doing.

We're a small group, so we want to make sure that we're welcoming. We want to encourage patients to really get involved. We involve patients in cross-cutting programs and activities, public-private corporations and partnerships and we also enhance external communication platforms.

So this is the Patient Affairs Team. Some of you may have interacted with my colleague, Susan Chitteran. She leads our FDA listening session initiative and I also included our contact information so you can get in touch with us. And we're happy to help you with whatever we can and if we don't have the answer, we will find someone at the agency that does. So I really encourage people to reach out to us with any questions or concerns or want to know more about what's going on at the Agency.

So Patient Affairs has a few initiatives that we coordinate. One of them is the Patient Listening Sessions. We have had a memorandum of understanding with NORD for several years. We work closely with

NORD as well as the Reagan-Udall Foundation to put together the Patient Listening Sessions. They inform regulatory decision making, they educate review staff, they help patients and their advocates understand the work, they're a starting point to form early stage research and development.

So this is one of the many ways the patients can share their experiences with us. You've got a chance to talk directly with FDA scientific staff and it's a way for patients to, and patient organizations to, quickly engage with the FDA. We had 18 Patient Listening Sessions in 2021. All of them have been virtual, but it's been great to be able to connect with so many different patients and organizations.

I just also wanted to note that each of the Centers also have listening sessions. The ones that my office coordinates are ones that involve multiple Centers, it's across the Agency whereas the listening sessions in the specific Centers a lot of times will focus around a specific product or specific drug, for example.

The Patient Engagement Collaborative is

another initiative that Patient Affairs leads. It is a partnership between FDA and the Clinical Trials Transformation Initiative or CTTI. We started this and modeled it after the European Medicine Agencies' Patients' and Consumers' Working Party model. I know earlier someone had asked whether we work with the European Medicine Agency and this is actually one of the examples that we have worked with them on.

So the Patient Engagement Collaborative is 16 members. We yearly switch up eight of the members, so as people cycle off, new people will cycle on and it's an application process. We just actually selected a few new members over the summer including Julie who you'll hear from in a minute. And the next time we will be requesting applications will be this summer. So I want to keep everyone informed and keep an eye out for the next call for applications. I also wanted to just emphasize that the Patient Engagement Collaborative, or the PEC, discusses a wider focus, so not necessarily specific medical products or diseases, but really ways that patients can be more involved in the work that we do, ways that we can improve our

communications and things along those lines that will impact product development and regulatory discussions.

I am going to go over a few of the other patient initiatives that are out of specific offices or Centers. The first one is the FDA Patient Representative Program. This is one of our oldest programs. It started in the early 90s and it has a direct input into the Agency's decision making process. There are over 300 diseases and conditions represented and the patient representatives participate on FDA advisory committees and in review division assignments. So this is also something that is an application process and I just wanted to emphasize that we really want the patients to remain objective as a part of this because they are reviewing confidential information. So there is a conflict of interest screening as a result for this particular group.

I also wanted to highlight some of CDER's, so the Drug Center's, efforts in particular related to Patient Focused Drug Development, or PFDD. I know, we use a lot of acronyms. I just want to make sure that

I emphasize what they all mean. If I've missed any, please let me know and I can fix that. So one of the main things that we do through CDER are the PFDD meetings. They also have guidance documents and grant programs. They publish reports, so it's the PFDD staff is very busy and the majority of their time really is spent on the PFDD meetings.

So the PFDD meetings are designed to engage patients and elicit their perspective on two main topic areas: the most significant symptoms of their condition and the impact of daily life and current approaches to treatment. So the PFDD program started with FDA-led PFDD meetings where FDA reached out and in 2020 and 2021 we conducted three PFDD meetings and below you can see the three that were conducted. Because the PFDD meetings were so successful, they branched out to do externally-led Patient Focused Drug Development meetings, or ELPFDD. So those are the meetings that are led by patients and patient groups. And there were 30 of them between 2012 and 2022. And it uses a similar model as the original Patient Focused Drug Development meetings and provides patient

organizations the opportunity to plan and establish these meetings. They get input from staff and the process is fairly standardized.

So this is just an example of some of the topics that have been covered on the externally-led Patient Focused Drug Development meetings. So often we get the question, what's the difference between a externally-led PFDD and an FDA Patient Listening Session? So first of all, the PFDD as I mentioned has some staff coordinated out of the drug center whereas the FDA Patient Listening Sessions involve my office, Office of Patient Affairs.

The participants are fairly similar, all -- both of them have patients, caregivers, and patient advocates. One of the main differences is the target audience. For PFDD, regulatory agencies, federal agencies, medical product developers, researchers, healthcare professionals all take part in these meetings whereas the patient-led listening sessions are really just FDA staff from a few of the different Centers and the patients. So, the topics of interest are fairly similar, too, for PFDD meetings. It's

symptoms and daily impacts and current treatment options. And like I mentioned, they're in regards to a specific drug or treatment whereas the patient-led listening sessions are patient experiences and needs related to their health or disease and treatment preferences.

So a little bit different of how they are conducted too. For PFDD meetings, it usually involves a few months of planning and they are four to six hour public meetings and they can be up to 100 participants. Before the pandemic, a lot of them were held in-person at hotels because that many people wanted to attend. Whereas, at the patient-led listening sessions are much smaller. They involve up to eight patients or caregivers, they're nonpublic and they last about an hour to an hour and a half and this is a chance for just a few patients to really share with FDA what's most important to them.

And then both of these have an output that you can look at. The PFDD meetings have a "Voice of the Patient" report and this is a lengthy report about the findings and outcomes from the meeting whereas the

listening sessions usually have just a brief summary that's available.

So as I mentioned, each of the Medical Product Centers have staff that are dedicated to patient engagement and patient involvement within the Agency. For example, CDER, the drug Center, has the Professional Affairs and Stakeholder Engagement staff, or PASE, and a lot of times the specific Centers also host their own meetings with patients and patient groups.

So I know there's a lot of information on this slide, but just wanted to emphasize that we all do work very collaboratively on patient involvement and patient engagement, so you can reach out to Patient Affairs and we can connect you with any of the other Centers and what they're doing as well as things that are going on across the Agency, so all of the contact information is here as well as websites where you can get more information on the specific initiatives.

So I wanted to turn it over now to the patients, the heart of this panel, and I am going to have each of them introduce themselves. I wanted to

remind everyone that you can submit questions via chat and thank you so much, Julie, Marc, and Aviva for participating today and I want to start off, Aviva, could you please introduce yourself?

MS. ROSENBERG: Thanks, Wendy, and thank you to the FDA for inviting me here this afternoon. My name is Aviva Rosenberg. I live in Pittsburg, Pennsylvania with my family. I'm a healthcare attorney and three years ago I cofounded the Gaucher Community Alliance which is a patient advocacy organization representing all types of Gaucher Disease. I am a patient myself of Type I Gaucher Disease and I'm raising a 15-year-old son who also is diagnosed with Type I Gaucher Disease and I'm really happy to be here this afternoon, so thank you.

MS. SLAVIT: Marc.

MR. YALE: Thanks, Wendy, and thanks again to everybody for joining the panel today. So my name is Marc Yale and I am with the International Pemphigus and Pemphigoid Foundation and pemphigus and pemphigoid are rare autoimmune blistering skin diseases and I was diagnosed in 2007 with the variant

mucous membrane pemphigoid and I'm just happy to be here and share my perspective today, so thank you.

MS. SLAVIT: Great. And I want to go ahead and have Julie introduce herself.

MS. BRENEISER: Thank you, Wendy. I'm honored to be here today. My name is Julie Breneiser and I'm the Executive Director of the Gorlin Syndrome Alliance. Gorlin Syndrome is a rare genetic illness that affects about one in 27,000 people, including myself and my two young adult children. The syndrome can affect every organ system and by far for most, the most burdensome manifestation are basal cell carcinomas. Some of us will have over 1,000 in our lifetime. I'm in that group. And some people have died from metastatic basal cell carcinoma. There are no FDA-approved treatments for any of our manifestations and again, thank you for inviting me. I'm honored to be here today.

MS. SLAVIT: Great. Thank you to all three of you for being here. I just wanted to take a few minutes and ask you some questions about your engagement with FDA and what your experiences were

like and hopefully the audience can learn a little bit more about particular programs as well as what it's like to be a patient or a caregiver for an organization that is working with us. So how long ago did you first connect with the FDA and why did you decide to become more involved at that particular time? I'm going to start with Aviva.

MS. ROSENBERG: So we started the process for a patient-led listening session pre-pandemic and the goal was, so the FDA, there is approved treatments by the FDA for Type I Gaucher disease which is the type that myself and my son has. There are no current FDA approved treatments for Type II or III or the neuronopathic form of the disease which affects the central nervous system.

So the goal was to bring families who are affected by this more severe, the neuronopathic, form of the disease to the FDA so that the regulators can really understand what these families are going through and the burden on them and the caregivers of not having any approved treatments for them. So unfortunately the pandemic happened and so we really,

our families and our community really wanted to come to the FDA and to meet the people and that we thought that that would be an empowering experience.

Although, as we soon learned, this was not going to happen anytime soon, so we moved forward with the virtual patient listening session in 2021 which was held. In addition to that listening session, I was also involved in another Patient Listening Session and this is with an international coalition called the International Gaucher Alliance and what we're doing there is we are forming a registry, an international registry of patient reported outcomes for the neuronopathic form of the disease. So the focus of that listening session, unlike the first one which was patient experience, this listening session was really to explain to the FDA the purpose of the registry, the type of data that we're going to be collecting with the PROs and sort of to see if this would sort of to get like the "temperature check". Like, is this going to be helpful in data, how could this possibly change the outcome of research and looking for new drugs and new treatment methods. So that was the second

listening session.

MS. SLAVIT: Thank you. Marc.

MR. YALE: Yeah, so I think we started kind of building our relationship with the FDA I would say early -- well, beginning in 2016 when we launched our natural history study in conjunction with NORD. So we have been looking to launch a natural history study to collect data and really help us characterize the disease. We didn't have any FDA-approved drugs for any of our diseases, so we really felt like a natural history study would help us understand the disease more and be able to help us inform the FDA on really what's important to patients. So that was really early on in 2016.

And then we reached out to the FDA, I just picked up the phone one day and called and said, "Hey, we'd like to -- we're going to be in Washington, DC. We'd like to meet with your staff," and I was a little intimidated at first to be able to do that but I have to say that the staff was great. I mean, they set up a meeting for us, we happened to be in DC for an advocacy event and so they were like yeah, come meet

with us. We spoke with Patient Affairs, and we set up a meeting with several of the division heads, dermatology department, CDER, and so on and unfortunately that meeting got postponed due to a weather event but we happened to be there again in the following February back in I think it was 2019, so 2018 we set up the meeting and the in 2019 we met with them and it was really a great meeting. It was our first interaction with the FDA to really help inform them about our organization, about the disease, about the burdens that patients were experiencing and again to try to help them understand what's needed from our community in drug development.

And then in 2021, we actually held our first listening session and I was part of the planning of that and that was really a great experience just interacting with the FDA and planning that. We had five patients kind of share their experiences with their disease and then now we're in the process of putting together an externally-led Patient Focused Drug Development meeting. So it's really just kind of been a gradual building of this relationship over time

and we've really enjoyed working with the FDA because it's allowed us to really share what's important to patients and what's important when it comes to, as Aviva said, patient reported outcomes and also help us understand the process as far as what the FDA does and how they approve drugs. So it's been a great relationship.

MS. SLAVIT: Great. Thank you. Julie.

MS. BRENEISER: I've been fortunate to be interacting intermittently with the FDA for a few years now. We at the Gorlin Syndrome Alliance work with both large pharmaceutical companies and a few smaller and innovative biotech companies and one of these partners, Palvella Therapeutics, suggested we consider conducting an externally-led Patient Focused Drug Development meeting a few years ago. So we submitted our letter of intent. That was approved and subsequently we were told that we needed to do a listening session and so this was conducted in November of 2020 and then with further support from Palvella and some of our other pharma partners, we resubmitted our letter of intent and did an externally-

led PFDD last fall.

Prior to these meetings, I had been invited by Palvella, Pella Pharm and Leo Pharma to speak as a patient and community representative at meetings they had requested with the FDA to help advance their respective programs. And the other way I have been involved with the FDA is actually just by sending an email. I was raised that it never hurts to ask. So last year at one point I sent an email to Dr. Woodcock and how cool was it to have her respond and we both need to follow up on some things that we discussed, but it's really pretty huge to be actually emailing personally with her. So those were my ways of involvement beyond the PEC which, Wendy, I guess we'll get to in a little bit.

MS. SLAVIT: Okay. Thank you. Thank you so much for all of your advice so far. And I just wanted to know what did you do as far as -- did FDA reach out to you, did you reach out to them? Some of you already discussed this, how did you know who to connect with, what were you hoping to gain through reaching out? Aviva.

MS. ROSENBERG: Sure. So similar to Julie's experience, our disease has many industry friends and collaborators because we have different types of treatments in this space. So one of the biotech companies that's working on upcoming treatment, they actually told us that we could do these Patient Listening Sessions which was something that we were not aware of and so it was thanks to them, to Aver Bio, that we were able, that I reached out to the FDA and then of course I did some research and learned how the process works and basically there is the website is great, there's a whole page of patient-led listening sessions and how you can go about doing it.

So just sort of followed the instructions and sent a letter and then got a response and we worked through there. So that was really the initial, that was sort of the initial discussion point and we don't see, our organization doesn't see that discussion as being one and done. We hope that this is a continuing relationship now that the FDA knows about us, they know about our families. We would like to continue that discussion and hopefully have updates and looking

forward to becoming more involved as some of these pipeline drugs work their way through and really the importance to our community.

MS. SLAVIT: Thank you. Marc.

MR. YALE: Yeah, so I mean, similar to Aviva and Julie, I mean, I think that there are therapies in the pipeline for pemphigus and pemphigoid and so we -- when we met with the FDA back in 2019, we really wanted to inform them about those drugs and let them know that our community was really suffering, particularly from the burden of corticosteroids, so we really needed alternative therapies to the mainstay to really help patients be able to live to their fullest and have a good quality of life in their daily lives. So the FDA didn't reach out to us as I mentioned earlier, and I think it's important for patient groups to understand the FDA is always extremely busy, so you have to take that first step and reach out and I think we had been doing a lot of advocacy work with NORD and doing advocacy up on the Hill and like I said, I just said, "Hey, I'm going to reach out to them and see if we can have a meeting," and we reached out to Patient

Affairs and again I was just pleasantly surprised they emailed me right back and said, "Hey, what do you want to talk about, when are you available, who would -- which divisions would you like to speak with?" and they set up that initial introductory meeting and we prepared slides and went in and we spent about an hour with the group and it was a pretty large group but I have to say, I think the best part of the meeting was walking away with feedback from the FDA staff saying everything you're telling us is very impactful. These are the things that we think you should do, next steps that you should take to really be able to move drug development forward in pemphigus and pemphigoid. So that was really I think probably one of the best aspects of that meeting is the feedback that we got like hey, you need to collect more data, you need to expand your natural history study. Those are the types of things that will help you move the needle and really help inform the FDA on what's important to patients.

MS. SLAVIT: Thank you. Julie.

MS. BRENEISER: Sure. I want to follow up

first on something Marc just said and we've heard a lot today, the term natural history study. Another term for that is a registry or a survey and a lot of patients don't understand what a natural history study is or why it's important. And my point there is that we really can't advance research in defining better treatments and a cure without knowing what issues rare disease patients face. So that's why the natural history studies or registries, surveys are important.

But to answer specifically your question, Wendy, initially for us it was reaching out and knowing who to connect with was a challenge because for an outsider, the different divisions and their acronyms, as you've already pointed out, Wendy, are a challenge and what each division does and who to connect with and how to connect with them. But by reviewing the information on the web, FDA's website on listening sessions and externally-led Patient Focused Drug Development meetings, you can figure it out. For each of those events, we wanted to invite specific people at the FDA and so finding names and email addresses in the various and complex directories took

us hours, but it was worthwhile because we ended up f or our externally-led PFDD, we had a total of 268 attendees and 36 were from the FDA. They weren't there the whole time, but we were thrilled with our turnout.

MS. SLAVIT: Great. We're getting some questions through the chat. A few people have asked how can they be a part of a listening session or become a patient representative and I just want to encourage you to go to our website, there is a section called "Patients ask FDA" and that's like a request form so you can put some information in there and fill that out and then we will get in touch with you and follow up about the different programs or initiatives. You can also just email Patient Affairs. It's patientaffairs@fda.gov and we will put you in touch with whoever would make the most sense.

Someone asked specifically how they can participate as a caregiver, a rare disease caregiver, and we encourage caregivers, advocates and patients to all get involved. The caregiver experience is very important to us, so if you're involved with a patient

organization, you can reach out to us through the patient organization but I also encourage individual patients and caregivers to reach out to us directly and we can help sort of navigate what's going on at FDA.

One of the other questions I got was about work we do outside of the United States and as I mentioned previously, we work with the European Medicines Agency or EMA and what I also failed to mention is we also work with Health Canada. The person that asked the question was specifically asking about Canada. So we work with those groups to get an understanding of what they're doing abroad as far as different diseases and conditions as well as just generally how to engage patients and best practices. So we work very closely with them to try to get an understanding and actually the Patient Engagement Collaborative, or the PEC, recently had a meeting with the equivalent group at EMA and talked about different things that are priorities for patients both abroad and things that are different and then things that are similar. So we really do try to learn from our

colleagues in Europe and in Canada.

All three of you have touched upon a little bit some of the specific initiatives that you were involved with. If you can just kind of talk about each of the initiatives that you were involved with and what you thought of those particular programs. We'll start with Aviva.

MS. ROSENBERG: Sure. So the first patient-led listening session was sponsored by our organization here in the US, the Gaucher Community Alliance and we sought out the FDA, we wanted to again explain what it was like living with neuronopathic Gaucher Disease which in addition to affecting the organs and being a lysosomal storage disorder also crosses the blood brain barrier and affects the central nervous system which can manifest itself in a wide variety of presentations from very, very severe to moderate.

And so as I said, there's no approved treatment for this form of Gaucher Disease in the United States. Although our patients are on treatment it is considered off-label. So we wanted to empower

our families that are and explain to the FDA how not having an approved treatment and the treatments that are approved are not -- they don't cross the blood brain barrier and really the difficulty of how it is difficult to live with this condition. And so it really, it worked both ways. Like, obviously the biggest goal was to inform the FDA so they know to please prioritize pipeline treatments, research, but also it really was a very empowering exercise for our families who were able to show their stories and to show what it's like both for the young adults and of the parent caregivers, I think it was a very empowering experience.

The second Patient Listening Session I was part of was about specifically about a registry. So the International Gaucher Alliance which is based in Europe but represents member or organizations all over the world has -- is starting a neuronopathic Gaucher patient registry. So this is not a pharma registry, it's not owned by a pharmaceutical company. It is going to be owned by the patient community and the starting point is really the collection of patient

reported outcomes to look at the natural history of the disease in hopes that it sheds light on disease progression, possible avenues for treatment, and so as part of this development of the registry which has been under development for many, many years, and it's just going live now, which we're really excited about, we wanted to meet with the FDA and share the plans, tell the FDA what's happening, what the starting point is for the registry and what hopefully we want to expand it to include clinical information sort of the different data points. And that was really, really helpful because they had both calls had between 30 and 45 regulators on, both listening sessions and the one for the registry I think was really helpful because first of all, they shared some concerns about the data points we were using which is very helpful since there were some times to sort of rethink the process and before it actually went live and concerns both in terms of the collection and also the validation and then finally the sustainability of such a thing without having the clinical data sometimes natural history studies aren't necessarily sustainable because

of funding.

So I think it was a really nice discussion. There was -- I don't want to say anything groundbreaking came of it but I definitely think it was really important for our team to hear some of the experts that have looked at this type of data for years, what they had to say, and I think that they had a lot of very respectful for what we were trying to accomplish as well.

MS. SLAVIT: Great. Thank you. Marc.

MR. YALE: Yeah, thanks. One of the things that I want to stress just kind of listening to Aviva and Julie is people might say, patient groups might say well, when? When should I reach out to the FDA? When is the best time to do that? I think my answer is really early and often. You want to reach out to the FDA as much as possible because it's really going to help you kind of navigate what's -- how to interact with the FDA but also to illustrate to them what's clinically important to your patients and your patient community. So I can't really emphasize that enough. So after that initial meeting, like I said, we had

that first listening session and we had five patients from different subsets of our disease, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, so we really wanted to try to be representative of all of the types of diseases that we cover within our organization and we worked with the FDA staff to kind of prepare that. But I think kind of on the lines of what Aviva was saying is I think what it helped us kind of illustrate to the FDA is that there isn't a -- especially when it comes to rare diseases, there isn't like a "one size fits all" approach to rare diseases and every rare disease is different. And so it's important that when I said earlier that we reach out early and often, we have to -- we want to be able to have that information passed amongst all the Centers. So there needs to be cross learning amongst all the centers so that information is passed along and the communication stream works well. Because in the end, there is really individualized outcomes for each disease and as patient groups we need to make sure that we're informing the FDA of that.

So that was great and then of course now as I mentioned we're working on this externally-led PFDD meeting, we're currently having monthly meetings with Patient Affairs to try to get everything together and we're developing our agenda and things like that. So I mean, again, it's just having that opportunity to meet with Patient Affairs and say we have questions about this or how do we approach this aspect of the meeting has been really helpful in the process.

MS. SLAVIT: Great. Julie.

MS. BRENEISER: Backing up a little bit, after we had been -- after Palvella had recommended to us that we do a PFDD, I really got thinking about why and it comes back to being a rare disease. As with all of -- as Marc's and Aviva's diseases, it's not a reasonable expectation for the FDA or for practitioners, healthcare providers to know about our diseases, our unmet needs and our burdens and so we went ahead with our plans in order to educate them, to show them what goes on behind closed doors where it's not necessarily a pretty and easy time for patients and families.

And by reaching out and doing our PFDD and our first our listening session, we wanted to teach the FDA about what it's like across the age spectrum and in doing so, I mean, the whole purpose ultimately down the road is to smooth the pathway for drug and product approval for better treatments and ultimately a cure.

We all want this to be faster, we all want it to be smoother and we really want it yesterday. But we also want to help the FDA understand our willingness to accept a certain level of risk and how much that risk would impact, positively impact our lives. So as is already been said, we've done a PFDD, we did a listening session and we feel like they were very successful. But, again, there is an urgency to it. I mean, for us to delay, we were put off almost a year by the FDA. First we had to do the listening session then the PFDD and a year for me means about -- the development of about 20 basal cell carcinomas.

I don't know what the year looked like for Marc or Aviva, but a delay is impactful. And so now we wait and hope that our listening session and PFDD

will have a positive impact on the FDA's review of different products that they see or different treatments and we feel confident that the subjective and objective information that we presented should make an impact and we can't wait to see some positive follow up from them.

MS. SLAVIT: And, Julie, I know fairly new to the Patient Engagement Collaborative or PEC. If you could just talk a little bit about what your experiences were like with the initial application, the interview process, and the -- we've only had a few meetings so far but if you could just talk a little bit about that? Because we get a lot of questions about the PEC and I want to be in the PEC and what should I do. So --

MS. BRENEISER: Sure. I heard about it and went ahead and filled out the application. It's somewhat extensive. It requires a recommendation from either someone, a board member or someone else who knows you well and knows of your advocacy experience. And there have only been two meetings since I joined, so I can't really say too much about them but I really

hope that we continue to focus on the charge of the PEC which as it says on the FDA website, is to help achieve more meaningful patient engagement in medical product development and other regulatory discussions at the FDA. For me, it's really thrilling to be a part of that.

MS. SLAVIT: Yeah, I wanted to emphasize that Julie is part of the second cohort, but the first group of PEC members helped us figure out why we needed a better website, what kind of information would be better to put on it, so we made a lot of changes to our website as a result of getting input from PEC members. Communication is very important. So PEC has been able to help us. Certain things that I felt like as a health educator should be up front were actually patients were like, no, that's not that important. We should put that lower down the page. So we spent some time with patients testing the website and trying to get that more in order.

One of the other communications initiatives that we have is we have these "Patients Matter" videos which focus on topics that are important to patients

and we talk to different patients to see what they would like us to focus in on. We did one on natural history studies and the importance of natural history studies and we had several patients talk about their experiences.

So I just wanted to let everyone know that those are resources that are available and you can take a look at our website and learn more about what we're doing. I just wanted to look and see if there was a question that came in. So a few people asked sort of how they can next engage.

I understand different organizations have different levels of experience interacting with us. There are some that have never interacted with us, there are some that have had been involved in multiple initiatives or programs. I, like Marc said, I encourage you to reach out early and often. Patient Affairs, we're here for you. We want to help you make good decisions about where to go to next as far as the work that you hope to achieve when working with us. So I encourage people to go ahead and do that.

I also wanted to emphasize that you can take

a look at our website. You can look at summaries of other Patient Listening Sessions to see what those are like and what people's experiences were. I also wanted to kind of highlight some of the more informal ways to get involved. As Lewis mentioned, we have a docket that's related to Rare Disease Day and so you can go to the docket and make comments on the docket. You can go ahead and just informally email me or anyone else on my team and we're happy to help in any way that we can.

So it's not always the super-formal forms of engagement but just sometimes some of the smaller quick ways to engage with us that we want to encourage people to take advantage of, too. And as I mentioned, the "Patients Ask FDA" form on the website can help kind of guide you in how you want to get involved.

So we have a few more minutes, but I wanted to discuss with you what your experiences have been like and what would you like to share with other rare disease patients? We have a lot of people attending today's meeting, like I said, with varying levels of understanding and involvement on the work that we do.

One of our initiatives has actually been to clarify a little bit better what FDA does. It's a lot of confusion around that. So what would you like to share with other patients that are watching today? I'll start with Aviva.

MS. ROSENBERG: Sure. I think that it was, both of my experiences have been very positive and it wasn't overwhelming. I don't think my patients and their family members felt overwhelmed. I think they felt very welcomed. The questions that they got were appropriate. And so I think that it was a very positive experience all around and so I would encourage patient organizations of rare diseases to reach out.

The one thing that I would caution and I, we learned early on, is that there is sort of a cottage industry of consultants, not government related, that have sprung up around this Patient Listening Session and the consultants offer a variety of services to prepare you for your listening session. And a few organization has if you have funding and you have deep pockets and by all means, I think these consultants

will certainly make your lives easier. That was not something that we had funding for and I want to explain that it is not necessary. So this is not to put down the consultants, they do a great job and I'm sure they've organized a very, very excellent listening session, but the finances should not be a barrier. We did both of our listening sessions without a consultant. The directions are very clear, the FDA will work with you to explain anything that you don't understand. So I think if you are starting this process and you find a consultant reaching out to you that they want to make your lives easier, if you have that type of resource, they will probably make your life easier. But it should not be a barrier.

MS. SLAVIT: Thank you. Marc.

MR. YALE: Yeah, I mean, again, I was intimidated. I was a little scared to have those initial meetings with the FDA because I guess more than anything I didn't know what to expect but I remember I was sitting in the basement of the Senate building like working on my speech like what I was going to say to the people of the FDA when I met them

and got in the room and everybody was just so friendly and nice and they're just like the rest of us. So I think the big thing is, the FDA is there to listen, so it's important as advocates and I know everybody on this call, all of the rare disease advocates are we're here because we want to share our stories. We want you to hear about these diseases and how we're living with these diseases and as Julie said, every day we don't have a therapy it's a delay and it causes significant impact on all of our lives. So really don't be afraid to share, speak up, speak out, and I would say the other thing is the FDA is a very data-driven entity. So the more data that you have, the more data you can collect on your disease, whether it be through a registry as Julie said or a natural history study or collaborating with other organizations to collect data, I think it's important and that it really will help illustrate the need and what's needed and help validate the outcomes that the FDA is looking for. So the data is important. Don't forget that piece. I think it's important.

MS. SLAVIT: Julie.

MS. BRENEISER: Sure. Following up on what both Aviva and Mark said, we went the other way from Aviva's organization and we used a consultant. We were very fortunate to have pharmaceutical funding or partner funding and it did make our life a lot easier and the advice they gave was very strong advice. So both work and I just want to say -- give that other side of the spectrum. And following up also, don't be afraid to send emails.

Don't be afraid to ask, to push for answers. As Wendy said in our -- Wendy who is our moderator here said in one of her prep calls, we at the FDA are civil servants here for patients. We are here for you. So don't be afraid to ask. Don't be afraid to push for answers. And let the FDA know what you hope for, what you expect. Give them a call to action. Give them a job. Make them know what you expect and what you hope for. You represent the people, your people in need or you are a person in need and the FDA is there among other things, it's as it says in their mission, to advance public health. So let them know how they can help to advance your health.

MS. SLAVIT: And we got a few questions and comments that came in and one of them was my patient organization doesn't know very much about FDA. How can we find out more? Well, actually, even though we're a small group, Patient Affairs, we do give presentations at organization meetings, patient organization meetings. We want to introduce ourselves. We want you to feel comfortable approaching us. So that's something you can also request that we speak at one of your meetings and talk about a lot of the things that I previously gave a presentation about, what the different choices are and what some of the initiatives, know what's involved with them.

Someone else also asked how do we keep track of all of our inquiries that are coming in on different topics? So the "Patients Ask FDA" web form is a way that we get information. Patient Affairs also has our own email address, so people email us directly and a lot of what we do at Patient Affairs is if something that we know that one of the other Centers can better answer, we will pass on your email or your

question to CDER or for example if you want to know more about Patient Focused Drug Development, we can pass your email off to the Patient Focused Drug Development team and they can answer a lot more specific questions. The initiatives that are coming out of Patient Affairs like the PEC and the listening sessions that are cross-Center, we're happy to talk to you about those but we want to make sure that if it's something that you need more details for that we're able to help. Robin Bent actually suggested that one of the benefits of the externally-led Patient Focused Drug Development programs, specific groups are assigned an Agency contact who helps and works with the groups that are planning the meeting and they handle publicizing the meeting within FDA. So she agrees that you don't necessarily need a consultant, you don't need to have large amount of funds to be able to do a Patient Focused Drug Development meeting, and so I just wanted to emphasize that we are here to help in any way that we can with any of your engagement activities. So we have I guess about three or four more minutes, not very much time left. But I

just wanted to see whether Aviva, Marc and Julie, whether you had any kind of ending comments or remarks that you wanted to make. I'll start with Aviva.

MS. ROSENBERG: Thank you for having me and I would say to the rare disease patient advocacy groups that don't discount the impact that having a listening session will have on your patient communities because a lot of times these are people that are -- that have nobody -- nobody will listen to them. They've gone through years of diagnostic journeys and doctors won't listen to them and so the idea of sitting at a table, or a virtual table, with government people whose sole reason are there to listen to them is really empowering. And so while I would love to have a treatment yesterday, there is a second there that we found a secondary purpose and it was a very easy process. I encourage it and I think it was -- we look forward to having more meetings like that.

MS. SLAVIT: Great. Marc.

MR. YALE: Yeah, thanks again, Wendy, for having me and just to kind of build on what Aviva was saying, you know, these meetings can really help long-

term in the drug development in your space, in your diseases. So having the opportunity to provide patient perspective and being allowed to have this Patient Focused Drug Development opportunities are huge because there may not be, as Aviva said, a therapy that's FDA approved today but it'll speed up the process. So as I said, we didn't have an FDA-approved drug before 2019 and then we finally after continuing to work and work and work, we finally got an FDA approved drug in 2019. But just engage. Go to -- attend these types of meetings, go to Rare Disease Day at FDA in person if you can, if that happens again.

But just take every opportunity that you have to engage with the FDA. I mean, I remember listening to Dr. Woodcock speak at a NORD Summit Conference several years ago about building natural history studies and how important that was and that was inspiring. I've left going hey, we need to do this and we can do this, but you just have to build it a little bit at a time. So be patient and just work at it. Be persistent.

MS. SLAVIT: Sounds good. And Julie, do you have any last minute comments you'd like to say?

MS. BRENEISER: Sure. The only other thing to add to what Marc and Aviva have brought up very nicely is that listening sessions and particularly externally-led Patient Focused Drug Development meetings take time to organize and put together. Don't think that you can do it -- don't think that you can plan one, particularly a PFDD, three months from now. You need to give yourself a good chunk of time to get ready and I don't really have anything else to add.

MS. SLAVIT: Okay. Well, thank you so much, Aviva, Marc, and Julie. This has been a really interesting conversation and I hope the audience learned a little bit more from your experiences and thank you again for speaking with us today.

MR. YALE: Thank you.

MS. BRENEISER: Thank you for having me.

MS. ROSENBERG: Thank you.

DR. FERMAGLICH: Thank you all. We'll now take a ten minute break. During the break, please consider "sticking around" to enjoy a slideshow of artwork from the "Beyond the Diagnosis" exhibit with powerful and beautiful paintings of patients with rare diseases. Please re-join us after 10 minutes for our next panel.

(BREAK)

DR. FERMAGLICH: Welcome back to FDA Rare Disease Day 2022. For our final panel of the day, we get to hear from each FDA Center about exciting and innovative initiatives aimed at improving drug development for rare diseases. This panel will be moderated by Dr. Sandy Retzky, the Director of the Office of Orphan Products Development. Dr. Retzky.

DR. RETZKY: Hello, everyone. Welcome back. This is panel five and it is called "Our Future Journey". What we want to do here is spotlight some of our initiatives from each Center that we're working on to help promote and enhance product development for rare diseases. So our first speaker today is Dr. Michelle Campbell. She is from the Center of Drug Evaluation and Research and she will be talking about the Rare Disease Accelerator. Michelle.

DR. CAMPBELL: Thank you, Sandy, and good afternoon to everyone. We still have a great crew out there who is hanging in there as we continue our discussion about rare disease and how FDA looks at our rare diseases and supports rare disease drug development and engagement from our patient community. As Sandy said, my name is Michelle Campbell. I am from the Office of Neuroscience and the Center for Drugs and I

wanted to talk to you guys today regarding when we think about our rare disease lifecycle considerations and for some of you folks, you may have seen some of these slides before.

But we know that when we think about medical product development, it is a lifecycle, it is a spectrum. And there are different aspects of that spectrum depending on what phase you're in of where we know we have challenges for our rare disease medical product development and what you see here is in our very beginning, our translational phase and often this is when we discuss the lack of natural history or disease characterization in understanding the progression or how the disease manifests through different patients. Often this is where we see the heterogeneity and the symptoms that our patients can live with and experience on a daily message.

We knew that some of our challenges is that with our small patient sample sizes can we difficult to really be able to do advanced studies and the need at knowledge development with those small samples. We know that our available testing for diagnostics

perhaps is often maybe developed at individual academic medical centers and may have uncertainties whether it comes to reliability and standardization across the board for the utility of a much broader population. And we know that work can be done sometimes in silos which of course we do not want to encourage, but we do know it happens. And so those are often some of our challenges that we face.

So then when we move into thinking about clinical developments, we think about when we may have a potential therapy option, what is -- how do those translational challenges then still continue on and it can be from still not clearly understanding the disease enough or the mechanism of action. We have unique challenges and the appropriate endpoint selection to support efficacy and we know that some of our trials, trial design and what is the appropriate way to design our clinical trials and rare disease can often represent a lot of challenges. And we need to be thinking about how can we maximize our patient population when we are conducting our trials.

We also know from the various patient

listening and patient engagement opportunities that was highlighted in the last session about engaging with the agency early and we learn a lot from these listening sessions, PFDD meetings, all the various topics that were discussed in the last session and we do continue to learn from them and encourage that if someone would like to reach out to the Agency to use the Office of Patient Affairs or the Center-specific patient engagement staff to start that dialogue.

But what could be another way for us to not only learning from our patients, but what is another option for us to really think about how can we help advance rare disease drug developments? And so I want to focus a second and talk about data sharing and what can data sharing offer to us? We know that one of our challenges is our limited sample size and that we may have small trials of various sizes for a condition, but what would happen if you would be able to pool all of that data together and to better learn about the patients have experienced through the data and look at that as we also hear from them verbally from that experience?

Data sharing offers that opportunity to potentially develop clinical trial simulations so we can learn better about how disease may progress. We could optimize our clinical trials with what the right population may be or if stratification is needed, so in poolling our data together into a shared system, we allow to increase the power of productivity potentially of a population to help us think about what may need to be done in a drug development program.

Data sharing we know can reinvigorate drug development when we pool resources together and we can do this outside of an individual drug development program and really work together we can collaboratively with all stakeholders continue to advance the science of understanding a rare disease and what may be appropriate to pursue for a medical product development program. We know that our larger datasets can reflect the broader patient population by pulling together and that can enhance our trial design and patient selection and as well as inform us on appropriate endpoint selections or where maybe there

are additional gaps that we need to focus in on to be able to optimize what is currently available to help support clinical trial endpoint. So data sharing is one opportunity that can really help us advance rare disease drug development.

Many of you have heard, we've been talking about this for a few years now, but CDER has funded the Rare Disease Cures Accelerator Data and Analytics Platform and this is something that we have funded the Critical Path Institute who is working with and collaborating with NORD regarding this. And the idea is to promote data sharing and data collection across rare diseases to help accelerate and understand disease progression and to optimize our clinical trial designs. And really the idea is for this to be an essential infrastructure for where all data as a repository can come in and be used.

We know that our stakeholders need to be engaged and that we need to work with all stakeholders and so that's our patient groups, that's industry, that's academia to be able to bring all other data together.

The final slide you see that is currently on your screen is a schematic of how we think data will flow. The left side lists the different types of data that can be brought into this platform. This platform is up and running and we currently have 74 datasets for 18 different diseases and disorders. While I know that may seem small, it's a starting place for us to help advance the science and help us be able to inform and make regulatory decisions with this.

FDA is also an important stakeholder in this effort because we hope that this information not only will be able to help our external stakeholders but also our internal stakeholders be able to understand disease progression themselves from their everyday jobs when we're reviewing applications that are coming in.

So I am going to thank you guys for listening briefly about this effort. I look forward to questions and I turn it back to you, Sandy.

DR. RETZKY: Thanks so much, Michelle. That was really terrific. I am going to just remind everyone if you want to send in a question, please do

so in the chat. It's in the bottom of your screen. There's like a bubble and you hit that icon and it will open up a chat and you can send us a question. We'd love to hear your questions. So I am next going to introduce our next speaker and it's Dr. Celia Witten. She's the Deputy Director of the Center for Biologic Evaluation and Research. Dr. Witten.

DR. WITTEN: Good afternoon, everyone. Thank you for inviting me to serve on this panel and I really appreciate the opportunity to talk and especially to follow Michelle's excellent talk because there are some specific relations, I think the theme of the day is collaboration and data sharing and I'm going to give an additional different spin on some of the needs for data sharing collaboration.

So I'm going to talk about two things. One is the need for collaboration in developing therapies for rare diseases and then I'm going to talk about a specific effort on the part of that CBER is participating in for a collaboration related to gene therapy.

So I want to talk a little bit about the role

of FDA in what could be called the product development ecosystem, meaning the constellation of organizations and individuals whose collective work results in bringing products to market. I think people already know this, but I just would like to make this point that our role is to ensure that medical products are safe and they meet a legal standard of efficacy. But I think for anyone who has been involved with FDA and product development will realize that we get involved very early in the process of product development from the concept through first market surveillance because I think we have a critical vantage point in terms of seeing what's needed or what some of the roadblocks are in ways that are just unique to our role as regulators.

But there are many other stakeholders in the product development ecosystem: patients and families, advocacy organizations, researchers, physicians, pharmaceutical and biotechnology companies and trade organizations and as many of you know, interactions of these stakeholders may come much earlier in product development than the initial clinical trials. There

could be discussions of identification of targets for therapy, strategies for manufacturing and other topics can be part of these early discussions. And as I think you already heard from Michelle's talk, but the need for collaboration and data sharing is essential. I think especially for rare diseases, efficient drug discovery and development is in part a team sport and efforts bring all stakeholders to the table may be essential in development for rare diseases.

So recognizing this need for collaboration on the challenges of development for especially very small diseases, CBER held a workshop in early 2020 on the topic of developing individualized therapies, meaning therapies for very small numbers of patients and as part of an outgrowth of that came our participation and vision for our participation in the Bespoke Gene Therapy Consortium which I am going to talk about.

So one thing I just want to mention and I think it's obvious to everybody that the challenges of developing therapies for rare disorders can -- are the same as the challenges for any development of a

therapeutic article and those include manufacturing nonclinical development, clinical development and product access, but I think to a greater degree that may be commonly recognized, some of the challenges such as manufacturing may need more attention than some of the challenges like clinical development that tends to get a lot of attention in meetings like this one, as it should, but it's not the only challenge that we face.

So in gene therapy, a lot of times there is -- it's possible to manufacture vectors for the 100 to 10,000 patient treatment range but it may be not viable because of the cost to develop much smaller product lots and it may not be possible because of the manufacturing technologies to manufacture more larger -- enough to treat larger numbers of patients. And one of the thoughts that that led to for us at CBER was the fact that perhaps for gene therapy, developing better manufacturing processes might help improve the ability for products to be available to treat patients at both of the other ends of the spectrum, both a very small patient numbers as well as potentially larger patient numbers for other kinds of products.

So I mentioned, I listed in a previous slide, the four basic baskets for challenge areas for product development and I mentioned that we in part think manufacturing for some of the gene therapies is a potentially rate limiting step. And so I just want to show this slide. This is one of the gene therapies that approved in the last couple of years and it was approved based on a very small number of patients because the result seen was just so overwhelmingly positive that it was possible to approve it based on this small number of patients.

And I'm just making the point that it's important to know natural history and it's important for gene therapy also to know natural history, very important. But it is also sometimes not the only thing that we need to focus on in terms of getting products available.

So this is my last slide and this is about the collaboration that we're participant in. It's called the Bespoke Gene Therapy Consortium. So one of the gene therapy vectors, AAV vectors, which are very promising for a number of rare diseases is an area

where improved manufacturing and improved availably of the vectors might help to speed the product development along. And of course there are other areas that are important, too, in developing these for clinical use including preclinical testing and clinical testing.

But this consortium, what is planned and it's a consortium between NIH, FDA, a number of companies and organizations and they're going to -- the goal is -- under the nonprofit organization being managed by the Foundation for NIH, and the goal is to take a couple of gene therapies through the process from idea through clinical study and treatment for patients and try to learn collectively from it. So instead of having four studies, four products developed in silos where each individual entity or group is developing their therapy and their treatment to have a collective discussion about what some of the roadblocks have been in manufacturing and testing and preclinical testing so that we can have a better idea as a community what works and what doesn't work and I think this is really the importance of this kind of data sharing of what's

a successful development program can't be overstated. So we're hoping that that will be a result from this Bespoke Gene Therapy Consortium, a recognition of -- recognizing that as an important value to perhaps serve as a model for efforts like this in the future. Thank you very much. I'll turn it back over to you, Sandy.

DR. RETZKY: Thank you so much, Dr. Witten. The Bespoke Gene Therapy Consortium sounds so interesting and promising. It's really great. I'm going to turn it now to our next speaker who will talk to us about real world data and the development of drugs for rare cancers, Dr. Donna Rivera. Donna.

DR. RIVERA: Thank you, Sandy. And good afternoon, everyone. Thank you to the organizers for the opportunity to share work on behalf of the Office of Oncologic Diseases and the Oncology Center of Excellence to advance the use of real world data in drug development for rare cancers. I am Donna Rivera, the Associate Director for Pharmacoepidemiology in the OCE and as mentioned by various FDA leaders throughout the day, there are collaborative efforts across the

agency where we are dedicated to finding ways to meet important challenges associated with rare disease drug development while keeping patients central to the process and our mission and I am going to share just a handful of these efforts going on in oncology.

We'll start out by talking a little bit more about real world data and defining a few key terms. Real world data is data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources and real world evidence is a clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real world data.

Real world data can come from various sources including EHR data, claims data, registry data, and patient-generated data and can be comprised of various data types such as pharmacy data, genomic data, patient reported outcomes and social determinates of health. At present, there is an increasing amount of real world data and the goal, the objective is to find ways to harness and utilize this data and generate high-quality, real world evidence.

The Oncology Center of Excellence established the Oncology Real World Evidence Program in December of 2020 and the goal is to collaboratively advance appropriate use of real world evidence in oncology product development to facilitate patient-centered regulatory decision making and our strategic priorities are to optimize knowledge building through centralized real world data research that ensures study efficiency, transparency, and diversity to advance the scientific development of resources, regulatory policy and guidance on appropriate use of oncology real world data informed by methodological research and collaborations to collaborate through strategic partnerships that foster pragmatic and appropriate use of real world data across FDA, federal agencies, and through public-private partnerships and finally to accelerate the field of oncology real world evidence through leadership and training and rigorous evaluation, methods development, and regulatory science.

We hope to accomplish this across four key focus areas of regulatory review, regulatory policy,

regulatory science research and collaboration and education and engagement. In each of these areas, we have ongoing work to support rare cancer drug development.

Currently our program goals include fostering consistent terminology through a real world data glossary, developing use case to enhance data at the source through collaboration such as M-code and ASH Collaborative to characterize data quality through development of an oncology QCARD and developing real world endpoints such as real world response through collaborations of friends of cancer research.

For rare cancers, better understanding real world data quality and also the capability for evaluation of meaningful endpoints are ways to potentially create advances.

From a drug development perspective, the use of real world data in regulatory submissions is increasing. When we think about appropriate potential uses of real world data, there should be a clear rationale where trials are infeasible or impractical, unethical or there is a lack of equipoise and there

is a clear rationale for lack of randomization. The use of real world data or evidence generation outside the gold standard of randomized controlled trials may be relevant to rare diseases and in pediatrics and specifically pediatric oncology as well as in areas of significant unmet medical need which is what we are talking about today.

So there is a need for innovative approaches to evidence generation and trial modernization which may be appropriate. For example, the use of external control arms is often discussed in this context and there is a clinical challenge that currently exists in interpreting time to event endpoints in single arm trials. One potential solution that has emerged is the use of well-constructed externally controlled designs. However, primary methodological concerns still remain in the ability to balance prognostic factors and account for confounding which could influence the evaluation of treatment benefit in the absence of randomization.

So real world data has a potential to be useful when done carefully and also may be useful in

understanding drug effects among underrepresented populations to advance health equity and in molecular subgroups.

I'd briefly like to mention that the Oncology Center of Excellence has several efforts aimed at advancing real world data for rare cancers and includes engagement across the Agency. A new program to advance drug development for rare cancers was just formed in OCE and is led by Dr. Martha Donoghue. The FDA Oncology Team discussed earlier today the example of selumetinib among others and gave a perspective on this development in OOD and OCE. And just two months into this year, the FDA has approved four new drugs for patients with rare diseases in the areas of hematology and oncology.

Furthermore, in 2021, the Office of Oncologic Diseases approved over 35 new or supplemental applications to treat patients with rare cancers. So touching on each of our focus areas and the area of engagement, we have worked with several patient advocacy groups through OCE Project Community and have participated in rare cancer forums and meetings

discussing external control designs, registries, and common control arms to create robust discussions on ways to advance the field.

In the research collaborations space, there is a collaboration through the CURE Drug Repurposing Collaboratory convened by the Critical Path Institute in collaboration with FDA and NCATS to validate real world data to advance drug repurposing for diseases with the highest levels of unmet medical need. OCE is specifically collaborating on methods to develop a rare disease app and case report forum similar to the initial app in infectious diseases that is currently available for repurposed drugs to hopefully lead to new discoveries.

In the regulatory aspect, I just mentioned our recent drug approvals and the most recent peds ODAC focused on how real world data and patient reported outcomes might advance drug development for pediatric oncology and briefly mentioning policy as well, there are several guidances available that have been recently released including guidances on real world evidence and other methods that can help propel

development in rare cancers.

And, finally, I'll conclude by mentioning a recent publication around the use of external control data as well as the public-private partnership with Project Datasphere to advance efforts on data sharing that includes exploration of external control methodologies.

So with that, I would just like to quickly acknowledge appreciation for all of the OCE RWE team, especially Dr. Paul Kluetz for his leadership in building this program and Team FoRWD, our multi-disciplinary team with diverse expertise which includes rare cancer experts. I would like to acknowledge my colleagues and thank you all for your attention.

DR. RETZKY: Thanks so much, Donna. That was really terrific. Just as a reminder, please, if you have any questions, put them in the chat bubble that's at the bottom of your screen. I'm going to introduce our next speaker, it's Sara Brenner who is from the Center for Devices and Radiologic Health and Sara will be talking about health technology in rare diseases.

Sara.

MS. BRENNER: Fantastic. Thank you so much. And thank you for the invitation to join the panel today. This will be a little bit of a switch in focus. As was mentioned, I'm from the Devices Center and specifically the Office for In Vitro Diagnostics. So we're going to talk through a little bit about how the device center approaches health technology, data, rare diseases, and I'll give some very specific examples of how in vitro diagnostics are used in that context.

So I believe a previous speaker earlier on today from my Center has already covered collaborative communities but I wanted to highlight this and I'll highlight a few different aspects of what goes on in CDRH outside of our office and across the other offices as well as across the Center to address some of the needs of this community and this stakeholder group and the focus on rare diseases. So as was previously mentioned and again with some of the speakers in this panel, there are a lot of different mechanisms that we have at CDRH to engage with

different stakeholders and get feedback and input from industry, from public and private entities including academia from the general public and from patients. So for more information on how we do that specifically at CDRH, you can check out our website. I'm happy to take questions afterwards as well.

I just wanted to give a few examples and these are again going to be different than the types of engagements that you see from other Centers at FDA, but those have focused on a variety of different applications with regards to devices, so you see imaging, ophthalmologic imaging. We have NESTcc which is a collaborative community for health technology coordination, laboratory practices and pharmacogenomics, liquid biopsy standardization alliance, we have quite a bit of activity going on in AI and ML and no doubt it was mentioned, I'll mention that again as we move on through some different examples, but with regards to device data and particularly diagnostic data, once you aggregate standardized, harmonized and aggregate that data, helping to perform enterprise-wide analytics is an important part of what

we do, especially when devices are integrated with software. We have cases for quality, heart valves, wound care, pathology, and so on and so forth. So this gives you a little bit of an idea of the different type of medical product spaces that we work in in the device center and also mention since I hinted at digital, we have a Digital Health Center of Excellence. So we all work together across the Agency but then also with stakeholders in the community to address a number of different conditions including rare diseases and their conditions.

This is going to give you an example of a little bit deeper dive on one of the examples in the previous slide which is the Liquid Biopsy Standardization Alliance. So you can see a few different entities here and different ways in which we sort of engage the private sector. One that we often highlight is MDIC or the Medical Device Innovation Consortium. We have a few different, actually many different lines of effort and specific projects under MDIC and some of those focus on and touch on rare diseases as well.

With those broad sort of overviews, I wanted to highlight a specific exemption and device pathway that is unique to our center that we leverage quite a bit in the in vitro diagnostics office that I sit in. So humanitarian device exemptions and humanitarian use devices are intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect no more than 8,000 individuals in the United States per year. So to the extent possible and consistent with the protection of public health and safety, and consistent with ethical standards, the purpose of this program is to encourage the discovery and use of devices intended to benefit that population. So to just kind of unwind that, you know, what we look at when we evaluate devices similar to drugs and biologics is we're looking for risk/benefit analysis and we're looking for the sponsors, whoever is submitting the application to reach a threshold with regards to validation data that gives us confidence that that device is going to perform for certain populations where the benefit exceeds the risk. And so from the perspective of a medical

perspective, this is the core issue with regards to how devices are rolled out and for which populations they benefit.

One of the challenges as so eloquently highlighted by the previous speakers is acquiring enough data to reach that threshold and gain that level of confidence. The same general principles hold true for diagnostics reviews and device reviews and so when we're dealing with small populations or rare conditions of rare diseases, achieving that threshold, reaching that threshold with regards to data collection analysis is a difficult thing. It's challenging for sponsors. And so we have a variety of different mechanisms and pathways that we try to be flexible on to encourage innovation in these spaces where we know it's hard to innovate and it's hard to collect enough clinical and analytical validation data to reach the thresholds for authorization or approval.

So these are important pathways and they're definitely worth taking a look at if you're interested in the regulatory details and what happens under the hood. There is a link there and I could certainly

provide it afterwards as well. I'm going to give a few examples just to make this a little bit more realistic.

One example is this assay. It's a molecular-based HDE and so this in vitro diagnostic test was intended or is intended, I should say, for the qualitative detection of this particular gene rearrangement and fresh bone marrow samples with patients with a rare disease and a high index of precision based on karyotyping that gets a little bit jargony pretty quickly but it's an example of how we're using a laboratory diagnostic test in this particular assay that went through this pathway for a small population or population where we wouldn't expect to have many people being enrolled.

This is the second example of the molecular-based HDE. It's another assay and this is an in vitro diagnostic test intended for qualitative PCR or polymerase chain reaction detection of another mutation from fresh bone marrow samples in patients with aggressive systemic mastocytosis. So again, another example where the rubber meets the road and

that pathway for a particular molecular diagnostic test that's come through this pathway.

Another big area, this is sort of an umbrella area where companion diagnostics are used to meet the needs of a smaller population. Companion diagnostics are those that are used to help inform a therapy. So we work in CDRH and my office in vitro diagnostics with CDER, the drug center, on some of these types of applications. So that's where there is really leveraging of expertise across the Agency.

Companion diagnostics, they're tested or required to determine whether specific drugs should or should not be administered to a patient and validation of this test comes from a successful drug trial. There are a variety of different challenges that can arise and we work through those collaboratively with our colleagues in CDER. We do bridging studies in a variety of different types of approaches to help those products reach the thresholds that we need.

I wanted to give one quick example, or a couple of quick examples, and I just talked to one of my colleagues who works with a lot of these for cancer

diagnostics. The first companion diagnostic that was done is a de novo for a non-oncology rare disease was recently approved or authorized, so we've done at least one for a non-oncology rare disease but most of the diagnostics that we deal with, at least in our office, for rare conditions do have to do with cancers.

There is another example I'll give which is Fragile X syndrome. That was a first authorized test to detect Fragile X. It's a molecular test that went to market in February of 2020 and there are quite a few others that are listed on the website, but I think we're running short on time, so I'm going to pause there with those specific examples and we can get into them more if we have time.

I know this was covered quite a bit already but I just wanted to highlight that we also in CDRH use real world evidence and data in regulatory decisions. I think that traditional, some of the challenges as well as the benefits and limitations have already been covered and they're generally the same across medical product spaces including devices and diagnostics. But just to highlight that we also

use these approaches.

Again, I don't want to -- since this was covered a little bit, maybe what I'll do here in addition to what's on the slide is talk about how this is hitting the road in our Center specifically. As folks are aware, COVID diagnostics have been one of the three main medical countermeasures and I've been involved on the frontlines of the COVID response for two years straight in diagnostics. So this has been sort of a national demonstration project to look at the balance of data collected pre-market and post-market from a particular set of diagnostics and that's COVID-19 IVD and how we balance looking at what data we used in the pre-market space versus the post-market space and help us to understand how these devices are performing in the real world once they go to market. Under emergency use, of course, the bar to market is lower than under full market approval so it's especially important to look in the immediate post market space and see if there are any signals with regards to how those devices or how the tests in this case were performing. So that is also true when we're talking

about other IVDs that have gone to market.

In general, it's relevant to this discussion for rare diseases because when you have limited data, again, extracting data across what we call the total product lifecycle which is a balance between pre- and post-market becomes especially important and it highlights an important way in which we're looking at flexibility and decrease in burden on developers and sponsors who come in to address needs that otherwise wouldn't be met or are hard to meet.

So we've been doing this for a while, the total product lifecycle approach and supporting and advancing real world data and evidence. As I already mentioned, we do a lot of engagement with stakeholders and these stakeholders help to guide our thinking and help to inform us with regards to looking at how creatively we might be able to accept data from nontraditional sources and also aggregate and standardize data so that we can really extract as much information as we would want to.

These are just a few of the different focus areas that we have going on in diagnostics: Real

world evidence, clinical diagnostics, health data infrastructure. We do quite a few evidence accelerators. We just actually launched a couple of pilots in terms of evidence accelerator generation focused on COVID but we can do that for anything within our purview with regards to devices or diagnostics and we try to promote innovation. So that's a thread that has sort of also kind of carried through many of the previous talks.

I think this is my last slide and it's just to say that I have to acknowledge, for folks that have brought in or sponsors, anyone who is interested in this space has brought applications into our office. We've had a lot of workflow challenges because of COVID and I know that's true of a lot of the offices and Centers are certainly feeling that burden here as we stretch into the third year of the pandemic. But I had to just acknowledge that these categories of IVD resubmissions are suspended but can be accelerated and we're hoping to accelerate them as the burden lightens from the pandemic and some of the programs that I mentioned fall into that category, so it's why I

mentioned that as part of this talk.

One thing I wanted to address which is part of the questions and I'll be brief on it and we can move on had to do with how can the community help us acquire high quality data? Again, I'll give an example that's fresh in my mind because I've been working on it every day for two years and that's COVID data but it exemplifies any sort of data.

So of the things we've been trying to work very, very aggressively with with the community and stakeholders including our sponsors, so the test makers essentially, is how can we identify core standard datasets and implement diagnostics data standards? What I mean by that specifically is which are the key pieces of data that a diagnostic test captures, how can they be coded in an underlying way using specifically HL7 messaging which is what laboratories use or mapped over to fire standards so that the data can flow into EHRs, how can we ensure that that data is standardized and harmonized as upstream as possible so that anybody who is managing or handling or transmitting that data downstream,

including ultimately the recipient that in a clinical setting or public health authority and in this case FDA, can aggregate and utilize that data from a regulatory stance?

So that's a big, huge challenge and we're sort of swimming in data in some sense, but not able to use all of that data because it's not been standardized and harmonized. So this is like the crux like kind of a bedrock issue when we're talking about trying to get the most out of the data that we have at hand and we're working really hard in that regard with regards to diagnostics and we have some new programs -- - well, they aren't new, but they've been going on for a while but we have new funding to really hit the gas on these types of programs - and I think that we'll benefit not only the diagnostics that we're dealing with today but those that could benefit into the future and certainly diagnostics used in the companion diagnostics program in the HDE and HED programs that I mentioned will also be feeling those effects. So I will turn it over. Thank you.

DR. RETZKY: Thanks so much, Sara. That was

really interesting. Our next speaker is Weida Tong. He is from the National Center of Toxicological Research. Weida.

DR. TONG: Okay. Well, thanks, Sandy. I have to say, I've very much enjoyed learning the perspective and efforts from our sister Centers about their efforts and their rare disease. So I'm going to add a few points from my Center into this discussion. Now, my role at NCTR is to address biological questions with computers. So today I'm going to talk about how we approach a rare disease with the computational approach.

So personally, my own introduction to rare disease is entirely accidental and actually, this whole rare disease issue was presented to me in a personal form. About 15 years ago, I had a young couple to work in my group and we were very close. They had two young boys about two years apart and they noticed that the younger one was much energetic and active than the elder brother, so they brought the elder son to many doctors for diagnosis which in itself was a frustrating journey since most doctors

won't be able to tell what's really going on with their boy.

After six months of struggling and finally they were told that their son had a rare disease called metachromatic leukodystrophy. Now, this is the first time I'd heard about that there is such a thing called a rare disease, let alone this specific disease. So later on, I learned that metachromatic leukodystrophy is a rare genetic disorder that caused the fatty substance to build up in the brain. It is a hereditary disease and both parents clearly carried that allele so that the chance of an offspring to have a disease is around 25 percent. By the way, their younger son actually is okay.

So in the following few years, I witnessed the tormented experience that the young couple went through and we tried very hard to help and we made a lot of the calls and read a lot of the literatures and then we realized that there were really not much we can do to help and particularly from the therapeutic point of view because there were not many therapeutic options available for most rare diseases including

metachromatic leukodystrophy.

So with that said, we did pick up a few ideas along the way and we also formulated our own opinion about the rare disease. We really feel that our computational skill could be useful to help out the development of the treatment options for the rare disease. Now, we know that rare disease only impacts a small number of patients so that's why not many doctors are specialized in this field and not many drugs are available. But this should not be interpreted that the rare disease is difficult to treat.

Furthermore, we are arguing that there might be already some FDA approved the drugs on the market that can be used for the treatment of the rare disease. Now, this assumption is supported by two observations. First we notice that on the patient discussion forum, some drugs were mentioned to treat a certain rare disease where the drug is not designed to. This is what we call the off-label use which actually is quite common.

Second, we also noticed that there are quite

a number of clinical trials that's on existing drugs for a disease. Now, these drugs are originally developed for entirely different reasons. So in our field, these kind of off-label use of existing drugs for the different disease is called the drug repositioning or sometimes also called a drug repurposing or drug reuse. Traditionally, this type of approach is largely depending on so-called happy accident. As a matter of fact, Viagra is a great example. Viagra is originally designed to pump blood for the treatment of the heart disease, clearly blood is pumped to the wrong place and voila, we had a blockbuster drug for recreational purpose.

Another good example is thalidomide was originally used for morning sickness in pregnant women but instead it has caused birth defects. However, later on people find out that thalidomide was effective for the treatment of leprosy and lupus. Nowadays it has been used for COVID-19 as long as we keep it away from the pregnant woman.

So clearly, the potential benefit of repurposing FDA drugs is quite attractive and

appealing because we have considerable scientific evidence about the risk so that they are repurposing, may require less time and less expense than the developing a new one.

However, this happy accident approach is not sustainable because it could miss opportunity to identify these drugs that have had not happy accidents yet. So this is where the computational approach can be very helpful because the computational method allows rapid assess and access all the drugs for their potential to treat the rare disease. So our computational approach actually is quite simple. It's based on two assumptions and if two drugs are very similar, and we believe both drugs can be used to treat the same disease, now if two diseases are similar and both diseases can be treated with the same drug. So what we did is to group all the FDA-approved drugs into multiple buckets based on their similarity and we also group rare disease into multiple buckets by their similarity. Then we're matching the drug buckets with the disease buckets. So in the end of the day, we will be able to propose a list of the

drugs candidates for rare disease. Currently we studied cystic fibrosis, lipid syndrome, we've also found that the cancer drugs actually can be effective for some rare disease. Most recently we are extensively using artificial intelligence in repurposing for the treatment of the rare disease. I stop here and thank you very much for listening and I am looking forward to your questions.

DR. RETZKY: Thank you so much, Weida. That was really interesting. I do have a question for you. Is there something -- can you point to any drug that is currently in clinical trials or has been commercialized using the computational methods that you described?

DR. TONG: For rare diseases themselves, we did not see that and so what we did at NCTR is we're using the computational method to propose a list of the drugs for the different rare diseases and then we follow up with experiment verification because the drugs were developed for the treatment of certain disease normally have a very different dose if you want to repurpose it for the different disease. So

that part and we have to go through experimental verification. So from our lab we have not really reached that point yet but on the market, we're also not aware there is a drug solely based on the computation.

DR. RETZKY: Okay. Thank you. Well, we have a couple of questions that we have. The first question that we have from the audience is this, and I'm going throw this to you, Michelle. How can academics and others improve quality of shared data in analytics?

DR. CAMPBELL: Yeah. Thank you, Sandy, and thank you to whoever asked that question. That's a great question to ask because the goal of RDCA-DAP is to actually try to harmonize and increase and perhaps even teach and learn to other stakeholders about data standardization, appropriateness of how to collect data, critical variables that may need to be collected and how to work under the fair principles when collecting data. So that is a goal. We know that every investigator probably has their own unique way of collecting data but we do recognize that when we need to pool this data together and curate it, we do

need to have a way to have our data try to be as standardized as possible. So that is one of the outcomes that is going to be examined and looked at and I think this is a continual thing that I think all of us as stakeholders and all of my colleagues in the other Centers will probably all be collaborating on at some point because data stances are critical. We know that we apply them to the data that we see that comes in into our applications but we know that it's needed and we know that if we can all learn together on how to really collect good quality data through data standards it will only enhance the abilities of what we can do with that data.

DR. RETZKY: Thank you. Sara, we had a question about pumps and health technology and pumps. Could you address that?

DR. BRENNER: I'm not really sure which pumps. So if the person who asked the question wants to be more specific, I can give it a try. I mean, generally speaking if the pump is part of the medical device and it's a regulated medical device, then yes, that would fall under CDRH and our Center. Not my

office which deals with diagnostics, but the CDRH device center.

DR. RETZKY: So I'm not -- the question was general, but what I'm thinking is in terms of health technology and all things that are available to make products more autonomous with some other innovations. Is there anything that's happening in the device world using technology to allow, say, others, even remotely to work on pumps?

DR. BRENNER: Oh, sure, so if we expand it to that, then absolutely. So one of the things that requires sort of cross office collaboration within CDRH is addressing these new emerging technologies and this is an exciting area. My bias is a bit showing here because I'm a bit of an innovator and regulators closing and have a background in nanotechnology and health technology. So I think what we're seeing is a convergence of different types of products with each other in unconventional ways. Pumps might be, depending on what that example is, one type of particular instance we could talk about and you'd raised the idea of more autonomous or remote

monitoring of patients, for example, telehealth services, there's certainly another area that's really growing and we spend a lot of time thinking and talking about the stakeholders in CDRH.

I think with regards to these conversion technologies, another example I can give is with diagnostics and that's again going back to COVID, but this is true for a lot of different types of diagnostic technologies. When you remove the device, in this case a diagnostic from its traditional setting like a laboratory and you move it into a point of care setting or an over-the-counter setting, there are ways that developers of integrated software and apps, digital tools, for example, like a phone app or a web-based app where patients can interact with an enter data or have data extracted from that device and sent to where it needs to go to a healthcare provider or prescriber, public health department, et cetera.

So those types of convergent technologies we review in-house and we're actually actively recruiting experts in disciplines and backgrounds such as software and cybersecurity, digital health, and those

all have to do with the data that's coming off those devices and how to use it maximally but also how to protect it from a patient privacy standpoint. So I'm not sure, it's a bit of a wandering sort of response, but I guess that's to say yeah, it's all fair game and it's exciting new territory.

DR. RETZKY: It's a general question but given the desire to try to decrease the burden on patients and caregivers and their families, I think it's a natural question to ask about even something like pumps, what could be done from a technology standpoint. But there is another question that we have that I want to get to. Donna, I'm going to ask if you can take this. It's not specific to cancer, but the question is, we are using a drug off-label and it works wonderfully but we need to get it on-label. So how do we help our doctors in getting this to happen? What would you suggest for that?

DR. RIVERA: I think this maybe goes back to the theme of the day which is data. We use rigorous evaluation of data and scientific evidence to meet substantial evidence in standards and allow drugs to

be approved so I think this really gets back to finding ways to evaluate off-label use in a rigorous setting. Depending on what evidence generation is appropriate, whether that evidence generation be in a randomized controlled trial or in a pragmatic trial or use of real world data and certainly that depends on the specific clinical setting, so I would always recommend speaking early and often with the relevant clinical review division in terms of designing and thinking about that but in order for it to become labeled and an indication that's from that standpoint, something the FDA could approve in labeling the requirements would really rely on high-quality, rigorous data and evidence to support that potential indication.

DR. RETZKY: Yeah, I totally get what you're saying. It's -- there's a lot of drugs that are used off-label but there's a lot of work to be done to get them on-label. We have a question for you, Weida. The question is, are you using artificial intelligence and computational biology to examine structure activity relationships and extrapolate that into drug

repurposing?

DR. TONG: Yes, we do, and this is just one of the approaches we use. Actually we use more than just a structure-activity relationships and the one specific approach we use the most actually, look at the rare disease patients the gene expression profile and then we look at the drugs gene expression profile and these gene expression profiles goes the opposite way, then we consider this as one of the match. So this is looking at gene expression profile. We also look at the pathways and protein-protein networks. So we are trying to gather as much information as we can to match the drug to the rare disease.

DR. RETZKY: Okay. Thank you. Dr. Witten, one question for you. You talked about the Bespoke Gene Consortium. It's all AAV vectors, right? There's no other type of vectors that are being used?

DR. WITTEN: Yes, that's correct.

DR. RETZKY: So when academics and industry are using those gene vectors, are they pulling any preclinical data so they don't have to keep doing the same animal studies over and over again?

DR. WITTEN: So right now the program is -- that's a great question, by the way. Right now the program is still getting developed and gearing up to start. So I just want to make that clear. It's not already -- these studies are not already ongoing. But that is the goal. The goal is that there will be a discussion of all aspects of the study, the product, the testing, including the preclinical testing, the clinical study design. Among the groups working on the different studies that will be part of this exercise and to try to see what kind of common themes or common knowledge might help develop more standardized protocols for how you would assess some aspect of the development.

I can't be really more specific because I think it depends on what part of it, but you -- the idea is to share the data as we go along and the approach and see what we can learn from that sharing. Because as I think someone has already mentioned, and I mentioned, but a lot of times the development gets done in a silo and what happens is one company learns from that company's experience but there may be

another company that's doing the same kind of testing, the same kind of learning and it may be that it's, it could be if it were informed by some knowledge from the other development program, that might be helpful. Not that I'm saying everything is going to get shared, but just there are some things that you can imagine might be gained from sharing development, especially from these teeny tiny diseases where there really might not be the appetite to do these siloed development programs for every single disease. I just think it might not end up working out to meet people's needs fast enough.

DR. RETZKY: Okay. Well, we're at time. I can't thank our panelists enough. That was a very interesting presentation from everyone. Thank you so much for participating today. Very interesting information. Thank you very much. I'm going to hand this over to Lewis and we're going to go ahead and go to the open comment period. Thank you. Take care, everybody.

DR. FERMAGLICH: Thank you, Dr. Retzky. We'll finish up FDA's Rare Disease Day 2022 with the

open public comment period moderated by Teresa Rubio from OOPD. Teresa.

MS. RUBIO: Hello. My name is Teresa Rubio and I will be moderating the open public comment portion of the meeting. Today we have 13 speakers registered. These speakers signed up on a first come, first served basis. Each speaker will have two minutes to speak. If a speaker finishes early, we intend to move on to the next speaker. If a speaker is over the two-minute mark, I will kindly ask you to stop.

We will call each speaker by their name. When it is your turn, please turn on your camera and unmute your microphone to provide your comments. For transparency purposes, we ask that you please disclose if you are affiliated with an organization or if you have significant financial interests in rare disease medical product development.

As a reminder, you also have the option to submit comments to the docket which will remain open until Friday, April 8, 2022. I will now call the first speaker in the open public comment period. The

first speaker is Nina Hunter. Nina.

MS. HUNTER: Hi. I'm Nina Hunter, VP Regulatory and Science Policy of REGENXBIO. My colleague Anne Ganot from Solid Biosciences and I are here representing the Pathway Development Consortium, PDC, a public-private collaboration. The PDC is a multistakeholder initiative which aims to identify, develop, expand and maintain pathways to effective AAV gene therapies for patients diagnosed early in life with rare diseases. The PDC seeks to achieve these goals by bringing together broad and diverse group of stakeholders from the rare disease and AAV gene therapy communities including patients, industry, regulators, academia and payers among others for meaningful scientific and policy discussions.

The PDC was cofounded because of a shared vision that collaboration can meaningfully guide how AAV-based gene therapy treatments can be more rapidly made available to patients and it seeks to bring together the diverse perspectives in the rare disease community with the interest of the patient at the forefront.

Broad stakeholder engagement has been recognized as an important factor by the agency to facilitate and expedite the development of AAV gene therapies for rare diseases. Recently, the PDC published a draft white paper which proposes a framework that can be applied to AAV gene therapies to facilitate the use of accelerated approval pathway of the FDA. The white paper identifies different categories of AAV gene therapies that target the underlying monogenic changes that cause disease and proposes generalized approaches that would clarify the evidence needed to support FDA approval. The PDC is actively seeking feedback on this framework which is available on our website at pathwaydevelopmentconsortium.org.

AAV gene therapies are emerging to address serious rare diseases with unmet medical needs. It is imperative that the community of patients, providers, AAV gene therapy developers and others work with FDA to expeditiously and safely bring effective treatment options to patients. Thank you for your time.

MS. RUBIO: Thank you so much, Nina, for your

comments. Our second speaker will be Annie Ganot. Annie, if you could unmute your microphone and turn on your camera. Thank you so much.

MS. GANOT: Thank you so much. I am Annie Ganot, VP of Patient Advocacy at the Solid Biosciences and mother of an 11-year-old boy with Duchenne Muscular Dystrophy. Following my son's diagnosis, I co-founded Solid Biosciences to advance the best science and accelerate the discovery and development of meaningful treatments that may benefit all patients living with this devastating condition. The PDC's activities in Duchenne kicked off with a roundtable discussion held last year to focus on this progressive muscle-wasting genetic disease. Children with Duchenne are typically diagnosed between the ages of three and five years old. They lose the ability to walk by their early teens and succumb to heart or respiratory failure in their mid-20s.

The roundtable focused on finding a path forward for meaningful endpoints in clinical trials and brought together more than 120 attendees from the Duchenne patient community, industry, academia and the

FDA. The PDC also published a white paper identifying areas where attention is needed to facilitate development of AAV gene therapies for Duchenne.

Work on Duchenne priorities and the application of the framework is continuing today with a working group that is exploring the use of FDA's accelerated approval pathway for AAV gene therapies intended for patients with Duchenne. The FDA's accelerated approval pathway is an important tool used to bring the therapeutic options to patients and demonstrates FDA's flexibility as a regulatory agency. We look forward to working with stakeholders including the FDA on this. Thank you so much.

MS. RUBIO: Thank you so much for your comments. Next up we'll be hearing from Bridgette Reynolds. Bridgette.

MS. REYNOLDS: My name is Bridgette Reynolds and as far as disclosures are concerned, I sit on as a patient advisor (Inaudible) of Northwestern university research laboratory. I'd like to say (Inaudible) patients voice and experience is paramount (Inaudible) outcomes and drug therapies for smaller rare disease

populations, persons with variations of rare diseases and the (Inaudible) near 25 percent variation of sickle cell anemia minority genotype within a rare disease (Inaudible) sickle cell disease, yet there are times when it's not (Inaudible) much of a difference.

Growing up I had many -- had experienced many pain crises that were in in my extremities which changed as I got older and became in my chest and I was vulnerable to chest syndrome, ended up in the hospital and in comas and had this really, really -- my hematologist described a wild ride. Pain can be merciless and growing up there wasn't a drug therapy, I didn't expect to live past 20 years of age.

You know, as science progressed for new drugs on the scene and new therapies, and (Inaudible) those long-awaited drug therapies were marketed. When they were marketed, I availed myself to them. I experienced serious side effects that (Inaudible) then a specialty pharmacist recommended (Inaudible).

How do you overlook (Inaudible) disease claim to have (Inaudible) researching how (Inaudible) only the majority heterogenous patients wonder if such

drugs applied to us. (Inaudible) still without a drug therapy (Inaudible).

MS. RUBIO: Thank you so very much for your comments. We've hit the two-minute mark but thank you so very much. Next up we'll be hearing from Amy Skiva. Amy, if you could -- there you are.

MS. SKIVA: Thank you. Hello. My name is Amy Skiva and I'm the Executive Director for the Lung Transplant Foundation. Our mission is to improve the lives and provide better outcomes for lung transplant patients and their families. We do this in a variety of ways by providing resources, mentorship, and support directly to our community as well as advocating for research for lung transplant patients, specifically in post-transplant rejection.

As a representative of the lung transplant patient community, I would like to bring awareness to a rare disease impacting lung transplant patients, bronchiolitis obliterans syndrome, or BOS. BOS is a 100 percent fatal disease that affects up to 50 percent of all lung transplant patients within the first five years post-transplant.

We will be engaging with the FDA in the first externally-led Patient Focused Drug Development meeting for BOS this year in June. We are encouraged by the FDA's interest and motivation to learn directly from patients and caregivers about the impact of BOS on our community and the current unmet need for an FDA-approved therapy. Thank you so much for your time today and for your dedication to the rare disease community.

MS. RUBIO: Thank you so much, Amy. Next up we'll be hearing from Julie Breneiser. Julie.

MS. BRENEISER: My name is Julie Breneiser and I'm the affected parent of two with Gorlin Syndrome, a rare genetic illness that can affect every organ system. The most common symptomatic manifestations are invasive tumors of the jawbones and basal cell carcinomas or BCCs. Some of us will have over 1,000 in our lifetimes. Some have died due to metastatic basal cell carcinoma. Gorlin Syndrome is one of the many serious rare diseases with no FDA-approved treatment.

For this reason, when evaluating treatments

and products for all with rare diseases, we urgently hope to see an even greater Agency-wide commitment to preside with the utmost regulatory flexibility including rare disease-specific approaches. Regulatory standards applied for the evaluation of common disorders are not appropriate in rare diseases which must be looked at uniquely to provide new and better opportunities. Without regulatory flexibility, how we feel, function and survive is negatively impacted.

Treatment goals in clinical trials of potential rare disease therapies need to be looked at differently and in most cases lowered for this population. For example, reducing the number of BCCs by 25 percent could result in one quarter of my face being skin cancer free. Alternatively put, a reduction of BCCs by 25 percent could reduce the lifetime burden from 1000 to 750. That’s huge. Reasonable approaches to rare disease trials need to be used including limiting the number of participants. In some diseases there just aren’t enough participants to reach the mandated quotas.

Inclusion of the voice of patients and advocacy groups in the orphan drug designation process is essential. Part of the mission of the FDA is to advance public health. Please provide this needed help to those of us with rare diseases by considering these adjustments when evaluating potential valuable treatments. This will allow individuals and their loved ones --

MS. RUBIO: Thank you so much, Julie, for your comments. We've reached the two-minute mark. Thank you so much. Next we will be hearing from Deb Murphy. Deb.

MS. MURPHY: Hi. My name is Deb Murphy. I am with the Hypoparathyroidism Association. Hypoparathyroidism is a rare endocrine disorder. The parathyroid gland maintains your calcium and your phosphorous and causes muscle tetany, brain fog, and seizures. 37 out of 100,000 have this in the US alone.

80 percent are from neck surgeries and 20 percent are from a much more trickier form to diagnose and we classify those as nonsurgical. They are

genetic autoimmune idiopathic. They include Barakat Syndrome, CASR, ADH1, TBX1, MEND1, Albright's, Hashimoto's, DiGeorge, and then there's also pseudo and pseudo pseudo hypoparathyroidism. These can take sometimes up to ten years to get diagnosed.

Right now we only have standard of care which is calcium and active vitamin D. This sustains us but that's it. Some patients suffer from calcium crashes -- which I'm doing right now -- which can be severe enough to land them in the ER or be hospitalized.

Long-term risk of the standard of care is hypocalciuria, chronic kidney disease, and development of calcium deposits in your brain and in your skeleton. With the help from Ascendis, we were able to do a survey to show the quality of life and we have a poster on our website that would help. It's at www.hypopara.org. Results of this survey underscore the high disease burden of patients with hypopara.

We do have some drugs in the pipeline and they are a ways away. My heart is to see them come faster rather than later. We are rare, we are chronic, and we need your help. Thank you.

MS. RUBIO: Thank you so much, Deb. Next we'll hear from Ella Vellasa. Ella.

MS. VELLASA: Hello, everyone. Thank you for having me. I do not have any disclosures. My name is Ella Vellasa and I am a rare disease patient with cystic fibrosis which is a progressive lung disease. And I've experienced significant health challenges throughout my life and I'm urging stakeholders from industry, regulatory, policymakers to collaborate in supporting the rapid development of novel therapeutics and identifying approaches to examining vast patient existing data to find solutions and treatments.

Many patients with rare disease cannot afford to wait for years for drugs and trials to get to market approval and with the advent of new gene therapies, rapidly expanding the possibilities for viable and valuable therapeutics, patients need emergent IND and expanded access to drugs in trials and experimental therapies as well. There is no time to waste.

The traditional means of clinical trial development must be shifted. There must be devised

with adopted features such as expanding trial inclusion based on accumulating data and elimination of placebo arms, expanding eligibility criteria to include a broader group of patients who experience the breadth of symptoms and disease manifestations is imperative. In rare disease, there isn't a "one size fits all".

Please recognize that patients and families in the rare disease community must fight so much more fiercely to gain access to therapeutics to spur research from biotechs and pharma companies and often even to get a proper diagnosis.

So work to reduce the barriers to treatment access and minimize denial from payers because expensive specialized drugs aren't on formulary.

So on behalf of the cystic fibrosis community and rare disease patients everywhere, I appreciate your considerations in making our lives have a future to look forward to.

MS. RUBIO: Thank you so much for your comment, Ella. Next we'll hear from Jillian Sabia. Jillian.

MS. SABIA: Good afternoon. My name is Jillian Sabia. I'm a registered nurse. My daughter Penelope has classic galactosemia. At eight days old in the NICU, a crash cart rested outside of her room. She had femoral lines, NG tubes, oxygen and her little body was tangled in lines. She survived a late diagnosis of classic galactosemia and as of right now has no cure.

Around her first birthday, I noticed seizures. It took a year to diagnose and treat. I carry a rescue med with me. Every time my daughter sleeps, I think did I miss the big one? Did she die? I live with this every single day. At two years old she started vomiting until her third birthday she stopped walking diagnosed with Chiari malformation.

She had brain surgery to avoid permanent disability. In her short life, she has suffered and struggled. Last summer we joined Applied Therapeutics AT007 drug trial in hope to help her. Last August she couldn't draw, had various delays, seizures, tremors and many other symptoms. Her IEP team at school agreed that she probably would stay in pre-k this year

and next.

As of today, her tremors are now gone, her IEP suggested introducing kindergarten for the rest of this current year. She's counting up to a healthy development for a four-year-old. Her progress is undeniable. The study proves 50 percent decrease in toxic galactitol which could help slow progression of the disease. This is a double blinded placebo trial.

Other moms in the trial, even with a double blinded placebo know they're not taking the drug. You cannot hide the progress of AT007 in other kids. We were denied accelerated approval resulting in a partial clinical hold by the FDA. Extending the placebo aspect is cruel. The progression of the disease continues for many people with CG. Please consider our dilemma as children can progress to seizures and other medical complications at any time. Many adults are in group homes, so please help us stop the progression in our children. Thank you so much for your consideration in this important matter.

MS. RUBIO: Thank you so much, Jillian. Next we will hear from Christine Sailor. Christine.

MS. SAILOR: I am Christine Sailor and I and my 14-year-old son has classic galactosemia as well. Galactosemia is a disorder that only affects a few thousand people in the US and it's a genetic metabolic disorder. My son Jake has lifelong impacts that have included apraxia which is a neurological disorder which affects his speech, fine, and gross motor movements.

Jake receives speech therapy and occupational therapy starting at 18 months old for him to be able to speak, read, write, and move properly. There is a possibility in the future he could face severe tremors and seizure disorders and other neurological complications. Our family has been involved in the Galactosemia Foundation since Jake was two and we have seen the other devastating effects of other children and families in our community ranging from severe mental cognitive disability, infertility in girls and neurological disorders.

Because of these effects on Jake and others, we made the weighted decision to enroll Jake in the clinical trial sponsored by Applied Therapeutics and

their treatment with the drug AT007. Jake started participating when he was 13-years-old and continues today. The participation has been hard on him with the demands of blood draws, testing, and life sacrifices but we believe in this clinical trial and we have seen no ill side effects and are committed to the study. We believe based on the reduction of the biomarker galactitol in this data and the safety of the drug, it should be accepted on the accelerated approval pathway for FDA approval.

We are committed to continuing this study for long-term outcomes. The galactosemia community as well as other rare diseases depend on the accelerated approval pathway. Rare diseases cannot produce the number of participants needed for a clinical trial. Galactosemia has no medical treatment. We ask the FDA to partner with our community in hopes for the AT007 to get into the hands of our community. Every day that passes is another day of worsening affects and we believe this drug can change lives. Thank you very much.

MS. RUBIO: Thank you so very much for your

comments. Next we will hear from Roy Nierenberg. Roy.

MR. NIERENBERG: Hi. This is Roy Nierenberg. I have Huntington's Disease and am part of the Huntington's community and this is the second time I'm talking to the FDA. I did it seven years ago. But I really, so much has changed and I really appreciate it and I hope this is recorded so I can view it in real time and really gather all the things.

I had technical troubles getting on. There was some time when I was -- had double sound. But by background I was a lawyer, an economist in Washington, DC, then a software guy, but now I'm dealing with Huntington's Disease. I'm very positive about what will happen and wish I had seen most of the webinar when I had more questions for you. I don't have prepared remarks but a lot of respect for you and I yield my time to the next person who hopefully will be able to be visible. Thank you.

MS. RUBIO: Thank you so much, Roy, we really do appreciate your comments. Our next speaker will be Ennis Macias Perez. Ennis. Do we have Ennis with us

at this time?

MS. PEREZ: Hi. Sorry. I'm the Principal Scientist at Cumberland Pharmaceuticals. I'm also the principal investigator for the Fight DMD trial, that's the first clinical trial for Duchenne Muscular Dystrophy that was awarded an FDA orphan product clinical trial grant. Cumberland is cosponsoring with the FDA the Fight DMD trial to determine if our small molecule inhibitor aphetrovan (ph.) can prevent the cardiomyopathy associated with Duchenne which is the leading cause of death.

Duchenne, like with other rare diseases is heterogeneous. Even patients with the same genetic mutation progress differently and this includes the heart disease. Our study was designed collaboratively with guidance from patients with Duchenne. We learned a lot from the Duchenne community: what study design features were of value to them like an optional open label extension and what matters most to them when deciding to participate in a clinical trial like assistance with travel and what barriers prevent them from participating such as requiring patients to be

ambulatory or taking or not taking specific FDA-approved medications. With the FDA OPDs clinical trial grant, we launched the Fight DND Trial at six Duchenne centers in the US in 2020 and our first study participant was set to start in March 2020 which was coincidentally and unfortunately when COVID impacted clinical research globally and all our study centers were required to freeze all clinical trial activities including our first study participant's visit. The Duchenne community was incredibly supportive and motivated to return to the clinic not just for their clinical care but also for participation in a clinical trial.

The FDA OPD offered grantees such as myself additional support in the form of a supplemental grant to help manage the challenges caused by COVID. Cumberland used these funds to open more trial centers so that we could expand the access to more Duchenne patients so they can participate closer to home and we opened a cloud-based repository for the cardiac imaging data so they could be analyzed remotely and in real time during COVID and post-COVID as we are seeing

today.

MS. RUBIO: Thank you so much, Ennis, we have hit the time.

MS. PEREZ: Thank you. I appreciate the opportunity.

MS. RUBIO: Thank you for your comments.

MS. PEREZ: Bye.

MS. RUBIO: This now concludes the open public comment period. We really appreciate everyone participating today. I'll now transition to Sandy Retzky to provide closing remarks. Sandy.

DR. RETZKY: Thanks so much, Teresa. Hello everyone, again. it's been a really wonderful day to be with you. We've had an incredible group of panelists and really appreciate all of the public comments we got. You know, I sit here and I'm thinking to myself, what do I take away from today? And I still -- I think what FDA does is really amazing. Patients are center to everything we do. But we understand we need to do more. We need to be more innovative, we need to be more flexible, and we need to be quicker. So we hear what you're saying and

greatly appreciate it. I think I was most touched today by the panel, panel five of the patients who have engaged with FDA. So if there is one thing that I can leave you with personally is please engage with us at FDA. Panel, if you look at the meeting materials, there is information on how to reach us at FDA and how to get engaged with us and we hope you'll really do that. We can't get enough information from you, so please engage with FDA.

I'd ask one more thing - you'll get a survey today about this event. Please tell us what you thought, good things, the bad things, so that we can improve. We look forward to next year's Rare Disease Day and being with you. That's all we have from today. Take care. Have a good day. Bye for now.

(Recording ends.)

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