Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub
Hybrid Public Meeting
October 16, 2024 | 10am-2:30pm *(eastern)*

Transcript

Welcome & Opening Remarks
Susan C. Winckler, RPh, Esq., Reagan-Udall Foundation for the FDA

Susan Winckler (00:00:32):

Hello, and welcome to those of you here in the room and the many of you who are joining us virtually. I am Susan Winkler, Chief Executive Officer of the Reagan-Udall Foundation for the FDA. We are pleased to convene this public meeting in a collaboration with FDA on advancing rare disease therapies through an FDA Rare Disease Hub. For those of you who are new to the foundation's work, we are the nonprofit, non-government organization created by Congress to help the FDA do more to protect and promote the public's health. One way we do that is by convening meetings such as this one to help the agency both share information and hear from stakeholders about important issues. These engagement opportunities help inform the agency's work. Of note, we do not advise the agency on regulatory decision making.

(00:01:23):

Before we begin, we have just a few housekeeping issues. Most of our speakers and several attendees are gathered here in person at the FDA White Oak Campus in Silver Spring, Maryland. We also have a significant number of virtual participants. Because of the size of the meeting, virtual attendee cameras and microphones will remain off throughout the event with one important exception. Those of you who were confirmed in advance to present stakeholder comment will be granted access to unmute and show video during the comment period. We are recording this meeting and will post the recording, along with the slide deck and transcript, on the foundation website, which is reaganudall.org, next week. For our virtual participants, a link to today's meeting materials can be found in the chat now, and those of you in the room should have received materials when you checked in.

(00:02:17):

So let's do a quick review of our agenda. In just a moment, we will open with remarks from FDA's Principal Deputy Commissioner, and then turn to two discussions with leaders from the agency to explore their vision for the newly formed hub. Then we will move to a critical part of our meeting, providing an opportunity for members of the public to share perspectives and experiences. I thank everyone who offered to provide public comment. We received more than 200 requests and regret that we were unable to accommodate everyone's request to speak. But each of you has the opportunity to provide input via the federal register, which is linked from our event webpage. We will include a recap of both the presented and the written comments on our website following the meeting.

(00:03:07):

Now, here's some logistic information that will be tedious for some but is very important to everyone who is providing public comment so you may multitask if you are not. If you are providing public comment, this information is important. We will be providing you three minutes to speak and we are organizing the speakers by topic area. We will begin with those of you who are joining virtually and proceed in alphabetical order by last name. I will provide a rolling list of three speakers so you will hear your name twice before I call on you to present your remarks. For example, we will begin public comment by announcing that our first three commenters will be hypothetically Jane A, Jane B, and Jane C. I will then call on Jane A to present her remarks.

(00:03:55):

For our virtual commenters, when you first hear your name, use the raise hand function. When the speaker before you concludes their remarks, turn on your camera, and then when I turn to you to present your remarks unmute and you will begin your remarks. Our in-room and in-person commenters will use something similar, although you don't have to use the raise hand function, but we will ask you to proceed to the stage and move to an empty podium. This allows us to keep the commenting moving through. I will note that we will turn off the microphone at three minutes but appreciate you sharing the insights that you may within that timeframe.

Principal Deputy Commissioner Remarks

Namandjé Bumpus, PhD, Office of the Commissioner, FDA

Susan Winckler (00:04:38):

So now we'll pause from logistics and turn to substance, which is far more important. Thank you all for gathering today and let's turn to our opening remarks. We're thrilled that Dr. Namandjé Bumpus is joining this event to provide opening remarks. Dr. Bumpus is the Principal Deputy Commissioner here at FDA, a role that she has held since early this year, and in that leadership position will help set the stage for our conversation today.

(00:05:06):

Dr. Bumpus, I'll turn the podium to you.

Dr. Namandjé Bumpus (00:05:14):

It's a very large photo of me up there. All right, thank you everyone so much for being here, I'm really excited and honored to have the opportunity to open this public meeting in support of this new initiative. So the hub represents an exciting model, a new model, for inter-agency collaboration that will enhance and formalize already existing collaborations and initiatives in the rare disease space. And importantly, it includes critical leadership involvement. We have worked closely with Doctors Cavazzoni and Marks and their teams as they thoughtfully develop the plan for the Rare Disease Innovation Hub, and I know that they are personally committed, as I am, to its success. So in the past several years, there have been a range of exciting advances in science technology, and I'm a biochemist and molecular pharmacologist so when I think about science generally and some of the things I see coming ahead that excite me, for instance, we're starting to get an understanding of biology at the level of the single cell. We're seeing more use of genomics, and proteomics, and integration, and data science, and artificial intelligence, so science is really accelerating and there's a lot that we can do to harness it. But we know that there's still quite a ways to go in understanding many diseases from the science and also the natural history.

(00:06:34):

We also understand that there remain challenges faced by patients with rare disease as many rare diseases still lack treatment options, leaving patients with unmet medical needs, and we know that there are complex development challenges. So we understand that people with rare disease have a unique journey, that many conditions lack effective treatments, leaving patients and their families with limited medical options and significant unmet medical needs, and that the rarity of these diseases as well as lack of understanding of the disease in some cases presents substantial challenges for clinical studies and the development of life-changing therapies.

(00:07:14):

But with all of this in mind, I'm very enthusiastic about the launch of the Rare Disease Innovation Hub because I think that it really represents an opportunity to leverage our vast cross-center expertise to spur the development of treatments for rare disease, and for issues broadly affecting rare disease drug development, to have greater understanding of those broader issues. The launch of the Rare Disease Innovation Hub marks a pivotal moment in our commitment to addressing these challenges and by bringing together experts from across our organization we hope to accelerate the development of treatments for rare disease.

(00:07:50):

So the hub will bolster and foster collaboration and advance regulatory science. We'll do this by fostering open dialogue and knowledge sharing and, through that, we can identify new approaches to drug development and overcome hurdles that have traditionally impeded progress. Importantly, by serving as a single point of connection and engagement with the rare disease community for matters that intersect CDER and CBER, we will help to ensure that the work the hub is undertaking to help advance rare disease treatments is informed by priorities and feedback from the rare disease community, including important feedback that we'll receive today.

(00:08:31):

The new director for strategic coalitions for the hub who we are in the process of hiring will work to engage external stakeholders so that we can be as transparent as possible, within our legal limits, about the work of the hub. I'm excited about the potential of the hub, as I've mentioned, really to advance what we can do around development and to advance science. I think that by working together we can improve patient outcomes and we believe that we can bring hope to countless individuals and families affected by rare disease to further facilitate the development and evaluation of safe and effective therapies. We're committed to transparent communication and look forward to continuing this dialogue with the rare disease community through this meeting and of course beyond.

(00:09:15):

So thank you again to all of you, both here and online, for all of your engagement. It's very important for us in our work. I'm really looking forward to today's event, so thank you again.

A Conversation with The Rare Disease Innovation Hub Co-Directors

Patrizia Cavazzoni, MD, Center for Drug Evaluation and Research, FDA
Peter Marks, MD, PhD, Center for Biologics Evaluation and Research, FDA

Susan Winckler (00:09:32):

Thanks so much, Dr. Bumpus. I'm going to invite Doctors Marks and Cavazzoni to join me on the stage and we're going to have a conversation about how the hub is emerging and what it is that folks should know about it.

Dr. Patrizia Cavazzoni (00:09:45):

Where would you like us to sit?

Susan Winckler (00:09:46):

If you take the two far, I'll take this close one. See, look at that immediate collaboration right there in deciding where we sat, it works so very well. So as I noted ... Well, this is the part of the conversation where we want to hear from the two leaders of the hub, and that being Dr. Marks as Head of the Center for Biologics Evaluation and Research, and Dr. Cavazzoni for the Center for Drug Evaluation and Research, and so let's jump right in. I'll note that I have observed, certainly the centers across FDA, you work together on a number of things. But this is a new collaboration and I think a new type of collaboration with such intentional interaction and engagement. I'll turn first to you, Dr. Marks, if that's all right. Would you describe the mission for the Rare Disease Innovation Hub, which I'm going to call the hub for the rest of today, if that's okay?

Dr. Peter Marks (00:10:54):

That's fine. Yeah, we can call it the hub and people will know what it hopefully means. I think this is really an endeavor to build upon something that's already ongoing. We already have collaboration across the centers but I think there's no doubt that we can do much better if we leverage resources. I think the idea is having a interchange between the two centers to have essentially a ... It is not a center of excellence per se, but it is a center of excellence. It's not a named center of excellence but it will have, I think, a lot of the moral equivalent of that, in that it is a virtual center of excellence. The idea is not to have people's reporting structures disrupted and have people worry about those issues, but to be able to have people in each of the centers collaborate together on what is, for the agency, a very large topic.

(00:12:02):

I think half or more than half of the products in our respective centers are now rare disease products and I think one of the questions that I might as well answer right up front is why not have a traditional center of excellence? The answer is that so many of our products are rare disease products now that it makes much more sense to leave people in place where they're reviewing other products that are part of the portfolio and have them collaborate across centers and have us do that rather than try to do something that's really not possible even. Because it would be such a large entity that it would be unwieldy and it would leave the rest of our review bereft of needed resources. I think this allows us to leverage the personnel in a way that I think will allow us to bring out the best in this. And after all, many of the expert reviewers that are reviewing more common diseases are also experts in these rarer diseases as well.

Susan Winckler (00:13:15):

So if I hear you correctly, then part of the vision here is how do we help those individuals who are doing this work and engaged in this work collaborate with each other, and being able to build from that experience and strengthen it but they're staying in place and enhancing. Is that?

Dr. Peter Marks (00:13:37):

Right. The idea is that, I think what the hub will bring us is the kind of enhanced communication that we need both internally and externally. It will bring us the coordination between the centers that I think will really help us make sure that things like biomarkers are coordinated when we give answers and responses to sponsors. It'll give us the collaboration in various endeavors, be they meetings like this or meetings with sponsors or meetings about biomarkers or other endeavors. And also, I think it will give

us a sense of community around this area for reviewers who are doing things around rare diseases but also, hopefully, will be a community for the larger community to join into at the agency, much the same way as has happened in other endeavors like the Oncology Center for Excellence at FDA.

Susan Winckler (00:14:36):

Dr. Cavazzoni, do you want to add anything to that?

Dr. Patrizia Cavazzoni (00:14:39):

Yeah. I think that I would just give the example of this meeting. When have we had a meeting like this before, right? This exemplifies how the hub will turbocharge our activities across the centers, build a lot of connective tissue in areas that are really important to the rare disease community. Now, we are here to listen and to hear what's important to the rare disease community. We have some working hypothesis, we really want to listen. It is also going to provide or build more structure. We are actually setting up meetings that we're going to have regularly. We are going to be setting up work streams on cross- cutting rare disease development issues that we know have been problematic; use of real world data, clinical trial methodology, statistical approaches and et cetera.

(00:15:45):

We can look at an expansion of our crosstalk across the centers, which will build upon what we have, and it will be complementary and build upon it, but also more structure, more visibility, more recognizability for both internally as well as, more importantly, for the community, more transparency. And so, this meeting really amplifies already, while we are in startup mode right now, how the value and the promise of this hub.

Susan Winckler (00:16:20):

Yeah, that's really helpful as we think about then you have the experts who are in place doing their work but they have the opportunity to share and learn together.

Dr. Patrizia Cavazzoni (00:16:30):

Yeah, exactly.

Susan Winckler (00:16:31):

Great. Well then, let's step from that broad mission and say what it is that the hub should do. There must be some initial priorities that you want to pursue. Dr. Marks, did you want to pick that one up?

Dr. Peter Marks (00:16:46):

Yeah. So obviously, in the not too distant future, we'll be able to announce a director for the hub, essentially, for the strategic programs. But I think, first and foremost, as a priority is to have a point of entry that people can see that's common to the centers, that people can come into and know that ... I very often have people come into me and they're not coming into the right place. They go to Patrizia, they're not going into the right place. It shouldn't be right or wrong, they should have a place to come into and it should really be an agency point of contact, and the idea is to make that happen, so having a single point of communication. It's not your problem to find the right place, it's our problem to get it directed to the right place, so leave it to us, just come in.

(00:17:39):

I think that's a really important thing to have, really a single point of entry that will allow us to. So that this is not something that people have to think a whole lot about, especially because we're seeing an increasingly complicated variety of products, some of which are drugs, devices, biologics. Figuring out who to go to first actually requires, even at FDA, it requires a jurisdiction officer, somebody to think about this formally, about what's going on, so we just want the inquiries to come in and to make that piece easier. I also think then that the next priority is to get our folks internally working together in a way that they have not done so before. That may be having our clinicians in various areas in the Center for Drugs, the Center for Biologics, and potentially even the Center for Devices, start to work together around various areas.

(00:18:40):

Our statisticians between the centers work together because there are probably statistical methods that need further development in this area of rare disease. Things like starting to apply Bayesian methods to these products and non-frequentist statistics, so those kinds of meetings. So first thing, communication with the outside. Second thing, internally, having working groups work together. And then I think, the final, third, urgent thing up front is to make sure that we get to a degree of regulatory consistency as quickly as possible so that when we're giving advice from our center, it's consistent with what is being given from CDER. There are consistent messages about things.

(00:19:33):

And I think Patrizia actually said a key word. For some reason we can't have the same policy about something, it's very transparent why we can't. There will be differences between gene therapies and protein therapeutics or small molecules that may mean that sometimes an endpoint or a policy may have to be different, but again, we're committed to being transparent about this. So I think communication and coordination around the agency, easy access from the outside into the agency, and then application of best practices in statistics, clinical development, that are coordinated between the centers, I think are all first priorities because, at least prior to today, that's something that we hear routinely from people in the rare disease community.

Susan Winckler (00:20:28):

So as you know, I often need to think through and say like, "Okay, so what's a practical metaphor or way to think about this?" As you were speaking on the communication part, I thought, "Okay, so it's the one Zoom link that we need to get into this meeting, or the entrance to Building One, which you know is where all the visitors come in." Dr. Cavazzoni, what would you add as that central point?

Dr. Patrizia Cavazzoni (00:20:50):

Yeah, I'm happy to give some color to what Dr. Marks had just said without repeating it because he said it so well. For instance, we have heard from several communities that there isn't really a way to talk to CDER and CBER and the experts that we have within the centers on cross-cutting development, drug development themes for a given disease that is not specific to one program, to the NDA that is under this center or the BLA that is under the center. But more conversations such as here is what we have accomplished when it comes to therapeutics with this disease. Now, these are the problems that we have now at this stage, and how do we think about advancing drug development at this stage of this disease, and how do we talk to CDER and CBER together? Historically, it would have been knocking at CDER's door and getting a listening session with CDER, and then knocking at CBER's door and getting a listening session with CBER. We are thinking, still in our startup mode, how to create a new vehicle to have in these discussions. Obviously, we're not going to be able to have a thousand a year and will talk about growth going forward, but this is something that we have already heard loud and clear from the

community that is a gap. And so, we really want to leverage the hub to be able to create these opportunities. Obviously, the role of Director of Strategic Engagement will be critical in then anchoring the intake and then what we reflect back to communities that approach us with such needs.

Dr. Peter Marks (00:22:42):

I would just add that I think one of the things that's pretty clear is the time is actually very ripe, whatever you want to say, for this collaboration, in part, because it's actually a celebration in the rare disease space. Not for many, but for some rare diseases we now have multiple ways of approaching them; small molecules, proteins and gene therapies, and even cell therapies, for some of them. To be able to have a holistic discussion with the community, you actually have to go across centers so I think having this kind of hub where we can allow our reviewers to engage in this will be really helpful.

(00:23:27):

I also think, as an aside for anyone from FDA who is listening, this is actually going to enrich our lives as well because I think being able to understand the whole of a disease in terms of what are available in terms of therapeutics in a really in-depth way by discussions with your colleagues who are incredibly knowledgeable, will actually really help as we move forward, whether you're on the drug side or on the biologic side.

Susan Winckler (00:23:55):

Yeah. So it's an important improvement even for the teams who are working on it, that they'll see opportunity.

Dr. Peter Marks (00:24:01):

Right now, oftentimes when we write reviews, when reviewers write reviews of a gene therapy, they might reference a small molecule that's used for a given disease entity. But all they really know about that small molecule is a very cursory amount of knowledge, such as a general physician might know, that it's a small molecule, it works via X pathway, and it might have this published side effect profile. But by actually, I think, working more closely together, they will actually be able to get a sense of what are the data that really underlie that approval? What's their strengths, the weaknesses, actually the current concerns, which sometimes are merged that aren't on the label.

(00:24:47):

And so this, I think, will again really help strengthen what we're able to do with a rare disease community. And again, it will, I hope, engage our folks more together, which will ultimately benefit the community more.

Susan Winckler (00:25:05):

So you've taken us on mission and priorities and talked a bit about this, but the hub is going to be successful. In that world, what rare disease community needs will the hub address?

Dr. Peter Marks (00:25:20):

Yeah. Let me just take it from what I think it will address both internally and externally. We talked about communication, it's going to be like four C's. It's going to help us with making sure we get communication going, externally to internally at FDA, and internally within FDA. I think that is a very important piece. I think it will help us with coordination as we have activities that are ongoing. Because

the goal here is when you have limited resources not to duplicate things, but to be synergistic, additive, in what we're doing. And so, that will allow us to hopefully be more productive.

(00:26:05):

I think additionally, we certainly want to cooperate in what we're doing so that, again, we become more than the sum of our parts ideally. I think finally, I already mentioned it but I do think that a key part of this is developing a community both in the agency and then around the agency in this area so that people feel like they're part of something larger. That actually circles right back around because people tend to communicate best in communities that they understand and trust, so I'm hoping that that's what ... Success, to me, is that cycle of C's. We probably could figure out some other C's to add in, but four C's is enough for now.

Susan Winckler (00:26:56):

Four is good, so in the communication, coordination, cooperation, and community. I think we can capture those four and my instinct is we'll hear comments about those throughout the day from the public as well as they share what they're looking for. Any piece you want to add there, Dr. Cavazzoni? You yourself have a C in your name, so.

Dr. Patrizia Cavazzoni (00:27:25):

I really want to emphasize the aspect of collaboration because collaboration not only pertains to CDER and CBER, we are going to collaborate with other parts of the agency. We are setting up a sort of steering committee that will bring together also the Ecology Center of Excellence, CDRH, the Office of Orphan Drugs, and et cetera. So collaboration across CDER and CBER within the agency, and even more importantly, collaboration with the communities and with the external world. That is really probably the C that [inaudible 00:28:07].

Susan Winckler (00:28:06):

That you would lift up there. Yes.

Dr. Patrizia Cavazzoni (00:28:08):

Not that the other two C's are important, they're extremely important, but we are really not going to advance what we build, what we want to build without collaboration.

Susan Winckler (00:28:21):

That brings us to, you've each mentioned and Dr. Bumpus mentioned the new role and the recruiting for that director. Dr. Cavazzoni, tell us more about that role and a bit of what you see. I think we know that person's going to be doing a little bit of traffic direction, in being a communication point, but tell us more.

Dr. Patrizia Cavazzoni (00:28:46):

So this role, which is going to be Director for Strategic Coalitions, is really going to be the anchor for the hub. Yes, there's going to be some element of directing traffic. There's a lot more. This role would be accountable to both Dr. Marks and me. We have worked hand-in-hand from the very beginning in thinking about the search, the job description. Every single step we have worked together, selections, and so on. Obviously, this role will be critical because it will provide a recognizable point of engagement,

expert point of engagement for the communities. It will be easier to get our attention rather than sending emails in multiple places and et cetera.

(00:29:48):

Also, this role will link into our rare disease programs, other parts of the agency, and also will be able to reflect back to the community, including what is going on in the agency. It will be a critical role in intaking, encapsulating, synthesizing the needs of the communities for the programs, and so this dyadic aspect of the role will be critical. We're obviously going to make sure that the person who takes this role really has a deep understanding of the rare disease work in the rare disease communities. And last but not least, we have Dr. Marks and I. In our initial rollout, we talked about we're going to make a plan, we have to make a plan. We're in startup mode now. I want to tell you that there's been a lot of activity and that we have some really good starting point and working hypothesis and et cetera. We're eagerly awaiting for this person to join the team so that we can actually start putting pen to paper. Now, we can only have put pen to paper, have a plan, have a strategy if we understand the needs of the communities. Which brings me back to the importance of this meeting today.

Susan Winckler (00:31:13):

That's great. Dr. Marks, do you anything?

Dr. Peter Marks (00:31:15):

No, I would just say that I would just echo that I think this meeting is a great opportunity to help develop and refine the agenda that we're trying to build here. I think one of the things I've learned from giving a lot of talks in life is you can talk about what you want to talk about or you can talk about what people want to hear about. I think we want to make sure that the agenda for the Hub actually reflects what the rare disease community needs rather than just what we feel like needs to happen. That's why this meeting today is so important.

Susan Winckler (00:31:52):

It's really helpful to have that vision of what it is that director will do. I'm reflecting those. I think for those outside the agency, when we see announcements, we're like, "Okay, this is great." And then there's that question of, so has everything changed or are some things still the same? And so maybe Dr. Cavazzoni, would you walk us through? I think there are some things that are changing, but some things that are not in terms of engagement with the FDA and that interaction.

Dr. Patrizia Cavazzoni (00:32:26):

A lot will be changing. Obviously the role that we just discussed will be critical and creating the support for that director to be able to fulfill that role will be critical. So more easier communication and more effective communication so that we also are more responsive to what the needs of the communities are and the concerns about the communities are. There's going to be a lot of change in how we operate sort of internally. Dr. Marks and I thoroughly enjoy working together and talk to each other a lot. You'll be amazed we're on speed dial weekends, nights and et cetera. That's great. And it's a good starting point when you are establishing a joint venture and we need to do more. We need to expand that and multiply that when it comes to our respective teams and have more of that dialogue. And so when I talked earlier about the Hub also creating a structure and the discipline that anchor more collaboration and more connectivity across the center, we're building that.

(00:33:40):

So I talked about establishing working group. We have already set up, we're already meeting. We have set up a rare disease policy and program council where we have our respective teams meeting regularly and we already, we have been engaged in sort of developing some working hypotheses of areas where we want to focus our work down to the working groups that we want to have reviewing the portfolios across what's in the hopper when it comes to rare diseases across both centers. So that is really game-changing to have that kind of forum and dialogue and structure which is complement, "Hey, what you think of this call," but also think about it. This will also be a forum for our reviewers and our teams to actually be exposed to what, as Dr. Marks said earlier, to a broader array of information, understanding what's going on in the other center and so on, which is going to be really critical because our reviewers really learn from the work that they do and the examples and use cases that they hear sort of across.

(00:35:05):

And our reviewers are really on a conveyor belt. It's one application after the other. They're very busy. They have their heads down, they have their goal dates they have to deliver. And so it would be really important for them to have exposure across both centers to understand what they can learn from programs that may that are under one center or the other. So I really want to bring that across that there's some tangible changes when it comes to structure. Now what will remain the same, and I know we have a highly educated group here today, so this wouldn't be no surprise. The way we review the process through which we review and make decisions and applications will not change. It will be obviously each centers and the divisions will be working in the same way.

(00:36:05):

The structure of advisory committees that there are some advisory committees for CDER and CBER, that is not going to change. And obviously the mechanics of how the work gets done are not going to change. And that's obviously very important because there has to be ultimately someone who makes the call in a disciplined and clear and reproducible way of making decisions. Now the inputs and the work that we do when it comes to establishing a sound policy foundations that then can provide a foundation for decision-making and explaining our decisions however will certainly be within purview of the Hub.

Susan Winckler (00:36:52):

So a lot of that strengthening of the infrastructure and the engagement around that traditional review division and that review process. And probably the most scientific conveyor belt I can imagine, as you said in reviewing.

Dr. Patrizia Cavazzoni (00:37:11):

Yes, it's a application conveyor belt belt. When the reviewers have the opportunity to raise their heads and say, "Hey, let's look laterally what's going on? Let's learn from the other assembly lines." And I am sorry to have to talk about... I'm not sorry. It's the reality that we have goal dates, we have timelines and they're very important to the communities. And so that process of review is very important. Otherwise, we would not be able to deliver. At the same time, really need to make sure that the review community have more opportunities to learn from each other within centers and across the centers so that we exchange best practices when it comes to the review is done, but also what we have learned through the review and the practices that then could be applied to the next program.

Susan Winckler (00:38:11):

So that continuous learning becomes really important. So let me do one final question to each of you. In thinking about this is being established, you have a sense of what the Hub will do and the impact that it will have. How do you see it growing?

Dr. Patrizia Cavazzoni (00:38:31):

Well, as I said earlier, we are in startup mode. We have not received one single additional resource to stand this up. So we have really working to stand up the Hub really through the passion and the commitment of Dr. Marks and I personally and our team. And you will hear too from two key members of the team in the next panel. So we will ask patients from the community that because obviously we have to grow and we have to get ourselves organized. Obviously the new role that we have talked about, the director role will be really critical. It would be one person with many, many communities and many stakeholders externally, but also internally if you think about it. And so as part of our plan and our strategy, we will also have to think about what is the growth plan for the Hub so that it would ultimately realize is what I think we collectively, I know we collectively wanted to realize. Peter, anything to add?

Dr. Peter Marks (00:39:50):

No, I think I would just add that I think the goal here is potentially to aim high, try to do as many things we can in a collaborative manner to bring people together to try to move what is a very exciting time in medicine. The fact that we actually have that we're starting to get to a place where we can have multiple treatments for relatively rare diseases or that we can actually come to treatments for rare diseases through genetic medicine relatively rapidly. And it's a matter of just how do you get those actually delivered to patients that were starting to become the question. I think it's an exciting time and I think one of the things that I think the other C that I would add, sorry, I'm going to add a fifth one-

Susan Winckler (00:40:37):

That's all right. I've got a list.

Dr. Peter Marks (00:40:37):

Is that the Hub is going to be creative in how we do things. We've already been creative about how we found funding for some of these things and we will continue to be creative because I think that actually is something that I think rare disease patients know what creativity is about because I've witnessed a tremendous amount of creativity and how in fact some parents just get through the daily life with their kids. So I think we'll try to embrace creativity also because with creativity goes a certain amount of joy in the process.

Dr. Patrizia Cavazzoni (00:41:12):

I couldn't agree more. And if we sit here and wait for Congress to give us $50 million for the Rare Disease Hub, we're going to miss that window and we're not going to be doing what we should be doing and what the science right now really compels us to do. Now if anyone has a spare $50 million, please don't be shy, all right, we'll take it. Having said so, we have rolled up our sleeves from day one, actually before our announcement. I mean our work started in the spring and Dr. Marks and I, our leadership team and the key people in our programs who have been really doing double duty and standing up the Hub and we cannot afford to be idle. And we hope that with time we'll be able to obviously add some additional resources. And I know that the next panel will talk about it and be able to do more. But I want to emphasize that as you have heard from Dr. Marks we cannot afford, nor are we planning to sit idle waiting from manna from heaven.

Dr. Peter Marks (00:42:25):

I would just say one other comment because it's a question that sometimes comes. Why such a focus on rare disease across here? And I think the easy answer to that is that there is an incredible serious unmet

medical need in this area. And it is a proving ground that if we can get it right here, it's undoubtedly true that we will get it right in larger populations as well, where actually things are in some ways easier because you have more patience for trials, et cetera. So I think this is a great place to develop things. I think that's why we have the start pilot in this area for looking at how we can perhaps move development more rapidly. There's nothing that says that if it doesn't work in rare diseases, it couldn't be exported to other places. So I think it's just an exciting place to be able to do and it's a place that we can make a difference in very soon. So I think that's the hope here.

Susan Winckler (00:43:26):

Yeah, actually, I really appreciate you saying that because we jumped in and said we're here to talk about the Rare Disease Innovation Hub with the presumption that everyone knew how very important this is and just really helpful to ground us in why we need to pursue the communication, coordination, cooperation, community, being creative. So at the end of the day, we're collaborative. Yes-

Dr. Patrizia Cavazzoni (00:43:52):

[inaudible 00:43:54].

Susan Winckler (00:43:53):

We might even be up to five and six by the time we combine them all together. So this has been really illuminating and it's so helpful to me. Anytime you can build in alliteration now I've got it. But thank you both for taking the time, sharing your vision and mission and let's thank them for joining us and providing that insight.

Dr. Patrizia Cavazzoni (00:44:16):

Thank you.

The Rare Disease Innovation Hub: Looking Ahead

Kerry Jo Lee, MD, Center for Drug Evaluation and Research, FDA
Julie Tierney, JD, Center for Biologics Evaluation and Research, FDA

Susan Winckler (00:44:19):

And I'm going to stay here because our next two panelists are going to come right up to the stage and join me for the next stage of our conversation. As I was reflecting on what Drs. Marks and Cavazzoni had said, I thought... Come on up because you're next. I'm just filling the time while you take your seat. That's all right. I am reflecting that there's the vision and what it is that we need to do, which is very important to set out up front. And then there is the incredibly important work of, and how do we do that. So I think this is the how do we do that panel. And so joining me on the stage at the far end, Julie Tierney, who is the deputy center director for Strategy, Policy and Legislation for FDA's Center for Biologics, Evaluation and Research. Welcome Julie and welcome Dr. Kerry Jo Lee who serves as associate director for rare diseases on the rare diseases team within the Division of Rare Diseases and Medical Genetics in the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine in the Office of New Drugs in the Center for Drug Evaluation and Research. She does have the longest title in FDA. I am going to confirm it, but it's a great title. So Julie and Kerry Jo, we've just heard from Drs. Cavazzoni and Marks about the emerging vision for the Hub. And I know you've been thinking about the nuts and bolts, how to make this, how do you turn that vision into a reality? So as we move toward implementation, let's think about those next steps. Dr. Lee, do you want to go first on that?

Dr. Kerry Jo Lee (00:46:05):

Yeah, sure. Thanks so much. So I really think that I'm an environmental biologist just to throw it in there, but another title, or sorry, an evolutionary biologist, but in order to evolve, we really need to understand the environment in which we are in. And I think that that is really the purpose of today's meeting is to hear from the community about what is the environment in which we are working so that we can evolve effectively to meet the needs of rare disease drug development. And so today's public meeting is really a first step in order for us to share both for you to hear from us about our vision and what we hope to accomplish, but also and more importantly for us to hear from you about what you need and that will really help us to shape our priorities and initiatives. And I didn't know Julie, if you want to talk a little about how we're going to do that.

Julie Tierney (00:46:58):

Yeah, thanks. And I think that today, and I don't want to spend too long on the stage, I want to get to hearing from folks because really the important part of today and the important part of our startup phase, in addition to hearing the priorities of external groups, patients and the rest of the community, I think as Dr. Cavazzoni mentioned, we have been doing our own portfolio review and having conversations internally, a lot of planning and have working hypotheses as some of the most critical important issues. And I think one of the benefits that the Hub is going to bring is to take that input that we're receiving to be doing a landscape analysis of FDA's rare disease programs and figure out how to marry the two so that we can figure out what the right priorities are to move the various fields forward as quickly as possible.

Susan Winckler (00:47:53):

So there's some of that internal reflection and then today as just part of that gathering, the external input.

Dr. Kerry Jo Lee (00:48:00):

Absolutely. And then I think just to add a little bit more on that, you heard from the center directors about the director of strategic coalitions and it will just be the work that we're doing now will be so enhanced by our ability to work with that person very closely in order to develop that next stage in the cross-center agenda that we need to help move this forward.

Susan Winckler (00:48:21):

So let's jump to one of the six Cs because I have expanded it now to all six, that a really important one for implementation is that communication aspect. Julie, how should the community expect to hear from FDA moving forward? So how should they be thinking about that communication?

Julie Tierney (00:48:44):

Yeah, that's a great question because I appreciate everyone's patience as we've been in startup mode and said we are working as hard as we can behind the scenes and we have been, but we appreciate a key role of the Hub is going to be also being as transparent as we can within our legal limitations and communicating what we're working on and some of the results. And part of that is going to be this cross-cutting strategic agenda which not only is going to give us some structure but also be a mechanism for us to communicate what we're working on and we're going to have to prioritize because even if we did get money, we would need all the money in the world to move forward everything.

(00:49:26):

You've got to prioritize things and we want to be clear about how we're prioritizing things and what we're working on next and then what the results are to the extent that we can. That's going to be a very important role of the director of strategic coalitions. Not just bringing it in but also figuring out how best to engage the community, moving information out as well.

Susan Winckler (00:49:45):

So to share that.

Dr. Kerry Jo Lee (00:49:47):

Yeah. And just as a very practical matter, so how are you going to know what we're doing? We do have various rare disease Listservs. Many of you're probably already signed up for some of them. We'll be sharing information that way as well as there is a website already launched for the Rare Disease Innovation Hub, and you can find that in whatever search engine you like to use. And so we'll be posting information there as well.

Susan Winckler (00:50:11):

Great. So it's a key responsibility of the new director to be thinking about how to communicate things out and then you've got the web page and a number of different ways to communicate and make sure that we do that.

Dr. Kerry Jo Lee (00:50:26):

Absolutely.

Susan Winckler (00:50:28):

So then I am going to imagine that everyone in this room and then everyone who's joining us virtually, many of them are thinking, okay, how do I help? So what are the types of things that are helpful from the rare disease community to help turn this vision into a reality?

Dr. Kerry Jo Lee (00:50:55):

Yeah, I can start. I think I'll piggyback on something that Dr. Cavazzoni said earlier and that is to have patience, a little bit of patience. And I know that that is a very challenging thing in the rare disease space when the needs are so pressing and the therapies are so scarce. But we expect that there will be certain efficiencies to developing the Rare Disease Innovation Hub that will be gained. And our plan is really to enhance our current collaborations and synergies. We are leveraging as foundation our existing success with the Accelerating Rare Disease Cures program and CBERS Rare Disease program. So that's what we are currently leveraging in order to really increase our engagement with the rare disease community. Our pace and our scale and the scale at which we can do this will obviously be subject to the ability of our collective staff to support these activities as we move forward.

(00:51:55):

So that's just what I would say. There's definitely that. And then the other aspect of that is to share. Share your thoughts on what you feel that you need because the most important thing is that we build this, designed to actually meet the needs and the gaps that exist. So that's meeting we thank you for those of you. Many, many people submitted to try and speak at this meeting. I just want to remind everyone there is an open docket that is open through the end of October. Please submit your thoughts.

We are really taking all of that feedback and utilizing it to build what the Hub looks like moving forward. So it's really, really important to us.

Susan Winckler (00:52:39):

Julie.

Julie Tierney (00:52:39):

And I think just totally agree with everything Kerry Jo said. And emphasize of course, the docket being opened through the end of the month. I think even if you're speaking today, submit comments to the docket. We're really interested in hearing priorities and different thoughts on how we could approach things. And I think there's been a lot of talk today about cross-cutting issues. I don't know if that's one of your Cs or not.

Susan Winckler (00:53:06):

It just added new one.

Dr. Kerry Jo Lee (00:53:09):

It's double C.

Julie Tierney (00:53:11):

The ABC, the Hub. But I think that really the efficiencies and the raising of all ships that will happen through the Hub is by bringing cross-cutting issues to the Hub. And so that means it doesn't function as an appeals board for review decisions that really belong with the experts, the subject matter experts. Not to say that senior leadership doesn't get involved in things, but to say let's think about what the cross-cutting issues are that work across a particular disease, that work across a particular set of diseases. And that's where we're going to see the most efficiencies I think with the Hub.

Dr. Kerry Jo Lee (00:53:48):

Absolutely. And the most gain.

Susan Winckler (00:53:50):

So that opportunity to work together and maybe explore a challenge together and then make the decisions according to the regulatory structures that exist. So I think I heard you both say it was a P word though, but I think it's worth underscoring and that's the idea of patience and not to say that this will take a long time, but it's not as if you could flip a switch and then you illuminate this and it happens. There are things that are taking place and are being assembled and will take a bit of time. And then also to underscore, you both were very clear that it's important for the Hub to hear from the rare disease community and more broadly about what the ideas are for the Hub and perhaps maybe even identifying pain points and opportunities, what it is that folks would like to see the Hub do and maybe even ask their questions of what they're most intrigued about in better understanding the Hub.

Dr. Kerry Jo Lee (00:55:04):

Yeah, I really think so. I think that for everyone that works in rare disease drug development, they really understand that it takes all of us to take a therapy from bench to bedside. It takes every person in your community in order to make that work. It is very challenging. You have a lot of things that you need to

figure out. So early planning is key, both to the success of rare disease drug development program and I really think to the success of the Hub. So patience doesn't mean inaction. It means we need to get this right. And so I think I would just say that when today's meeting concludes, I want people to understand that it's not the end, but it's a beginning and the dialogue will continue and we are putting things into place to ensure that that happens. The Hub is really a commitment to ongoing dialogue between the centers, the FDA, and the rare disease community in order to develop safe and effective therapies, so.

Susan Winckler (00:56:00):

Excellent. Julie, I'll give you the last word here.

Julie Tierney (00:56:03):

Well great. And I echo Kerry Jo. Again, we spend a lot of time together, but patience doesn't mean inaction. And I hope that you've gotten a sense this morning of the urgency that we have at FDA around this issue, around our leadership teams to moving forward the Hub. We did not wait for congressional action to put something in place. We recognized a need and really came up with what we think is the best model to move forward right now. And we are doing a lot of work. So this is the beginning and we understand the urgency.

Public Comment

Susan Winckler (00:56:38):

Excellent. All right, let's thank Kerry Jo and Julie. So helpful to have that better understanding of the next steps in where we might take the Hub. With that, I'm going to switch microphone. Sorry to the virtual people for whom that was a very loud microphone switch because we are going to pivot then as well from as we said, one of the things that happens in these meetings as we move in convening is to allow the agency to share information and to receive information, to hear from you. And so we will move to the portion of the meeting that is now dedicated to hearing from you. As a component of that, this is not an opportunity where the agency or anyone will be responding to the comments. Rather we're gathering the input and listening intently. I think we all know it's easier to listen when you are focused on what is coming in versus formulating your response.

(00:57:48):

So that's why it is structured this way for the agency to hear what it is that the public commenters are sharing. As we noted, we had more than 200 individuals request to speak and we have slots for 41 of those. And so I do need to remind you of some of the logistics so that we can proceed through this section and focus on listening to the insights that you share. So we are going to work through four predetermined topics. We are going to hear from our remote speakers first and then move to our in-person speakers on that same topic. Then we'll move to the second topic. Our first topic is cross-cutting disease-related scientific regulatory or policy issues not related to a particular disease or condition that should be prioritized for consideration by the Rare Disease Innovation Hub. As I noted, I will be listing the three speakers in the queue.

(00:58:47):

The first three virtual speakers for topic one are Kara Barassi, Gabrielle Conacher, and Agnes Jensen. So as those first three speakers prepare, let me recap the logistics. When I announce your name virtually, use your raise hand function. The second time you hear your name, turn on your camera and prepare to unmute. The third time you hear your name, unmute your microphone and I will introduce you and we

will turn the podium over to you. Our producers will bring the virtual speakers on screen as you are introduced.

(00:59:20):

Your timer of three minutes will start as you begin speaking. If you do not begin speaking, within 10 seconds of my turning the virtual stage over to you, we'll move to the next commenter and we'll round back to you as we are able. The countdown on screen showing the time you have remaining. And I will come back on screen when you have about 15 seconds left. At the three-minute mark, we will mute you and move to the next speaker. So again, in the first topic, our first speaker is Kara Barassi, then Gabrielle Conacher and Agnes Jensen. Giving our queue. If we could pull Kara's video up. And then Gabrielle Conacher, Agnes Jensen and Mary Kohler. So Kara if I... Yes, Kara, please proceed.

Kara Barassi (01:00:10):

Thank you. I'm Kara Barassi, a rare disease mom and the CEO of Haystack Project, which represents over 140 rare and ultra-rare patient organizations. Thank you for the opportunity to speak today and offer our recommendations. And while I'm responding on the first topic today, I believe our comments cut across all four. First, we recommend that the Hub find a way to include data collected between when a trial closes and when an application is filed. We've seen this make a difference in approval in the US versus the EU in familial chylomicronemia. Is it possible to find a way to include these findings and add additional data?

(01:00:53):

Secondly, the FDA must address composite endpoints that give equal weight to both the mildest and most severe disease presentations as protocol developers are forced to piece together endpoints for very heterogeneous ultra-rare diseases. We've been worried about this and we've recently seen it occur with galactosemia. How can statistical approaches that include weighting be developed and employed?

(01:01:20):

Thirdly, I challenge us all to think about how adequate and well-controlled studies rather than adequate and well-controlled clinical trials meet the statutory requirements that reviewers were trained on. We need a predictable and transparent approval pathway in rare disease. And regarding patient engagement, first, drug company funding should be viewed at the FDA as the only way patient groups can do their valuable work and not just as a conflict of interest that discounts what we share. Patient group interaction with the FDA should be done without the presence of drug companies. And at the end of the day, the FDA works for patients. And so do we. Patient groups should be able to interact with actual reviewers, because quite frankly, if we are taking the time to learn the science, participate in clinical trials, and continue to stay in them even when we see that our kids aren't in the treatment arm, then I think the reviewers can listen to the insights we bring from those trials. I'm talking about engaging during and after trials are done, not just PFDDs, as there's often important information that cannot be captured in a simple data point. Additionally, provide patient groups feedback on what was useful and what was not and why. None of us get better at our jobs without constructive feedback, and currently, all we get is silence. We look forward to working with the hub to address these and other ideas in the future. Thank you so much for your time today.

Susan Winckler (01:02:57):

Thank you. Our next public commenter will be Gabrielle Conecker, Agnes Jensen, Mary Kohler, and then Kathleen Troeger. Gabrielle Conecker, if we could pull your video up.

Gabrielle Conecker (01:03:10):

Hello.

Susan Winckler (01:03:12):

Excellent. Gabrielle, please proceed.

Gabrielle Conecker (01:03:15):

Thank you so much. I am Gabby Conecker, and I join you today as the Executive Director and Co-Founder of Decoding Developmental Epilepsies, which encompasses the International SCN8A Alliance, DEE-P Connections, and The Inchstone Project. First of all, I want to thank everyone for their leadership on behalf of the rare diseases in building this exciting hub to expedite improved treatments and outcomes. I also come to you as mother of Elliot, my eleven-year-old son who has SCN8A, which in his case presents as a severe DEE. He's a beautiful and sweet kid but very profoundly impacted. He's unable to walk, talk, eat by mouth, has a vision impairment, and he is currently working on head control. He's just one of over 150 severe and complex epilepsies. As you all know, there are very few, if any, approved treatments for most of these developmental and epileptic encephalopathies and rare epilepsy or NDD, neurological disorders.

(01:04:17):

My work has really focused in on trying to improve quality of life and outcomes for these communities, and we've seen that there are many shared concerns across these disorders. That has come to light in data from our recent broad survey across more than 250 rare epilepsy disorders and NDDs with caregivers. First thing that I want to talk about is as trialing new treatments comes and it's done disease by disease, where there are cases that there's preclinical work that already indicates that a broad epilepsy indication is applicable, I would love to see us move in that direction, because otherwise, it is delaying access to new treatments. As you know, our children are suffering and dying at alarming rates. Whenever possible, we should be working to bring as many treatments as possible to as many people as possible as soon as possible.

(01:05:22):

Obviously, I would like to encourage increased use of basket trials, which I know we're seeing in an emerging trial that's coming soon in the rare epilepsies and the DEEs. I applaud that work moving forward. I think you may recall that for medicines like fenfluramine was approved in 2020 for Dravet, 2022 for LGS, and there's no further indications yet. We know that many people use it and have a desire to use it but have challenges with clinicians and insurance coverage. The other thing is that with the emergence of more gene therapies and personalized medicine, advocacy leaders and families have major concerns about the limitation and appropriate non-seizure outcomes. Many are suffering from many challenges, and DEE-P Connections initiated Inchstone Project, which is working to develop innovative measures to capture small but significant improvements among those who are profoundly impacted by disease. Thank you very much.

Susan Winckler (01:06:20):

Thank you. Our final three virtual speakers are Agnes Jensen, Mary Kohler, and Kathleen Troeger. Our first in-person speaker will be Caryn Alagno. I want to turn the virtual stage over to Agnes Jensen.

Agnes Jensen (01:06:39):

Thank you very much. My name is Agnes Jensen, and I'm here today representing the Salla Treatment and Research Foundation. We are a fairly small patient advocacy group based out of New York State, but we have a community of families from 17 countries around the world and across the U.S. Salla disease is a form of free sialic acid storage disorders. We'd like to bring up a few points today. First of all, organizations like ours and our families want to be involved. We want to be involved with the FDA and therapeutic approval, but we often don't exactly know how to do it, so we look forward to the hub communicating more how organizations like ours can effectively help move things forward.

(01:07:33):

Second, in order to do that, we really need all of the communication to be written in clear lay language for families to better understand. On a practical note, many organizations like ours have patient registries or even have had natural history studies. However, many of those initiatives have been siloed, so we'd like to know are there ways that we can improve or add things to our registries or to a natural history study that would help across all diseases. We would love some practical advice on that. As I said, we are an international organization, as many of our rare disease organizations are. Having a international community adds a dynamic input to our family of to our family. However, it does add complexity via logistics, language. There are different privacy laws across the world, so small organizations like ours don't exactly know how to navigate those international boundaries as well as we could, and that's something that, cutting across organizations, we feel that we can need help with.

(01:08:57):

We also would like to engage more of the international scientific and medical partners. As far as collaboration goes, we are thrilled to say that we recently were awarded a Chan Zuckerberg Rare As One grant, and we would like to see more partnership between the federal government, the FDA, and these nonprofit opportunities just to move things forward. As you've mentioned, time is of the essence for our communities. We thank you so much for moving things forward and look forward to all working together. Thank you.

Susan Winckler (01:09:38):

Thank you. Our next virtual speaker will be Mary Kohler, followed by Kathleen Troeger, and then we'll turn in-person. Caryn Alogno will be at that podium and Jamie Babin at this podium. Our next virtual speaker, Mary Kohler, if we pull the video up, please proceed.

Mary Kohler (01:09:56):

Thank you. What's good enough? That's a question I never thought I'd ask FDA, yet here we are. I watched last week's advisory committee meeting, a room full of experts spent an entire day weighing compelling community evidence against a tiny patient population and really tough data questions. I heard them struggle to wrap their minds around your efficacy ask. We're all so conditioned. That magic word comes from the agency alone, and that's when it hit me. Creating this hub is going to be really hard. I think you know that. I have some ideas on priorities. I'm a lawyer, of course I do. I'll submit them to your docket, but for now, let's click up. I think the real trick here is to avoid getting lost in the details.

(01:10:49):

When the question becomes what's good enough, some of those Cs will be big challenges. This question sparked real debate in the context of a file last week, and I can only imagine how hard it will be to get people collaborating on this idea in the abstract, but I can see how easily this hub could be derailed. Yet, we all want this, right? The patients are making their voices loud and clear, because those who don't have the luxury of times do see things differently. You have a tall order, FDA is undergoing massive

change, and you're challenging some deeply held views. Kudos to you for that. But that may seem threatening to some, and your new director may soon have detractors, especially if they start making inroads on that good enough question.

(01:11:41):

I launched healthcare compliance into a reticent biotech at the dawn of the Pharmacode. I know how hard it is to move a big organization. May I suggest, one, help your new director find their champions. Leaders who share the vision can help so much. Two, find some high-impact quick wins. They're easier and you'll get traction, then you can dig into the hard stuff. Three, give this person real authority and then get out of their way. You have an impressive steering committee and that's fine, but another C, consensus, can stall progress. I've been there. Trust your director, encourage them to act, and support them when they do. Let them surprise you. Finally, don't let perfect be the enemy of good. There's only one bad outcome if we're still just talking about this in three years. Onward, best wishes, and thank you.

Susan Winckler (01:12:42):

Thank you. Our final virtual comment on topic one will be from Kathleen Troeger. I'll ask Caryn Alagno to move to the podium on the far end of the stage, Jamie Bobbin to approach the stage on this side, and E'Lissa Flores to be ready to proceed shortly, but let's turn the virtual stage over right now to Kathleen Troeger. Please proceed.

Kathleen Troeger (01:13:07):

Thank you very much. Good morning. My name is Kathleen Troeger. I'm representing the Digital Medicine Society, also known as DiMe. We're grateful today for the opportunity to provide comments to guide FDA as they establish the Rare Disease Innovation Hub. Founded in 2019, the Digital Medicine Society is a global nonprofit for the professional home for digital medicine. Together, we drive progress and broad acceptance of digital medicine to enhance public health. Our mission is to advance the safe, effective, and equitable use of digital approaches to redefine healthcare and improve lives. DiMe, as many of you know, also hosts the Digital Health Measurement Collaborative or DATAcc. It's through DATAcc that we work with each of you to provide a unique forum for collaboration, where partners and experts, from across the digital health field, including clinicians and patients, work to advance the use of digitally-derived measures. Together, today, we stand a unique moment to capitalize on the advances in genetic testing, digital technology, drug and device development.

(01:14:07):

We're excited to welcome the arrival of the innovation hub to enhance the existing collaboration and further advance the understanding that allows digital technologies to expand access to clinical trials and accelerate therapies for patients with rare disease, especially children. We've seen firsthand the power of this multidisciplinary partnership across groups to rapidly develop innovative solutions. We're currently furnishing the collective power of clinicians, patients, manufacturers, and regulators to address the needs of the rare disease community and creating an industry framework, to guide the use of digital health technologies in pediatric rare disease reducing cost, length in the clinical trial burden associated with medical product development. This is intended to speed the diagnosis and improve access to therapies, where traditional approaches have fallen short and been largely unsuccessful. We ask each of you to join us in this effort.

(01:14:57):

Our commitment to this anchors on the ability for digital technology to provide unique value to the population of children with rare disease. The use of digital endpoints and clinical trials has been

demonstrated to accelerate the delivery of new therapies and mitigate risk by reducing the time and investment associated with traditional development programs. Digital technology supports a patient-centric approach to decentralize trials and can expand the reach of treatment options. We invite each of you to join us in our efforts to expand the application of digital technologies and drive these important initiatives forward, with the focus on the needs of the youngest and most vulnerable patients impacted by rare disease and ensure advances in digital medicine are prioritized for those who need them most urgently. Thank you for the opportunity to present these remarks today.

Susan Winckler (01:15:44):

Thank you. We will now proceed to our in-person presenters for topic one. Caryn Alagno will begin shortly, followed by Jamie Bobbin, E'Lissa Flores, and Richard Horgan. Please proceed.

Caryn Alagno (01:16:00):

Good morning. My name is Caryn Alagno with the NPHP1 Family Foundation. It's a pleasure to meet you all, and I'd like you to also meet my son Davidson. Today is Davidson's 12th birthday. He's a pitcher and a first baseman on his baseball team. He loves his dog, his friends, and ordering takeout from California Tortilla. Davidson is also missing the NPHP1 gene, and as a result of that gene deletion, he had a kidney transplant in 2020. We were very fortunate that I could be his donor, but recently, Davidson was also diagnosed with a blinding inherited retinal disease caused by the same gene deletion. These two things together are the hallmarks of a rare condition called Senior-Løken syndrome. It affects about one in a million people worldwide. Davidson would be here today, but he's in math class.

(01:16:51):

But if he were here, I know that he would, as I do, want to thank each of you for the work that you do and for holding today's meeting to hear from parents and from caregivers. Our foundation is in its very early stages, but in the last 12 months, on our own, we've identified potential research collaborators at four universities. We've located mice with Davidson's same genetic defect available for cryorecovery. Davidson and I have donated skin cells in order to establish iPSC cell lines. We've secured a partnership with a nonprofit biotech to guide our drug development effort. We built a patient community and we're in the process of establishing a data collection platform on our website to inform an eventual natural history study. Fortunately, for us, what's needed is really more drug assembly than drug discovery, and we have so many things working in our favor.

(01:17:42):

Our goal is to create a gene replacement therapy for the eye, which has been done before. The NPHP1 gene fits on an AAV vector. There's available mice. A team in China has already done a proof of concept in mice that proves successful, and so we're just putting the pieces together that nobody else will, but the science we've been told isn't the hard part. The two biggest hurdles in front of us are paying for it and navigating the FDA. When it comes to the FDA piece, we've been told the following. "Even if you do the extraordinary, the FDA might not move fast enough. You need to hire consultants to help you navigate the place. It's expensive, but it's worth the cost. You should only work with investigators who've done it before. Anyone else won't know how to work with the FDA and you'll waste your time and money." We've also been asked if we've considered moving our program to Europe.

(01:18:32):

Every family you're going to hear from today is seeking temporary collaboration with the FDA, temporary because either we'll be successful or we'll run out of time, and the FDA has an impact on which eventuality will face. The agency is without a doubt to be commended for initiatives like this one,

but there's an opportunity to do a lot more to be a partner, to streamline and consolidate information and resources, to remove the layers upon layers of bureaucracy required to engage, and to be equal parts approachable, effective, and clear, and to give us actionable expectations around what you want to see from us and the research teams who say too often they don't know which way the wind's blowing. We look forward to working with you and we thank you for your time.

Susan Winckler (01:19:12):

Thank you. Our next speaker will be Jamie Babin, followed by E'Lissa Flores, Richard Horgan, and Edward Kaye. Please proceed.

Jamie Babin (01:19:20):

Hello, everybody. My name is Jamie Babin, and I work with Dr. David Fajgenbaum at Every Cure, a nonprofit biotech that utilizes AI to unleash the potential of every approved medicine to treat every disease it possibly can. Of the approximately 18,500 recognized diseases worldwide, only about 4,000 have FDA-approved treatments. This leaves hundreds of millions of people without effective therapies for their conditions. Notably, over 80% of currently approved treatments are generic or off-patent medications that could potentially unlock new treatment options. Unfortunately, systemic barriers and a lack of financial incentives stifle further research on these medications resulting in life-saving drugs, sitting underutilized on pharmacy shelves while patients continue to endure limited or no treatment options.

(01:20:09):

We, at Every Cure, strongly believe that drug repurposing should be prioritized by the Rare Disease Innovation Hub. This approach can accelerate the development of life-saving treatments at a fraction of the cost and time required for novel drug discovery. Traditionally, drug repurposing has depended on serendipity and focused on isolated diseases. However, at Every Cure, we are committed to transforming this approach by seeking out shared connections among all existing diseases and all approved drugs simultaneously. While these connections may not always be immediately apparent, our advanced AI capabilities allow us to optimize the search for effective drugs enabling us to explore the broader landscape rather than targeting individual cases one at a time.

(01:20:53):

If the Rare Disease Innovation Hub were to emphasize drug repurposing, it could significantly broaden the FDA's drug development scope, introducing alternative and cost-effective treatment options. Collaboration among repurposing organizations, including Every Cure, patient advocacy groups, and the Rare Disease Innovation Hub, would enhance access to repurposed treatments for patients who currently lack effective options. This effort aligns seamlessly with the FDA's mission to ensure timely access to new therapies for rare diseases. By leveraging innovative strategies and advanced AI technologies, we can uncover promising repurposing opportunities and foster meaningful collaboration across the rare disease community. We invite the Rare Disease Innovation Hub to engage in discussions about how we can combine our resources and expertise to develop a strategic framework for drug repurposing. Let's prioritize repurposing as a key strategy in combating rare diseases and ensure the best possible outcomes for patients. Thank you.

Susan Winckler (01:21:53):

Our next public commenter will be E'Lissa Flores, and then in the queue, we have Richard Horgan, Edward K, and Casey McPherson. Please proceed.

E'Lissa Flores (01:22:04):

Thank you. Good morning, everyone. I am E'Lissa Flores. I'm Director at the Biotechnology Innovation Organization, known as BIO, and I lead our Rare Disease Committee. BIO's the world's largest [inaudible 01:22:14] association, and we thank you for this opportunity to provide our feedback today. There are several key points we believe the hub should prioritize, adding a few more Cs today. First is improved coordination and consistencies across the centers. Many companies face challenges navigating these varying requirements across the centers, and a unified approach through sharing best practices, lessons learned, especially in their regulatory flexibilities, would lead to a more efficient regulatory process. Not only internal, but external communication is key as well, so establishing regular and transparent lines of communications will ensure perspectives of industry, patients, and other stakeholders are incorporated into the hub's agenda.

(01:22:59):

Given the number of rare diseases, there is a pressing need for co-education across and among the FDA leaders and with external experts in the field. The hub could facilitate access to these experts for FDA reviewers as well and to empower them with a deeper understanding of the underlying science leading to more informed evaluations of drug applications. To further understand the underlying science, the hub could be a catalyst for scientific research and innovation through developing the following novel approaches, including real-world evidence, natural history studies, innovate clinical trial designs, and emphasis on this next point is create a clear framework for accelerated approval pathway and how to best utilize surrogate endpoints and biomarkers.

(01:23:47):

On how could the hub do this, we suggest the hub host scientific workshops and forums designed to convene FDA officials and experts in the field to enable scientific and education alignment. Beyond this public meeting, we encourage the hub to have a method of ongoing continuous feedback as the rare disease landscape is ever-evolving. Finally, we would recommend the hub develop a strategic roadmap. Outlining how it'll operate over the next five years, this roadmap should include short-term and long-term goals, metrics of success, and clear timelines for achieving their various objectives. Note, BIO will be submitting a comment letter to expand on these priorities. But in summary, we believe the hub has the potential to create a transformative impact on the rare disease community through all the success, and we can work together to address the unique challenges faced by sponsors and patients and other stakeholders. We thank you for your time and we look forward to the continued development of this vital initiative.

Susan Winckler (01:24:52):

Thank you. Our next speaker in person is Richard Horgan. Then, in the queue, we have Edward Kaye, Casey McPherson, and Kiran Musunuru. Do we have Richard Horgan here? Edward Kaye, would you please proceed to the microphone? Mr. Kaye, please proceed.

Edward Kaye (01:25:19):

Good morning and thank you for the invitation to the Reagan-Udall Foundation. My name is Edward Kaye. I am a CEO of Stoke Therapeutics. Stoke Therapeutics is a company that's trying to be the first company that treats the underlying cause of a severe genetic epilepsy. I've had the privilege, over the last 30 years, of working only with children with rare genetic diseases, either as a treating physician or as a drug developer. One of the things that I've discovered is that not all rare diseases are treated the same. My first experience with this was as a clinician at the Children's Hospital of Philadelphia where I

was asked to see a 30-day-old child who was in a coma. We found out that this child had maple syrup urine disease, a rare genetic metabolic disease. The problem was this child was born in Pennsylvania.

(01:26:13):

We would've never seen this child in a coma. We would've treated it because we would've had genetic treatment because it was on the newborn screening panel. I had to tell the mother when she asked, "If your child was born on the other side of the Delaware River, this would've never happened." One of the things, I think we are at a time of treating genetic diseases where the genetic therapies are well in advance of where we are for the regulatory science. We need to be able to catch up to the advances that we're making and make a difference. We are seeing now diseases that, even 10 years ago, we thought were untreatable. Diseases like Angelman syndrome, Rett syndrome, Dravet syndrome, that we're working on, where you can actually see improvements in cognition and behavior that we were once thought not possible. The problem is we don't have a way to measure these improvements.

(01:27:09):

How do we quickly get therapy to patients that desperately need it? We don't have a way of doing it. I think this innovation Hub, the center of Excellence for rare disease is a way to get all of the information that's present at the FDA to everyone, to every patient who needs it, and to make sure that we can do it quickly and efficiently. We don't have unlimited resources, we don't have unlimited time, and we don't have unlimited patients. We have to do this quickly. There's an urgency that really is necessary. I think as we think about this foundation, I think it has a great potential to bring everyone together, the clinicians, the companies, the FDA, to make therapies available to these patients quickly. I think we need to be as brave and as worthy of the patients that we're treating. It shouldn't matter what side of the Delaware River you were born on, and it shouldn't matter if your drug is being treated by CBER or CDER. Thank you.

Susan Winckler (01:28:11):

Thank you. Our next in-person comment will be Casey McPherson. In the queue, we have Kiran Musunuru, Heidi Ross, and Marshall Summer. Please proceed.

Casey McPherson (01:28:24):

Hi. Good morning, everybody. My name's Casey McPherson. I'm Chairman of To Cure a Rose Foundation, Founder of Everlum, CEO of Chrysalis Genetics now, but I come to you this morning simply as Rose's dad. My daughter Rose was born with an ultra-rare neurological disease. She lost her ability to talk. She struggles with walking. She doesn't have any friends. We're still changing diapers, and she's eight years old. Rose doesn't have a treatment not because we don't have the technology to treat her disease. She doesn't have a treatment because there's no sustainable path to getting access to this treatment on an U.S. or global scale.

(01:29:09):

If we look at diseases like Rose, hers has maybe 140 known patients. We're seeing that genetic disease, most of genetic disease, is we're seeing as ultra-rare. What that means for Rose is that she's waiting for a treatment. She's waiting for a new path. She's waiting for a sustainable model. We built an ASO, an antisense oligonucleotide for her disease. We plan on taking it into the clinic, but it's going to be a challenge. I am so excited about this hub. It gives me hope that for a future for children like her, that we can create this sustainable model. I see some really incredible opportunity to innovate on clinical trial design looking at these types of genetic treatments that are more modular and platform as almost like molecular surgery.

(01:30:12):

Could we look at process approvals? What are the rinse and repeat places that we can create efficiencies in? Also, with diseases like hers, generalized endpoints don't work. The phenotypes are super wide, so I'm excited to think about ways of implementing the patient has their own control and looking at a more individualized and personalized approach. Ultimately, I want to hear Rose say daddy again. I want to see her play in the park, but without a new strategy and system and a genetic treatment, she never will. My hope is that we create a future together that allows diseases like hers and children like her to be able to be treated at a global scale. I'm excited about the hub's ability to be creative and innovative, and I'm committed to helping. Thank you for having me today.

Susan Winckler (01:31:13):

Thank you. Our next in-person comment will come from Kiran Musunuru. In the queue, we have Heidi Ross and Marshall Summer. We'll then turn to topic two, which is rare disease specific scientific regulatory or policy issues to prioritize. Our first virtual speaker there will be Esther Hars. But here, we turn to Dr. Musunuru. Please proceed.

Kiran Musunuru (01:31:36):

Thanks so much. I'm a physician and scientist at the University of Pennsylvania. It's also my pleasure and privilege to represent the NIH's Somatic Cell Genome Editing Consortium, whose aim is to reduce the burden of diseases caused by genetic changes. I'd like to make a few points that are relevant to the FDA's Rare Disease Innovation Hub. Most genetic diseases are caused by a wide variety of genetic changes, of variants, and it might well be the case that some patients with a particular disease have different variants than other patients with that disease. It might be even that one patient with that disease has a variant that's unique to them that they don't share with anyone else in the world. We now have tools that will allow us to precisely edit and correct these genetic changes, these variants. But if we adhere to the traditional model of drug development, where a lot of effort, many years, and tens of millions, if not hundreds of millions of dollars, are put into making one particular drug, it's simply not going to be feasible for us to make a drug for every patient with their own variant. Because of commercial considerations, we're seeing that drug development efforts are now biased towards certain disease genes and certain frequent variants in those genes, and most other patients are being left behind. Fortunately, like some other technologies, genome editing readily lends itself to a platform approach. We can make a drug that works well for one group of patients that would correct their variant and their disease, and then we can easily repurpose that drug by changing just one small component out of, say, six or seven components. All those rest would be exactly the same, and now that drug can help a different group of patients with a different disease. And we can do that again and again and again and even help those patients who have unique variants. The drug's almost exactly the same. The safety considerations are the same. There's no need to redo expensive safety studies and prove the drug's worth over and over again. In fact, we shouldn't even really be thinking about these as drugs per se, but rather as one-time interventions, almost like molecular surgery. And of course with surgery, a lot of discretion is given to physicians to determine when it's appropriate or not appropriate to intervene for a patient.

(01:33:33):

And so I would urge the Hub to focus on regulatory innovation that would unlock the power of platform technologies like genome editing, but also to focus on equity. There needs to be a move away from siloing patients based on their particular disease and their particular variants. If that continues to happen, there's a real risk that however inadvertent it might be, there will be discrimination against

many patients who have ultra rare diseases or diseases so rare they might not even have a name or who have unique variants and who don't have communities to advocate for them. We need to cover all patients with a particular disease under a single umbrella, and then we need to cover all genetic diseases affecting a particular organ, no matter how rare the disease is, under a single larger umbrella. There needs to be a paradigm shift. Once the safety and efficacy of a genome editing drug is proven for one group of patients, it needs to be very simple and straightforward from a regulatory perspective to start bringing a much larger variety of patients under those umbrellas.

(01:34:32):

Let's make sure all patients have a fair shot at this. They deserve nothing less.

Susan Winckler (01:34:37):

Thank you. Our next presenter will be Heidi Ross, followed by Marshall Summer. Then we will turn to our virtual presenters for topic two. In the queue we have Eszter Hars and Mary McGowan. Please proceed.

Heidi Ross (01:34:50):

Thank you. My name is Heidi Ross and I'm the Vice President of Policy and Regulatory Affairs at the National Organization for Rare Disorders. NORD was founded over 40 years ago after the passage of the Orphan Drug Act to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. We proudly work with individuals affected by rare disease, our 350 plus member organizations, our corporate council and our network of 40 rare disease centers of excellence across the country to advance rare disease research and funding to support the development of new treatments and cures, raise awareness and addressing key knowledge gaps, advocate for affordable comprehensive healthcare, including access to safe and effective therapies.

(01:35:33):

NORD applauds the FDA's creation of the Rare Disease Innovation Hub and believes it should initially focus on three key priorities: improving communication between the rare disease community and the FDA, strengthening alignment between CDER and CBER and better explaining the rationale behind differences in decision making between the two divisions, and developing tools and approaches that can be leveraged across drug candidates and diseases, including learning from past activities and establishing opportunities for impactful patient engagement, also with academic investigators and small emerging biotech companies.

(01:36:06):

To make tangible progress on these priorities and improve the health outcomes for individuals living with one of the 95% of rare diseases that don't have a safe and effective treatment, NORD urges the Hub to prioritize in the short term creating standing mechanisms for patient and clinician-focused dialogue, including the creation of a standing advisory council to advise the Hub's Director and ex-officio CBER and CDER directors, fully integrating CDRH into the Hub to help sustain rare disease diagnostic and device innovation, and establishing an academic researcher assistance program to provide investigator-initiated I&D assistance. This should include training and a structure for continued mutual engagement and learning to better understand the requirements for and improving the design of rare disease preclinical enabling studies. In particular, this type of assistance program could provide valuable clarity for investigators developing therapies to treat N of one and very rare diseases.

(01:37:09):

Finally, for many in our community, FDA approval represents a huge milestone, but it's just one of many barriers to affordable access to that treatment. Therefore, NORD urges FDA through the Innovation Hub to work with the Centers for Medicare and Medicaid services, patients, clinicians, and other stakeholders to standardize data collection including the use of real-world data and data from post-market commitments to enable robust coverage policies by payers.

(01:37:34):

NORD looks forward to working with the FDA and our community to make the Hub a success from the perspective that matters most to the patient. Thank you.

Susan Winckler (01:37:41):

Thank you. Our final in-person comment for topic one will be Marshall Summer. Please proceed.

Marshall Summer (01:37:48):

Thank you, Susan. My name's Marshall Summer. I've been in the rare disease world for about 40 years, mostly as a clinician. When I retired from clinical practice last year, being a compulsive meddler, I got into the field of clinical trials. I've been part of about 130 during my career, whether as a PN or a PI or a collaborator. So I've learned a couple of things along the way and I really appreciate the FDA's efforts around this new Center for Excellence and Innovation. I think it's a marvelous, marvelous initiative and I look forward to how it goes forward.

(01:38:22):

Three things I've learned over the years and working a lot with FDA along the way as well as with sponsors, patients, and then the clinicians. There are a couple, three factors. One is trial time. Trial time, whether it's from the design built in and what you're going to find, the common theme in my comments is design, which reflects the FDA interaction, is one of the key elements to how well these trials go. Trial time can kill off companies with short runways, can frustrate parent organizations, can make folks run out of runway basically and never finish what they started. That can be a product of regulatory requirements. It can be a product of the few patients in any given group. The inability to sometimes pull patient groups together so you can get sufficient numbers.

(01:39:10):

Cost, interestingly enough, is a reflection of both time and design. The design, how big the trial is, things like that. And that's where I think innovative interaction with FDA between sponsors, patients and the agency can really impact that. There are a lot of innovative things that could be done that aren't currently being used. And that kind of brings me to my third point, which is trial design.

(01:39:34):

That elevator button on the right I think reflects sometimes what we try to do in rare disease design. We're using a model that's obsolete. It was designed around common diseases. It was designed around using that and I think this new center, this new Center of Excellence can really be a pathfinder, a leader in trying to bring new ways to do these things or at least share the information. If someone does something that's novel that seems to work, making sure that information spreads to other parts of the agency.

(01:40:04):

Predictability and consistency are something that sponsors, patients and I think the regulators crave. But what I'd say what we really need is consistent flexibility or flexible consistency. I'm not sure which one, I kind of toyed with both of those, but we have to have flexible designs, but we need to consistently

approach whatever section of FDA it is, we really need to consistently approach all of these studies with an open mind on what's going to be best for the patients, what's going to give us the best information and try to get these treatments to patients. We've had over 12,000 rare diseases now and counting. This is going to take a lot of time and a lot of work.

(01:40:44):

So I thank you for the time to make these comments. Very excited about the new program. 4, 3, 2, 1.

Susan Winckler (01:40:52):

Thank you. With that, we conclude the public comment for topic one. I must observe that each of our public commenters not only provided really helpful and passionate insight, but in an exquisitely timed manner, which is appreciated, allows us to hear from more of you.

(01:41:11):

Let's now turn to topic two, which is where we turn from cross-cutting to rather rare disease-specific scientific, regulatory or policy issues to be prioritized. We'll begin with our virtual commenters. Our first virtual commenter is Eszter Hars. In the queue, we have Mary McGowan, Jennifer McNary, and Elad Sharon.

Eszter Hars (01:41:33):

Hello, my name is Eszter Hars. I'm joining you today as the President and CEO of the Schwachman-Diamond Syndrome Alliance and the mother of a child with Schwachman-Diamond Syndrome. Thank you for the opportunity to share some thoughts with you today and most of all to initiate the Hub as a project.

(01:41:55):

SDS is a rare genetic disorder that causes many problems in the body, but what unifies us as patients the most is the fear of a specific complication, which is the development of leukemia. It's estimated to hit about 30% of patients by age 30 and is almost universally fatal. So what we are most concerned about as parents is really an invisible aspect of the disease, and what we would like to see in the Hub is support for the development of outcome measures and biomarkers to be able to assess this type of risk for all sorts of possible modalities to treat the disease.

(01:42:45):

So we see this as almost like a platform asset to the FDA and for us as a patient community because once we know how to measure this risk, this can then be applied to gene therapy for small molecules, drug repurposing, all sorts of possible interventions that can save our patients' lives.

(01:43:08):

In particular, I'm proposing that the Hub may be able to help patient organizations and patient communities stand up multi-stakeholder approaches, meetings, consortia to address the development of biomarkers and endpoints, whether it's with logistical support or possibly even some sort of funding, maybe a grant that could go towards this type of work.

(01:43:41):

So to tie this back to what we heard in the very beginning as some of the priorities for the Hub is to have a single point of entry, this could support this kind of need as well where patient organizations and communities could approach the Hub asking for help to stand up this sort of multi-stakeholder project. And it would also include the holistic discussion across multiple functions of the FDA communities, past

clinical trials and data, pulling it all together, but not just for the benefit for the FDA, but for the whole community including a research and patient community.

(01:44:27):

So I'll leave it on that and thank you very much for the opportunity to contribute these thoughts to the development of the Hub.

Susan Winckler (01:44:35):

Thank you.

(01:44:36):

Our next speaker is Mary McGowan, followed by Jennifer McNary and then Elad Sharon. We'll then turn to our in-person, commenters, beginning with Carole Ho. But now we turn to Speaker McGowan. Please proceed.

Mary McGowan (01:44:51):

Thank you. Good morning. I'm Mary McGowan, CEO for the Foundation for Sarcoidosis Research, the world's leading international organization supporting 175, 000 patients impacted by sarcoidosis. I'd like to extend my sincerest gratitude to the FDA for the opportunity to speak on this important topic for the formation of the Rare Disease Innovation Hub.

(01:45:13):

FSR has been proactively engaged with the FDA to drive change. We've had private meetings, patient listening sessions, a patient-focused drug development meeting that is taking place on October 28th from 10 to 3 P.M., and has been providing responses to requests for comments in order to plant seeds for consideration of impactful change. For far too long, the rare disease community has waited for transformative innovation to catalyze treatment. Although the 21st Century Cures Act has been responsible for an increased number of new drug approvals in rare disease, the orphan drug and accelerated approval designation has been a significant motivator for industry and especially biotechs in investing in the rare disease space. However, there remains disconnect from the individual divisions and the offices leading orphan drug. We are encouraged by the role of the Hub in serving as a single point of contact for the rare disease community and the interaction with CDER and CBER.

(01:46:10):

For too long, rare disease clinical trials have been made to fit into trial design and data strategies created for larger populations. Data models, natural history requirements, endpoints and outcomes assessment strategies are not one size fits all. Trials should be designed for the patients most likely to use the therapy, not the healthiest version of someone impacted by the disease. We hope that you will engage with patients and caregivers as you begin to think through work streams that consider new approaches to data collection, novel endpoints, biomarker development, innovative trial designs, real world evidence and statistical methods.

(01:46:52):

Finally, and perhaps most importantly, FSR as the lead organization of the Coalition for Clinical Trial Equity encourage you to build these shifts that are more accommodating of clinical trial diversity, including innovative strategies to support clinical trials. We hope the Hub will be committed to working with policymakers to advance meaningful improvements and address established barriers. Thank you for this bold step in the right direction, and we welcome the opportunity to continue to work with you as you build out the Hub.

(01:47:21):

Thank you very much.

Susan Winckler (01:47:24):

Thank you. Our next speaker will be Jennifer McNary. In the queue is Elad Sharon. We'll then move to in-person comment from Carole Ho and Annie Kennedy are the two in the queue there. Jennifer McNary.

Jennifer McNary (01:47:38):

Thank you.

Susan Winckler (01:47:39):

Please proceed.

Jennifer McNary (01:47:41):

Thank you. My name is Jennifer McNary and I'm the mother of three young men living with rare conditions. I'm also the co-Founder of Canary Advisors, a firm that's committed to supporting patient-focused drug development, especially in the rare space. Thank you for the opportunity to share my thoughts today on priorities that should be considered by the Rare Hub, which will only enforce many of the points already raised by FDA Senior Leadership this morning and of many of the public comments by my peers. It is my hope that the formation of the Rare Hub will reinforce pull through of senior leadership viewpoints in considering totality of evidence and placing added value on avoiding the type two error when facing decisions around a condition with unmet need.

(01:48:23):

To that end, the Hub should further enable inter-office communication and cross-center consistency to ensure that we are moving forward with urgency, especially in situations where outcomes and biomarkers have been established with previous programs or in like conditions.

(01:48:37):

The Hub should serve as a conduit for enhanced patient caregiver advocacy organization, academic and company access to the agency. In addition to ELPFDD and listening sessions, earlier, more frequent, deeper multi-stakeholder conversations are paramount to better collaboration. The Hub should be a space for real-time discussions so that even products for the rarest of indications may have a path forward. Natural history control groups are incredibly important, especially in ultra-rare conditions. This should be a topic of focus and discussion amongst the Rare Hub experts. Communities go to great lengths and expense to collect this valuable data in hopes that it may be useful during the drug development process. I have seen firsthand the power of patient experience data not to replace but to add context and meaningfulness to the available data set. Actually hearing in the patient's own words the impact of product on how the person feels and functions in their everyday lives is invaluable.

(01:49:37):

The Hub should consider ways to further incorporate patient and caregiver experience data into reviews, especially in smaller data sets. The Hub should also enable the identification and utilization of outside experts when needed. In rare and ultra-rare populations, internal expertise may not always be available, and especially in the case of advisory committee meetings, external experts in these conditions can help contextualize data. Waivers should be more routinely utilized where conflicts may arise because experts in ultra-rare diseases are almost always conflicted, especially if they're one of a

handful of global experts. I am hopeful with such passionate leadership and commitment from the agency that the Hub will offer opportunities for more innovative therapies to make a difference in people's lives.

(01:50:24):

Thank you.

Susan Winckler (01:50:26):

Thank you. Our final virtual comment in topic two will come from Elad Sharon. In the queue for in-person comment, we have Carole Ho, Annie Kennedy and Becca Reef.

(01:50:38):

Elad Sharon, please proceed.

Elad Sharon (01:50:43):

Thank you so much for the opportunity to comment. My name is Elad Sharon. I'm a medical oncologist now at Dana-Farber Cancer Institute. I guess I should note that for 16 years I worked for the federal government at the National Institutes of Health, in particular at the NCI and the Cancer Therapy Evaluation Program, and I was involved quite a lot of that time in rare disease drug development, specifically rare cancer drug development leading to FDA approvals for new therapies and new avenues for patients with rare cancers in general.

(01:51:15):

I applaud the FDA for this Rare Disease Innovation Hub. I think that there's an extraordinary need for innovative thinking in rare disease drug development in general. I moved from the NCI to Dana- Farber Cancer Institute in August, 2023 in order to stand up a program in clinical and translational research in immune-related adverse events. During most of my time at the NCI, I was primarily involved in immunotherapy drug development, and I was also involved with the Beau Biden Cancer Moonshot Initiative in immunotherapy research in general.

(01:51:54):

What I noticed during that time was that we leave some patients unfortunately behind who have immunotherapy-induced toxicities, immunotherapy toxicities that can sometimes be debilitating, lifelong, or even be fatal. Those individuals oftentimes benefit from other therapies that are available through autoimmune disease research and other translational research methods to help identify and characterize and better understand the mechanisms around immunotherapy toxicity are available.

(01:52:29):

But unfortunately, industry and even the NIH and academic colleagues do not emphasize this enough. We need innovative thinking, but we also need guidance from the FDA in order to provide for clinical trials and drug development with pathways to approval for new agents that might ameliorate the situation for this new class of patients developing essentially a new set of diseases. Immunotherapy is amazing and I'm still involved with immunotherapy drug development. I care very deeply about bettering the world for cancer patients, but that involves not only giving treatment for patients with cancer, but also taking care of those patients who suffer from harm caused by the treatment for the cancer that we give. And the only way for us to do better is to both do research certainly, but research with clinical trials with clinical intent in order to aim to ameliorate the situation for these patients. Thank you so much for the opportunity to speak.

Susan Winckler (01:53:33):

Thank you. We will now turn to our in-person comment. First, we will hear from Carole Ho. Then, Annie Kennedy, Becca Reef and Kent Rogers. Dr. Ho, please proceed.

Carole Ho (01:53:45):

Thank you, and good morning. I'm the Chief Medical Officer and Head of development at Denali Therapeutics. I'm a drug developer and a neurologist. Our technology enables delivery of protein-based therapeutics to the brain. With this innovation, we aim to significantly improve the lives of patients and families living with brain disorders, including ultra-rare lysosomal disorders such as MPS diseases. We are facing an urgent need. Children are losing skills daily to these diseases because current therapies do not address the toxic accumulation of waste that causes brain damage. Fortunately, the pace of advancing science and technology has accelerated. Leaders with regulatory, scientific, medical and advocacy expertise are needed for more frequent opportunities to share data and apply these cross-cutting learnings to therapeutic development and approval.

(01:54:36):

I recommend that the Hub prioritize a pre-competitive form to enable multi-stakeholder therapeutic development ecosystems to convene to address challenges, including companies, academicians, advocacy and the FDA. I will summarize a powerful example for this proposal and also provide two topics that could be discussed in an upcoming such forum.

(01:54:57):

First, the example. In 2018, the FDA issued a draft guidance for accelerated approval for single enzyme deficiencies such as MPS, recognizing the challenges of these diseases. Even with this guidance, by the end of 2023, therapeutic development for brain diseases and MPS remain challenged by the absence of a clear and sustainable path for regulatory approval. This situation impacted both therapeutic development progress and investment in these diseases. In February 2024, the Reagan Udall Foundation led a collaborative scientific workshop on the use of a biomarker to support accelerated approval attended by CBER, CDER and a community of stakeholders. Only six months after this foundation meeting, a peer review paper was published on the community consensus of the utility of this biomarker to support accelerated approval. Several companies are now pursuing accelerated approval pathway to bring these novel medicines to patients. This foundation meeting provides a very powerful model for a future pre-competitive forum that engages FDA leadership and the community to enable translation of FDA regulatory guidance to action, enabled by cutting edge science.

(01:56:07):

Now, two examples of topics that could be discussed at an upcoming forum. The pre-competitive forum is needed to address consistent approaches across regulatory standards, approaches to acquiring open label or randomized studies to support approval should be harmonized across a specific disease area. Enabling open label studies for one therapeutic modality but not another has an unintended consequence of discouraging participation in therapy with a randomized design. Building on this first example and considering strong preference for open label studies, there is an urgency to embrace innovative study designs and utilize natural history data consistent with the FDA natural history guidance from 2019.

(01:56:47):

I'm grateful to be here contributing.

Susan Winckler (01:56:50):

Thank you. We'll now hear from Annie Kennedy, Becca Reef, and then Kent Rogers. Please proceed.

Annie Kennedy (01:57:00):

Good morning. I'm Annie Kennedy and I am pleased to be providing remarks on behalf of the Every Life Foundation for Rare Diseases and the broad rare disease community. My comments today reflect the insights of our diverse coalition comprised of patient advocacy organizations, industry leaders, and other stakeholders who together inform our policy efforts.

(01:57:21):

Since convening a series of town hall meetings to assess our community's needs, followed by a scientific workshop in 2018, our community has advocated for the creation of an Inter-Center Institute for Rare Diseases to serve as the FDA's Coordinating Office for the optimization of rare disease expertise, processes, and engagement with rare disease stakeholders. On behalf of the hundreds of patient advocates, many of whom are pictured above or are here today who advocated for the establishment of this Inter-Center, we are delighted that today signifies. So, first, thank you. As the Hub launches, we urge the prioritization of projects and infrastructure that will enhance consistency and improve the predictability of how any given Office, Division or Center will approach the application of regulatory flexibility. Highlights of the initiatives we recommend the Hub undertake include establishing cross-functional consultation processes that will enable internal experts to be efficiently consulted at the request of either FDA staff or a sponsor, supporting the creation of a knowledge management system that will increase access to and awareness of information on how FDA has approached the application of regulatory flexibility in rare disease, supporting the dissemination of FDA pilot program learnings and data to enable rapid application of information to relevant rare disease work, advancing ultra-rare policy by issuing guidance that can be operationalized, consistent approaches to evaluating ultra-rare therapies within FDA's existing authority, and advancing Advisory Committee's rare disease knowledge by establishing a rare Disease Advisory Committee within the Hub to serve in a consultative and disease agnostic approach, enabling external experts to support review committees across the centers in providing guidance on emerging issues.

(01:59:28):

And for today, most of all, the community, we would like to say thank you. We look forward to the Hub being a catalyst, another C, for collaboration and innovation, so that the promise of today's pipelines can benefit this generation of children and adults living with rare diseases. Thank you.

Susan Winckler (01:59:48):

Thank you. We have three additional public commenters here in person for this topic, and then we will be taking a break. So Becca Reef will be our next speaker, followed by Kent Rogers and Christine Waggoner. Please proceed.

Becca Reef (02:00:04):

Hi everyone. My name is Becca Reef. I'm the Scientific Coordinator for the Adult Polyglucosine Body Disease Research Foundation, an organization which focuses on a rare adult onset recessive neurodegenerative glycogen storage disorder. I'm honored to be here to provide insights on what we believe should be prioritized by the Hub, and we really want to express our genuine gratitude for the invitation, as well as all of the exciting insights provided during the opening remarks and all of the voices of those in the broader rare community.

(02:00:36):

Recently, our foundation hosted a biannual conference where we asked our community of 200 stakeholders in two to five words, "What does advancing APBD research look like to you?" The responses that we received were powerful and revealing, including not a straight line, perseverance, data sharing, funding and urgency, a marathon, expensive, commitment, slow and my only lifeline. While we're incredibly grateful for the diverse group of academic industry and community partners committed to advancing our mission, the conference where exciting updates on potential biomarkers, gene therapies, and small molecule treatments were presented left us with more questions than answers on how to move forward.

(02:01:18):

In light of these insights, we strongly urge the Hub to prioritize efforts that foster greater collaboration and improved coordination, as we've discussed greatly today, as well as increased engagement between the FDA patient advocacy groups and research organizations. So how do we propose that we begin to try to tackle this monumentous and enormous task?

(02:01:39):

Address regulatory inflexibility to streamline approval processes, compress drug development timelines to accelerate access to treatments, harness creativity to overcome practical challenges and trial design, increase the accessibility of consortium grants that promote collaboration and data sharing, either by expanding funding or offering more frequent application opportunities. Developing best practices and clear frameworks for drug repurposing, which is three to five times faster and about half as costly as developing a new drug from scratch. Create new incentives for the development of drugs that target pathways beneficial to multiple rare diseases. Establish a task force to review previously abandoned drug development plans as a 2022 study found that nearly half were shelved due to business decisions rather than clinical inefficacy. Lastly, hold regular meetings with groups of patient advocacy representatives to share scientific updates and foster greater transparency and collaboration among all stakeholders.

(02:02:40):

Advancing research for not only APBD, but all rare diseases requires a concerted collaborative effort. Together, we have the opportunity to change the course of rare disease research and provide hope to those whose lives depend on these advancements.

(02:02:54):

Thank you so much for your time and your consideration of these urgent priorities.

Susan Winckler (02:02:59):

Thank you. Our next public commenter will be Kent Rogers, followed by Christine Waggoner. Please proceed.

Kent Rogers (02:03:06):

Thank you. Good morning. My name is Kent Rogers, and I'm the CEO of EveryONE Medicines, a company committed to designing and developing individualized medicines for children with fatal and life-threatening neurodegenerative disease, individualized medicines that target a single mutation that is unique to an exceptionally small number of children, or perhaps even just one.

(02:03:28):

Mila, who was diagnosed with Batten disease at the age of six, became the first person in the world to receive a medication designed and developed specifically for her, an antisense oligonucleotide, an ASO,

which was named after her called milasen. ASOs can effectively treat genetic mutations afflicting the very few or the one. And while guidance has been issued for the research of individualized ASOs, it does not address the potential opportunity to scale this solution for treatment. While these diseases are unique, they add up to a disturbingly significant number of children with genetic mutations amenable to ASO treatment like Mila or more will be diagnosed as access to whole genome sequencing improves. Time is not just of the essence for children with neurodegenerative disease, it is the enemy. If each ASO is considered a different drug as defined in statute and subject to the current regulatory pathways, time will continue to run out for them and treatment cannot be scaled. Regulatory agencies across the globe are quickly recognizing the dilemma of not having an appropriate process in place to assess, evaluate, and approve treatments for the individual which cannot be adequately studied in a randomized controlled clinical trial and may not have adequate biomarkers for evidence of effect. We know Bayesian theory alone is not the answer, but concepts can be drawn from the Platform Designations program, the Device Center's proposed Pre-certification program and possibly elements from the Risk Evaluation and Mitigation Strategies program.

(02:05:05):

These are just a few among the many possible solutions and we are encouraged the Innovation Hub has the goal to create a collaborative process that involves active engagement and hopefully the development of a tailored regulatory review and approval process for individualized medicines with a continued focus on clinical safety standards, but may have to rely upon establishing a body of clinical evidence in a real-world setting instead, which gives these children often facing a daily risk of death, a fighting chance at life like Mila had. Thank you for the effort of creating the Innovation Hub for your attention today and we look forward to working with you.

Susan Winckler (02:05:45):

Thank you. And for our final public comment before we go to break, we'll turn to Christine Wagner. Please proceed.

Christine Wagner (02:05:54):

My name is Christine Wagner and I'm the founder of the Cure GM1-I Foundation. GM-I gangliosidosis is a neurodegenerative lysosomal storage disease that primarily impacts babies and children. My daughter Iris has suffers from juvenile GM-I. She was diagnosed at age five and she's now 16. For 11 years, we have done everything in our power to help the drug development process, raising millions of dollars, publishing papers, participating in natural history studies, conducting a caregiver preferences study and organizing the first externally-led patient-focused drug development meeting for GM-I, With respect to scientific regulatory and policy issues, I'd like to highlight three key topics that are relevant to GM-I and other similar conditions. First, accelerated approval based on primary disease biomarkers. Second, the ethics of placebo-controlled trials in neurodegenerative diseases and finally, much-needed flexibility for highly heterogeneous populations and ultra-rare diseases.

(02:06:53):

GM-I was distinguished as a unique condition in 1968. It has an incidence of one in 100,000 to 200,000. The deficiency of β-gal and the accumulation of GM-I ganglioside is the very definition of the disease. We must ask ourselves why treatments which have corrected GM-I ganglioside to normal levels are still out of reach of dying patients. Has a framework designed for common diseases caused the abandonment of our programs. In recent years, four companies have gone bankrupt and shelved their programs, despite several of the trials demonstrating excellent results in biomarkers and even stabilizing patients and improving quality of life. Accelerated approval based on primary disease biomarkers could

save programs that are now on the precipice of being lost forever. Children and babies impacted by GM-I are experiencing brain damage, some with degeneration beginning in the womb.

(02:07:54):

Our disease is so severe and so intense that nearly no family is willing to risk receiving a placebo. The youngest and healthiest children are being asked to give up their fleeting minuscule period of normalcy and to forego possible treatments that have a reasonable likelihood to benefit them. Finally, our disease is a spectrum, is extremely heterogeneous and ultra-rare. GM-I requires regulatory flexibility with respect to labeling of products. This is a real possibility that overly strict labeling could prevent swaths of our community from ever having a treatment. Innovation and flexibility are desperately needed for ultra-rare neurodegenerative diseases like GM-I. Let's create a more compassionate framework and meaningful change. Thank you.

Susan Winckler (02:08:45):

Thank you. Please join me in thanking all of our public commenters on Topic 1 and Topic 2. It may seem easy to step in front of a microphone, virtual or in person to share insights in three minutes, and I believe that each of our commenters would assure you that it is not and yet it was very important input. We're now going to take a break. We will return at 12:50. And we will start at 12:50, so we welcome you back in the room at that time. For those of you who are in the room, there's lunch to purchase outside in the kiosk, but take a moment, stretch your legs and we will see you back here at 12:50 for our virtual audience. We will see you at the same time. Thank you.

(02:09:38):

All right, I'll welcome everyone back to the meeting. We have two more sections of public comment and we are most interested in hearing those remarks. As a reminder, we have two topics left, Topic 3 and Topic 4. We are going to hear from a Topic 4 speaker first, we have a virtual representative who has a scheduling conflict that requires him to speak first, so let me start our queue. Our first commenter for the afternoon will be Robert Kolwinsky. Then we will turn to our in-person comment, specifically for Topic 3 and we'll hear in the queue we have Mark Dant, Kath Gallagher and Deven McGraw. So let me confirm that we have Robert Kalwinsky ready virtually to present comment and if we pull up his video and please proceed.

Robert Kalwinsky (02:10:45):

Hello? Can you hear me?

Susan Winckler (02:10:47):

Yes, we can.

Robert Kalwinsky (02:10:51):

Okay. Thank you for accommodating me. The topic I'm discussing is the approaches that the Hub can take to engage with patients and caregiver groups and scientific academic organizations. I'm going to talk about as a patient representative, recurrent lymphocytic meningitis, and I want to suggest that the Hub interact directly with three entities. The first is several representatives from the recurrent lymphocytic meningitis group on Facebook, which has 1,500 registered people, they're all PCR verified users. Some of them are MDs. I would let the administrators of that group, which is also related to the herpes advocacy group, choose some people to represent the group and maybe only one MD because we have several MDs in the group. But I think a patient, a non-MD, some non-MD patient advocates

would also be useful. And I also suggest for secondly that they work with Dr. Alan Schneider-Heidt MD, PhD, PMPH at Tel Aviv Medical Center.

(02:12:07):

He's done a lot of research into this entity. And then finally, the group at the University of Washington, Dr. Keith Jerome MD, PhD and Dr. Anna Wald MD, MPH who have been researching and interacting with the Facebook group of the most viable scientific research for a treatment here based on in vito and in vitro studies into rare-cutting endonucleases and are knowledgeable about this disease. Dr. Heidt is particularly involved with studying recurrent lymphocytic meningitis. The next statement's a little absurd and you'll know why when I say it, but I'm going to say it anyway.

(02:12:47):

In tandem with interactions, it's vital that funds be directed when possible to the most effective research approaches. And the laboratory of Dr. Keith Jerome evidence this without reasonable funding for research, the discussion becomes relatively meaningless. As a patient advocate, I believe that streamlining the approach to these three entities, the Facebook group representatives, Dr. Jerome and Anna Wald, and Dr. Heidt will be the most efficient means of advancing treatment for this disabling disease of recurrent lymphocytic meningitis. And note that this approach using the rare-cutting endonucleases is also valid for other viral diseases like HSV-I, HSV-II, COVID, HIV, so it's not limited to just recurrent lymphocytic meningitis. Thank you.

Susan Winckler (02:13:42):

Thank you. We'll now turn to our in-person comment for Topic 3. As a reminder, Topic 3 is Rare disease-related activities or initiatives that are currently being undertaken independently by the Center for Drugs or the Center for Biologics that you believe would benefit from being undertaken by the Rare Disease Innovation Hub as a joint activity. So as a reminder, our first in-person speaker will be Mark Dant, and then in the queue we have Kath Gallagher, Deven McGraw and Kasper Roet, please take the microphone and proceed.

Mark Dant (02:14:21):

Thank you. The Hub is a reality because of the groundswell of the patient voice. Thank yourselves and thank you FDA for responding and we look forward to the future. Thank you very much. We cannot afford to lose another generation of children. We must shift the current clinical trial model to reflect the unique challenges of rare disease research. We can no longer use the gold standard of clinical trials, double-blind placebo control for pediatric rare diseases. It is unethical to sacrifice the child's life for the sake of a science experiment. When there are better ways to measure effectiveness such as primary disease activity biomarkers. We hear repeatedly that we need lengthy trials with control groups because inadequate natural history data is available. This simply is not true. In fact, there have been numerous published, rigorously designed observational studies over the years to confidently predict natural history. Our kids suffer and die prematurely. Meet Hayden with MPS-IIIA at the age of three was waiting for treatment.

(02:15:37):

By eight she's still waiting and has lost mobility, speech and the ability to eat by mouth, skills she will not regain. This is a perfect example of the devastation children do experience in a control arm. Our current system is doing harm, trials for our kids often take eight to 10 years. We are losing generations of kids. It is vital for rare disease Innovation Hub not to become another bureaucratic check mark for our government. We do not need more policies and regulations, we need action. We need the clinical trial

process streamlined for quicker approval so more children can be dosed. Children are dying waiting for treatment. There has to be consistency between CBER and CDER.

(02:16:26):

If not, caregivers are forced to weigh clinical trials based on the practice of each regulatory division rather than on potential treatment outcomes. For too long, we have had others speak for us, scientists, companies, physicians, even our own FDA, yet none of them are with the patient 24/7. Patients and caregivers must be represented and systematically integrated into the Rare Disease Innovation Hub. The priority must be envisioning clinical trials. Trials are taking too long and our children cannot wait. Swift action to change the paradigm for rare disease clinical trials can save this generation. Thank you.

Susan Winckler (02:17:15):

Thank you. Our next in-person comment will be from Kath Gallagher. Then we'll turn to Devon McGraw and Kasper Roet. The virtual queue, Dorothea Lance will be up following our in-person comment. So speaker Gallagher, please proceed.

Kath Gallagher (02:17:31):

Thank you so much. Hello. Thank you for allowing us to be here. I've really been thinking about this and this feels like a real legacy moment for the rare disease community, this meeting today, right here. And it's really an honor to be a part of it, so thank you for that. I'm Kath Gallagher. I'm the Chief Program Officer at Avidity Biosciences, and Avidity is pioneering the revolutionary delivery of RNA therapeutics to places outside the liver. That is our goal and we have shown that in three rare disease programs that are all in clinical development today. We have three things we're asking for. The first is aiming for exceptional. The second is consistent development pathways and end points. And the third is communication and education. So aiming for the exceptional, being able to work with FDA in my own programs, there is a lot of exceptional work already going on both in CBER and in CDER.

(02:18:30):

And of course there's room for improvement and our vision is that what this Hub allows us to do is have the exceptional happen for rare disease across the board. And that is really what we are asking for is to take the best practices from both and bring them to rare. And it sounds like that's very much in point with what you're trying to do. The other one is consistent development pathways and accelerated approval. The Human Genome Project was this amazing thing and we are seeing the fruit of that now in the clinic. And with all of these genetically targeted diseases where you know the gene and you know how to target it, there really shouldn't be differences in what the pathway is. And so we're looking for that as well and I've heard a lot of support for that today too from the leadership and thank you for that.

(02:19:14):

And the third one is communication and education. And in this case, rare is different. We all know that. And oftentimes it's the patient community, a handful of physicians and the company that's working on them that actually are the experts in these diseases and it requires all three of them working together really well to make that happen. And we've heard that over and over again today. And so we're looking for the Hub to be a place where they can utilize these experts and bring them in and allow them to be part of the process where it's appropriate. And in terms of education, also making sure that you utilize those people to help educate the people that are viewing these.

(02:19:55):

I think often about the FDA employees and how many, that conveyor belt was a really powerful image, how many different things are looking at every day. They can't possibly know every single rare disease.

And so really using the Hub to utilize the experts would be an amazing step forward for the agency and for rare diseases as a whole. One of the things as a rare disease company that really keeps my heart here is that part of what you do, especially when you're working in a disease where there is no treatment, is you work with the community and you write the history book for that disease and this is FDA's chance to do that for rare diseases as a whole. Thank you.

Susan Winckler (02:20:35):

Thank you. Our next commenter will be Deven McGraw, followed by Kasper Roet. Then we will turn to the virtual commenters including Dorothea Lance and Rob Purdie. Please proceed.

Deven McGraw (02:20:48):

Thank you, Susan. Thank you to the FDA and to the Reagan-Udall Foundation for the opportunity to speak today and for this moment, really been impressed by what I've heard so far and excited about what's ahead for rare diseases. I'm Deven McGraw, I'm the chief regulatory and privacy officer of a company called Citizen Health. We help patients to utilize their rights under law to get complete copies of their medical information from every single place where they've been seen so that they can then leverage that data for their own care and also to contribute it for research purposes. It's a really important source of potential real world data and lots of opportunities to help contribute to research including in medical product development. The five Cs are great and everything that I've heard about the Hub so far again makes us completely excited. But the key to advancing treatment for rare I think, is really in the I, in the innovation part of the Hub's name traditional gold standard approaches to data collection and clinical trials often unintentionally end up creating insurmountable barriers to the development of drugs in rare.

(02:21:52):

And these have led companies to abandoning potentially life-saving programs, leaving millions of rare disease patients without any hope for treatment. There is definitely examples where the FDA has deployed novel approaches to evaluating and approving therapies for rare disease patients, but it's not being done consistently across all of the centers. For example, using patient-level real-world data collected through routine clinical care and novel devices that monitor patient's activity daily. It represents a really promising and yet vastly underutilized resource in the regulatory process to date. Some areas where we see expanded use of real-world data include establishing longitudinal characterization of patient symptoms and experiences to support an optimized clinical trial design, focusing on clinical endpoints that are measured in routine clinical care, which can show modification of the disease over time. Using a patient's own natural history data or the natural history of a cohort as the placebo or baseline control, reducing the ethical dilemma associated with withholding treatment in rare disease trials and then enabling a more expedited path to much-needed treatment.

(02:23:04):

And then in fulfilling long-term follow-up requirements and post-marketing registry obligations around both safety and efficacy, streamlining the process for sponsors and patients alike. When we're confronted with uncertainty, I think it's so much easier for us to say no, but the consequences of failing to approve a drug are equally as problematic and are borne by the patients, so we are very excited about the opportunity for this Hub to help establish some consistency across the centers in the use of novel approaches to product approval and to serve as a point of connection to the rare disease community. We stand ready to help and are excited about what's to come. Thank you.

Susan Winckler (02:23:47):

Thank you. Our next in-person speaker is Kasper Roet, and that will close out our comment on Topic 3. Our virtual speakers in the queue are Dorothea Lance, Rob Purdie and Kristen Vanags. Speaker Roet, please proceed.

Kasper Roet (02:24:04):

Thank you. I just wanted to remind everyone that we're all here to help patients and I'm really excited. We are really excited with the creation of this Rare Disease Hub. I want to thank the FDA for this important step and I hope you don't mind that I'm going to address a pain point that we've been experiencing and I also want to come with potential solutions, with some recommendations. My company QurAlis, is developing precision medicine for neurological disorders. We have three programs targeting genetic targets for ALS. We have currently six programs on genetic targets in our rare disease pipeline, but the US is at a critical inflection point. We have seen these advances in genetics and they're accelerating, but we are losing competitiveness to other countries that provide regulatory environments that more encourage and embrace early phase regulatory science. So QurAlis actually together with a number of other companies leading a consortium of more than 20 companies that are all experiencing similar and consistent challenges with the US regulatory requirements.

(02:25:17):

The go-to strategy for many companies developing RNA Therapeutics at this moment is to start clinical trials outside of the United States, and that is small companies, mid-sized, but also large companies. And I hope you all agree that that is not a situation that we want to be in. At QurAlis we have three clinical programs ongoing. All of these at this moment being conducted outside of the US, in Canada, the UK, and in Europe. You heard from Dr. Ed Kaye from Stoke today and also from Kath Gallagher of Avidity. Those are members of our consortium and others will also be submitting written comments to the Hub. We hope the Hub will be able to provide these solutions because we all want American patients to be able to have access to our therapies to this American innovation.

(02:26:05):

The primary issue that we identified is the advancement of rare disease therapeutic development is appropriate risk benefit assessments, and so this we think should be a priority in the Hub's comprehensive cross-center strategic agenda. And our specific recommendations include advancing regulatory science in early phase development. We request a dedicated workstream for specific guidance development and FDA reviewer training and preclinical and pre-IND development phases. We also request dedicated and experienced reviewers from the Hub to work closely with industry and academia on new regulatory science techniques for preclinical toxicology and early phase risk benefit assessments calibrated to disease state, and as well as to available therapies. Secondly, we ask for more rapid phase of engagement and constructive communication with sponsors. And third, we ask for an expansion of the start program to early phase development. Thank you very much.

Susan Winckler (02:27:08):

Thank you. That concludes our public comment on Topic 3. We'll now turn to Topic 4, which is Approaches that the Rare Disease Innovation Hub should follow for engagement with patients and caregiver groups, industry organizations, and scientific and academic organizations. We will first hear from Dorothea Lantz. Then in the queue for virtual speakers are Rob Purdie, Kristen Vanags, and Meihui Wang. So if we have Dorothea Lantz ready, please proceed.

Dorothea Lantz (02:27:42):

Thank you so much. I appreciate the opportunity to be here with you today. Good afternoon, my name is Dorothea Lantz. I am the Director of Community Engagement with PWSA USA. But most importantly, I am Mom to Hunter who is seven years old living with Prader-Willi syndrome. As we look to maximize the impact of the Hub and provide for engagement with patients and caregiver groups, industry organizations, and scientific and academic organizations, it's essential that we establish a formal mechanism for advocacy group engagement. This engagement needs to go beyond consultation and evolve into co-creation. Advocacy groups not only provide critical data and insights through natural history studies, but they can be pivotal in creating outcome measures that truly reflect patient needs. Advocacy groups frequently develop disease-specific clinical outcome assessments, which are essential for evaluating treatment effectiveness and can help to improve the design and relevance of clinical trials.

(02:28:44):

Furthermore, there needs to be a structured platform for ongoing advocacy group engagement and collaboration between advocacy groups and FDA throughout the entire drug development process. This will allow advocacy groups to contribute meaningfully to protocol design, to clinical trial frameworks, and regulatory guidelines and ensure that the real-world impact of rare diseases are fully understood and considered in every evaluation. The integration of advocacy groups into decision-making frameworks can help to define criteria such as patient-reported outcomes and quality of life improvements. Advocacy groups can ensure that therapies are not only scientifically sound, but also make a meaningful impact on patients' lives. Patient input is crucial during protocol development. People living with rare diseases and their families bring unparalleled insight into the daily challenges and nuances of their conditions. By actively involving them in the trial design and treatment protocols, we can ensure that they're not only scientifically sound, but truly patient-centered.

(02:29:48):

And finally, it's essential to have a formal assessment of patient involvement. The Hub should work with sponsors and require companies to evaluate and report how they've engaged with patients throughout the entire protocol development process. This ensures that patient perspectives are an integral part of the development rather than an afterthought. A transparent system for tracking and evaluating patient engagement would hold companies accountable and establish a standard of practice, not only for the FDA to incorporate the patient voice in their approval process, but really set the standard for incorporating the patient voice from day one of the drug development process. Again, thank you so much for giving me some time to share with you all today. For additional information on how the hub can create structure to support the entire rare disease community PWSA and FPWR are submitting written testimony that should be in the portal later on today. Thank you again and we look forward to future collaboration.

Susan Winckler (02:30:50):

Thank you. Our virtual speakers in the queue are Rob Purdie, Kristen Vanags, and Meihui Wang. Then we will turn to in-person commenters, the first being Nina Nazar. So if we could pull Rob Purdie's video up.

Rob Purdie (02:31:08):

And I apologize, but my camera has been problematic.

Susan Winckler (02:31:12):

That is okay. We can hear you, so please proceed.

Rob Purdie (02:31:16):

And trust me, you're not missing anything.

(02:31:19):

I'm very excited to be able to give comments on this Rare Disease Hub, and I'm going to keep my comments very high level because I intend to submit written comments as well, so I just wanted to touch on and reiterate some certain things and the first being that we're very excited to see this model moving forward. MyCare is what we believe is the first pan-fungal patient-driven organization to address fungal diseases globally, meaning around the world, so while rare diseases are often associated with genetic disorders and specifically impact, a lot of them impact pediatrics, which we've already talked about and touched on today, it's important that this Innovation Hub takes a broad view of rare diseases and infectious diseases can be rare. COVID is not the only infectious disease and many of them are rare diseases and some are even ultra-rare.

(02:32:10):

And fungal diseases certainly fit that bill. There's an estimated 1.5 million fungal species in the world. It's an entire kingdom, 8,000 cause disease in plants and 300 or so are known to cause disease in humans, and many of those are considered rare, at least in the US. And fungal diseases have one difficulty with that is not common in other infectious diseases, which is the length of disease and the high level of morbidity. But across all these diseases, we think that patient engagement is key. We know that patients can be difficult to engage, so we need to look at ways to maximize these engagement opportunities. Looking at groups of rare diseases to pull patients together to address commonalities in those diseases is one way to do that, especially since most patient organizations are small and focused on patients and not policies it's going to be difficult to engage, especially if you were to break us up by specific rare disease.

(02:33:18):

I think there are some good ways to look at what's already being done. Obviously the patient-focused drug development work at CDER is great. Also, the PCORI model, Patient-Centered Outcomes Research Institute, which is having their meeting in DC next week and would be a great opportunity to look at how they're doing it through their ambassador program and through the resources that they provide. Additionally, when you're looking at patient engagement, it's important to provide clear instructions, guidelines, access to patients is going to be difficult and language barriers exist not just outside the US but within the US, especially when you engage with rare disease communities. We can't allow language to be a barrier, whether it's a difference in language spoken or just in a lack of plain language because we don't want to confuse and intimidate patients, caregivers, and others who may not have a scientific background. Additionally, the data needs to enable researchers to compare data across similar.

Susan Winckler (02:34:23):

Thank you. We'll now turn to our last two virtual public comment in this section and then proceed to the in-person. Kristen Vanags will be our next virtual speaker followed by Meihui Wang. Then we'll start in-person remarks from Nina Nazar, and then Simone Day. So if we could pull up the video. Thank you. And it's there already. Please proceed.

Kristen Vanags (02:34:48):

Hello everyone. I'm Kristen Vanags, a parent of a teenager with Phenylketonuria and the Community Engagement Director of flok Health. Flock's mission is to rally the inherited metabolic disorder community to improve our care and accelerate scientific progress. We serve the classical

homocystinuria, MSUD, PKU, tyrosinemia, organic acidemias and urea cycle disorder communities. Thank you very much for the opportunity to share these priorities. First, establish equitable representation of patient advocates in decision-making. Increasing the number of patients and caregivers working alongside industry and researchers where ideas are generated and decisions are made is critical. Patients and caregivers have valuable insight that only individuals living every day with the condition can contribute. More representation will also provide a broader view of individual conditions and rare diseases overall.

(02:35:46):

The more patient advocates at the table, the better. We would also like to see the hub emphasize patient quality of life in endpoint definition. For example, in the PKU community, we are grateful to have phe as an endpoint. While measuring phe will continue to be important, we know it does not provide a complete view of an individual's quality of life. I see this in my own home. Future treatments addressing other endpoints for inherited metabolic disorders have the potential to vastly improve what it's like to live with each of these conditions every day. I would like to emphasize this next request. We feel prioritizing patient-generated data and product development will increase understanding and lead us to new therapies faster.

(02:36:31):

In rare diseases, we know it's difficult to meet the thresholds of adequate and well-controlled studies. Taking advantage of mechanisms like registries, natural histories, and patient-generated data through care tools and self-reports is essential to support traditional data collection methods. Flok would like to work with the hub to understand how we can be better partners in providing the wealth of data available within our rare communities. Regularly communicate hub progress in a way that encourages patient engagement. It's hard to get patients involved in research. To realize its goals, the work of the hub has to return evidence of progress to the patient community.

(02:37:12):

Town halls and reports readable by the layperson are two examples of ways to show patients that their engagement makes a difference. This will encourage them to stay involved. Lastly, build capacity of rare disease organizations to enable their robust participation in FDA programs. Most rare disease organizations have small budgets and are overtaxed. Providing funds to build their capacity, training and opportunities to share best practices will enable them to better partner with the FDA in the rare disease hub. Thank you for allowing me to share our perspective. The flok Health team is very excited about helping in it.

Susan Winckler (02:37:52):

Thank you. Our final virtual speaker for topic four is Mei-Hui Wang, then we will move in-person remarks beginning with Neena Nizar then to Simone Day and Kristen Hatcher. I see you on the screen so please proceed.

Mei-Hui Wang (02:38:11):

Thank you. Thank you for the opportunity. I'm Mei-Hui Wang. I'm from Children's Hospital of Orange County in California. I'm the administrative manager for our research institute specializing in metabolic and rare disease. I have three suggestions I would like to present to the FDA Rare Disease Innovation Hub. The first is just about the single patient IND for rare disease compassionate use. At CHOC, we do submit multiple single patient IND per year. When we treated the patient on the list mechanism, the

result can offer valuable insight. If FDA and NIH could collaborate with the mechanism and the funding opportunity, perhaps within the 12 months after the treatment.

(02:38:59):

This will allow the clinical team to apply the for rare disease research funding through the NIH. This will help advance our understanding for treatment plan. Since the NIH is a research and funding opportunity, I believe the FDA could benefit from the strengthening of its partnership with NIH in this area. The second is I want to suggest a streamlined documentation process and minimize overlap between the IND and NIH application. In the table you will see that what is covered in the IND submission actually all the content is what do we need for the NIH grant proposal application. So for example, NIH currently has a funding opportunity for the open product addressing unmet need for rare disease.

(02:39:52):

Much of the information needed for NIH proposal actually is included in the FDA. If we can have the streamlined mechanism for the IND approval automatically have the NIH funding, that would be great. So our physician and the research team, they can focus on the solutions and the scientific finding instead of just a lot of administrative work. A lot of the time they just waiting to transfer the information that already exists in the IND to the NIH format. The last one I want to address is the structure of the Rare Disease Innovation Hub.

(02:40:28):

If we can have a better landing page, provide all the stakeholders and especially patients family with a clear information and a solution map for an efficient navigation instead of just a collection of the program and the news. And the better the searching and the quicker we identify the writer in the correct information will help us to understand or take the correct action. Thank you.

Susan Winckler (02:40:58):

Thank you. We'll now proceed to our in-person commenters for topic four and we will begin with Neena Nizar. Our folks in the queue are Simone Day, Kristen Hatcher and Paul Kruszka.

Neena Nizar (02:41:14):

Thank you all. My name is Neena Nizar and I am a patient with an ultra-rare disease affecting less than 30 people worldwide. I moved from the Middle East seven years ago and I'm happy to say that we are having a first-in-human treatment in the beginning of next year and I will be the first patient with Jansen's metaphyseal chondrodysplasia to be treated. My journey has been a long one and as an outsider coming in from the Middle East and looking at what's happening here, I have to say these are my lessons learned and this is what we need to prioritize. Mandatory patient engagement. Establish a requirement for tailored patient engagement plans at each stage of the drug development, starting with a PIND. When it is submitted ask, where's your engagement plan? What does that look like? Active role for patient advocacy organizations involve PAOs as key stakeholders. We've heard it all through today. Make sure they're at all pivotal meetings rather than treating them as passive advisors. We should not be knocking at doors. Incentivize engagement with academic institutions. They are the heart and soul of this development. Create incentives for academia to advance drug development and reward successful collaborations among academia, industry and patient advocates. Integrate patient engagement training. Incorporate patient engagement training into medical education to foster inclusive practices among future clinicians and researchers.

(02:42:48):

Data engagement framework. Utilize existing data to minimize patient burden, ensuring transparency and sharing insights from both successful and unsuccessful studies. Please don't ask us for another natural history study when you know one is already available. Again, trauma-informed design. Gather feedback from patients and caregivers to provide necessary support and engage stakeholders in discussions on innovative trial methodologies. We should have ideas. We should be in the room. We should be able to give you insight in all these areas.

(02:43:23):

Facilitate global collaboration. Enhance communication and connection for patients with global clinical trial opportunities. Streamlining regulatory discussions through inclusive working groups. And finally, make engagement frameworks a requirement. I'm saying it again and again for seven years I've heard, "Listen to the patient." I don't know why we aren't doing it. In a more structured and formal way, establish patient and community engagement as a core requirement in drug development processes. Thank you very much.

Susan Winckler (02:43:59):

Thank you. And our next three speakers, we will hear next from Simone Day, then in the queue we have Kristin Hatcher, Paul Kruszka and Allison Slabaugh. There we go. Please proceed.

Simone Day (02:44:15):

Good afternoon. My name is Simone Day. I'm 33 years old and my perspective is shared from the lens of living with sickle cell disease for the first 27 years of my life. While now navigating life as an advocate, seven years into survivorship after being cured of sickle cell via bone marrow transplantation. When I think of patient engagement, the first thing that comes to mind is that before any individual is diagnosed with an illness and receives the patient label, they are human beings. So think of any challenge you may have overcame as a child, adolescent, teenager, et cetera. Now think of having to overcome that same challenge while being physically limited.

(02:45:04):

Having systems in place to help patients navigate each unique challenge they may face as they grow through life is key. Chronic illnesses, especially ones like sickle cell disease, that are dynamic in presentation where one day I'm physically able to take on the world and the next I'm fighting for my life takes a toll on a person's mental health. Having your life defined by such unpredictability makes it difficult to lay the proper foundations necessary to thrive in adulthood. The capacity an individual has to create the life of their dreams is limited because thriving with an invisible chronic illness is a luxury that most can't afford because they exhaust a great portion of their energy on just surviving alone.

(02:45:53):

So if you want authentic, valuable, and long-term patient engagement from a community, investments must be made on a consistent basis. Investing time and resources that can take a community out of survival mode, allow space for true partnership to be birthed. The relationship must be nurtured in a symbiotic manner, allowing for both parties to benefit. This prevents patients, caregivers, and advocates from feeling like a prop where their traumatic lived experiences are used as insights to further a mission that may ultimately be disconnected from the community it was intended to serve.

(02:46:32):

My hope is that with the advent of the Rare Disease Innovation Hub, genuine partnerships will form that intertwines the rare disease community to not only strengthen the voice of the patients, but to also

pour into these communities to allow them to one day become innovative change makers themselves. Thank you.

Susan Winckler (02:46:50):

Thank you. We'll next hear from Kristin Hatcher, then Paul Kruszka, Allison Slabaugh and Alyssa Wyant. Please proceed.

Kristin Hatcher (02:47:05):

Thank you so much. My name is Kristin Hatcher and I'm the director of a Rare Liver Diseases for Global Liver Institute. It's a non-profit, a consortia of over 20 rare liver diseases looking to fast-track to a cure through synergies. But I'm also a rare disease patient. At 42 years old, I'm the oldest living alpha-1 patient in my family and currently there's no cure. I also come from the mountains of East Tennessee where government plumbing wasn't even a staple in everybody's house until I was 10 years old. So it says a whole lot already about this innovation hub that you've invited this Smoky Mountain girl to even have comments.

(02:47:55):

About how to truly engage patients and not just the patients that are in this room, but all of the patients. To use our expert voices to further research. And following Dr. Mark's C theme, I actually came up with three Cs of my own to do that. And the first one is communication. And it's communication channels with dedicated staff. And I think that we can see just by what happened today, the power of in-person cannot be denied. And then my second C would be collaboration, but not just having me in the room as a token person, but collaboration with the intent of co-creation. Co-creating materials that are useful for everybody, including the 60% of Americans who read below a sixth grade level that have rare diseases too.

(02:48:57):

And finally, the last thing I would ask for you to do is cut the confusion for us. Reviewers at every level should be following the same guidelines and often leadership is actually open to flexibilities in alternative and confirmatory data, but newer staff are usually a little bit more conservative, so cutting confusion for us by developing guidelines with us in mind would be my idea of how to really use us to make this hub go forward. Thank y'all very much.

Susan Winckler (02:49:37):

Thank you. Our final three comments will come from Paul Kruszka, Allison Slabaugh and Alyssa Wyant, and I'll say those are the final three. Unless we heard from any of our virtual folks who did not respond earlier today. I will turn it over. Speaker Kruszka, please proceed.

Paul Kruszka (02:49:56):

Thank you. Good afternoon. My name's Paul Kruszka. I'm a clinical geneticist and chief medical officer at GeneDx. We're a diagnostic genetic testing company that does a large fraction of rare disease diagnoses in North America. First I want to say thank you to the FDA and the Reagan-Udall Foundation for letting us talk about critical role of broad-based testing and how we can support the innovation hub. I heard earlier that time is the enemy. I've also heard that rare stands for the race against time. Certainly we must do everything in our powers to end the current six-year diagnostic odyssey. I will focus on three key points for consideration by the innovation Hub.

(02:50:40):

The first one is precision therapy starts with the genetic diagnosis. Accurate genetic diagnosis is the cornerstone of personalized treatment plans. Whole genome sequencing and whole exome sequencing are supported by the medical literature, the professional guidelines, and allow patients and families the best opportunity for a diagnosis compared to less informative testing such as gene panels. These technologies significantly reduce the time and uncertainty in diagnosing rare diseases and effectively end the diagnostic odyssey for many families. This is the therapeutic entry point for patients, families and researchers. Point number two, understanding biology to develop therapy begins with gene discovery.

(02:51:23):

We see this over and over again. Identifying disease causing genes is crucial for understanding what's going on with rare diseases. Genome sequencing, exome sequencing facilitate the discovery of novel genes and pathways involved in these conditions. This knowledge reveals potential therapeutic targets. Adding in the development of novel therapies by understanding the genetic basis of diseases, we can create more effective and precision therapies. And final point, very important, and I see a lot of families in this room that I recognize, we've talked about this. Clinical trials require genetic testing to assemble cohorts.

(02:52:06):

Genetic testing is essential for selecting the right patients for clinical trials. Large clinical laboratories like ours where we've completed over 700,000 exomes and genomes allow for efficient process in identifying rare disease patients and families where the prevalence is often less than one in 30,000. This leads to trials accelerating the path to new treatments. In conclusion, broad-based genetic testing through whole genome sequencing and whole exome sequencing plays a pivotal role in advancing rare disease therapies. It starts with a precision genetic diagnosis. Thank you.

Susan Winckler (02:52:47):

Thank you. We will now turn to our final two commenters today. I'll turn the podium now to Allison Slabaugh and then we will close out with Alyssa Wyant. Please proceed.

Allison Slabaugh (02:52:59):

Thank you. Hi, I'm Allison Slabaugh and I am the acting executive director of a Center for Rare Diseases at the University of Notre Dame, and also help co-create our patient advocacy initiative. I just want to take a minute and thank everyone at the FDA for continuing to push themselves to dedicate the time to try and better serve the rare disease community. As I know all of the organizations here are all committed to doing as well. I have a lot of specific comments, many of them were seen on the bio slide and other slides that I'll submit later.

(02:53:28):

But I think I wanted to take a step back and encourage the hub to take a general mindset and approach around integration and break the six C model around coordination and collaboration, but really focus their activities on ways to integrate existing resources and programs and voices into their activities. When the center at Notre Dame started, we were one of three academic research centers in rare diseases in the last decade. There are hundreds of organizations, programs, resources. It's a complete era of information overload for families without real transparency or guiding principles for people to follow when they're new in this game or for regulators or industry in terms of what they need to get across the line.

(02:54:10):

So before creating any new programs, I would encourage the hub to work with various stakeholders and create an assessment and alignment of the existing resources, understanding what gaps need to be filled, and creating a easily accessible kind of pathway and roadmap to understand what questions need to be answered, where the resources are, what gaps exist, who needs to be involved in the discussion before continuing to add to that resource and information overload. A key component of that is the FDA kind of roadmap, I'll call it. Again, clearly outlining as we've all said today, we have no idea who to talk to and when.

(02:54:47):

It shouldn't be the single job of the director, but there should be a living, breathing platform document that states each of the different entities, what their goals are, their activities, progress towards goals, and then help navigate in order for all the different stakeholders to have more meaningful engagement with the FDA. I'll also say that I see outreach listed all over the FDA and I would really encourage we get away from the term outreach, which is very much a one-way share of information and go to an engagement model that is meaningful two-way and continuously evolving the information based on what's available at the present time.

(02:55:26):

And in all activities, I would actually encourage them to not focus on what each individual stakeholder needs, what the patient needs, what the researchers need, but rather prioritize activities that are at the intersection of all of those. Simultaneously engaging all three groups or all the various stakeholder groups that are at the intersection of traditionally siloed areas of research, advocacy and education. The more that we can bring these together, create clarity and transparency, the more progress we'll be able to make together.

Susan Winckler (02:55:57):

Thank you. And now we'll turn to our final public comment for today. Speaker Wyant, you have that privilege.

Alyssa Wyant (02:56:07):

Thank you for the opportunity to speak here today. My name is Alyssa Wyant, chief regulatory and quality officer at Praxis Precision Medicines. Our company motto is dare for more and we recognize the urgency to help patients with rare epilepsies by delivering life-altering treatments faster and more effectively than has been ever done before. The FDA is tasked with applying rigorous safety and efficacy standards to emerging treatments, including precision small molecule therapies and ASOs, which have the potential to deliver unprecedented positive outcomes for patients.

(02:56:41):

The hub should mandate education requirements to review staff on the unique challenges and potential of emerging therapies for rare diseases by engaging with clinical and academic experts. And also share expert feedback with industry sponsors. The FDA's review process is sometimes inconsistent between its review divisions, even divisions within the same office, which leads to confusion and inefficiencies. Transparency is lacking especially with reduced number of in-person interactions since Covid. With a written response only for any formal meeting, companies don't know which expertise supported the review or if other offices within the agency were consulted.

(02:57:20):

What will be the role of the hub in increasing the frequency and quality of interactions on rare disease development? The hub could support expansion of the Start program and increase real-time

communication between the rare disease drug sponsors and the agency. They can evaluate the success of the pilot program, identify factors to consider when deciding to expand eligibility, and could also be a coordinator for the review of start applications. Too often we hear that drug developers are put on clinical hold for an initial IND for reasons that are likely related to the thirty-day review period being too short.

(02:57:57):

Clinical holds have a significantly negative impact on a company's ability to efficiently move rare disease programs forward in the US and reduce confidence in the physician and patient communities and their ability to participate in clinical trials. Many biotech companies have limited funds and often must make difficult decisions on which programs to continue when faced with prolonged FDA delays. Can we reduce clinical holds by having additional review time and allowing the hub to be involved? More innovation and clinical trial initiatives is needed and the hub could provide some best practice recommendations to sponsors seeking guidance on how to decentralize rare disease trials in partnership with companies like Praxis who are successfully running them.

(02:58:42):

Companies developing rare disease therapies want to streamline an efficient path for development. Acting as a single point of contact for rare disease sponsors could reduce bureaucratic hurdles and red tape. For rare diseases where there are no treatments or ineffective options, it's critical to have clarity on how a company should navigate multiple offices, programs, and initiatives so that we can bring therapies to patients and families as fast and as safely as possible. Thank you.

Closing Remarks & Adjourn

Susan C. Winckler, RPh, Esq., Reagan-Udall Foundation for the FDA

Susan Winckler (02:59:08):

Thank you. Please join me in thanking all of the individuals who provided public comment today. Those insights and personal stories are so valuable and we truly appreciate you investing your time in providing this input to the innovation hub. I'll note as well as has been mentioned, we welcome additional public comment through the docket. There's a federal register announcement that you can link to from the ReaganUdall.org website. With that, I want to do just a quick recap and I'll first note, we are ending early. We had some commenters who didn't show up and then everyone was so efficient that the time that we built in for inefficiency we simply did not need, which may be efficient. So we really appreciate all of that input. I was reflecting on our Cs from this morning and I think where we might land, if we remember the initial four, were communication, coordination, cooperation and community. I think with the goal of yielding creative cross-cutting collaboration. So we'll write that down somewhere and it may appear again and there won't be any special attention given to comments that build on the C theme, but they will be noted as having perhaps been informed by the discussion today. So thank you all for joining. Please watch for the meeting recording and transcript, which will be on our website by the middle of next week.

(03:00:44):

Thank you for sharing your thoughts and we hope to see you again soon. Take care.