Rare Disease Framework Initiative
Hybrid Public Meeting
October 28, 2026 | 1pm - 5pm (*eastern*)

Transcript – Part 2

Remarks from the Acting Commissioner
Kyle Diamantas, JD, Acting Commissioner of Food and Drugs, FDA

Susan C. Winckler (00:00:00):

All right, everyone. We are back for our meeting. And to provide a little more context and underscore the importance of this meeting to the entire agency, I am thrilled to turn the podium over to Acting Commissioner Diamantas. Thank you for joining us.

Kyle Diamantas (00:00:17):

Thank you. Thank you. Really appreciate the opportunity to be here. Reagan, you'd all the tremendous work that you all do. Before we begin, I do want to extend my sincere thanks to the FDA Rare Disease Innovation Hub led by Amy Comstock Rick to Mike Davis, director of CDER, Kareem McHale, my good friend sitting here, director of CBER, and the countless others who have helped bring this effort to life and who will continue to work on its growth, including my colleagues in the Office of New Drugs and the Office of Therapeutic Products.

(00:00:51):

By now, you all have heard about FDA's core commitments to the rare disease community. This includes our Rare Disease Framework Initiative, giving rare disease drug development the fit for purpose customized approach that every rare disease patient deserves. While the details of this framework will continue to be developed and rolled out over the coming days, weeks, and months, I want to share with you the cornerstones we are committed to in its development, greater clarity, consistency, and predictability in the FDA process, incorporating the patient voice early and at key milestones in the development and review process. Reaching out to external experts for their knowledge, especially with those very small rare disease populations, and looking at risk-based approaches to CMC review and pre-approval inspections to support earlier patient development. The first phase, excuse me, of this framework initiative begins today and it begins with all of you. I feel strongly that sustained stakeholder engagement is the best way to ensure this agency is responsive to the needs of the entire rare disease community. My first public meeting as acting commissioner was with 15 rare disease advocacy groups, excuse me.

(00:02:09):

I saw then and continue to see the commitment, the sophistication and partnership that you bring to ensuring powerful cures and treatments are brought forth for everyone diagnosed with a rare disease. Today, we want to start a conversation with the full rare disease community, certainly patients, caregivers, and disease advocates, but also the drug developers, the researchers, clinicians, and our own FDA drug and biologics reviewers.

(00:02:36):

It will take the voices and perspectives of all of us to make the framework initiative successful. When we began internally discussing this initiative, my first question was why now? What is it about this moment that makes it not just a good time to reevaluate rare disease review, but the best time?

(00:02:55):

And the more we discussed it and the more that I have learned about the rare disease community, the clearer the answer has become. We're at the center of a confluence of events for the rare disease community. Our understanding of the science of rare diseases is the best it's ever been. We've made tremendous advancements in methods for developing and assessing rare disease therapies, and we have a patient and advocacy community that is galvanized and ready to help us focus on the best therapies to help your lives and your families.

(00:03:25):

The urgency of the need has not changed, but now we, the agency, drug developers, researchers, and patients are ready to meet that need together. I want to thank each and every person joining us today here and online for your input, for your candor, for your vision, and for your support of the agency. We're eager to hear your perspective and learn from your experience. Thanks, and I will turn it back over to my friend Susan. Thank you.

Susan C. Winckler (00:03:55):

Thank you so much, commissioner. We appreciate you being here today.

Public Comment:

Susan C. Winckler:

And now it is time to hear from the members of the public who requested time to address everyone who is part of this meeting today. As I noted earlier, due to an overwhelming response, we were unable to offer a public comment slot to everyone who requested to speak.

(00:04:15):

As I noted, we had more than 200 requests to provide public comment. So, let me explain how we will proceed. I'm going to give a rolling list of three commenters. We're going to hear first from a set of folks who are here in person, then we'll turn to some of our virtual commenters. We'll come back in the room, we'll go to the virtual, we will come back in the room.

(00:04:37):

This will all make sense as it starts to happen. And so, as I give you the cue of commenters, I want to give our virtual commenters some specific instructions. If you are a virtual presenter, you are going to be delivering your remarks as a panelist on the platform. That means when we ask you to accept the invitation to be a panelist, accept that with joy and promptly so that we can turn to you.

(00:05:05):

So, you're going to hear your name three times. The first time, make sure that you have accepted that invitation. The second time you hear your name, prepare to speak. And then as the speaker before you completes their remarks, unmute your microphone and turn on your camera. And then I will turn to you and tell you when your time begins.

(00:05:22):

If our speakers, pardon me, our producers have a slide, we did invite speakers that the public commenters could give us one slide. If you gave us a slide, that will appear about 10 seconds into your remarks. One just warning, if you do not begin to speak 10 seconds into the time that after I have turned to you, we will move to the next commenter. If we have time, we will come back to you.

(00:05:52):

Then the in-person instructions are quite similar. The first time you hear your name, please get the attention of the person in the back of the room. And so, right now that means Annie Kennedy, move to the back of the room because you will be moving up to a podium. Actually, you don't have to go back. You can just go right to that podium. And then our others in order are Caryn Alagno and Tammy Anderson.

(00:06:15):

If you would go to the back of the room, we'll get you to the right podium so that you are prepared to deliver your remarks. So, with that, we have our first commenter at the podium. We will start our two and a half minutes. I will note that at the end of two and a half minutes, audiovisual support will cease and we will move to the next commenter. So, commenter Kennedy, if you are ready to proceed, please do so.

Annie Kennedy (00:06:43):

Good afternoon and thank you. I'm Annie Kennedy and I'm honored to be representing the Rare Foundation. Today signifies an inflection point in rare disease and our community is eager to partner with FDA to harness the potential on our pipelines to create a system that ensures that no individual living with a rare disease is too rare.

(00:07:04):

Today, we're pleased to inform the process for optimizing engagement and to propose additional outcomes for consideration. As you plan the process for engaging with our community, we'd like to highlight rare disease subpopulations for inclusion, foundation or academic-led sponsors, stakeholders across all sizes from N-of-1 to N-of-many with heterogeneity challenges, rare communities with approved not yet disease-modifying or curative therapies, and those who currently may fall outside of the label of an approved therapy or of a clinical trials inclusion criteria, such as very young pediatric populations and young adults.

(00:07:43):

We're also pleased to see the intent to conduct internal sessions with reviewers. We encourage that the review team representation include teams that are rarely seeing rare disease programs as well as those that have high volumes of rare disease applications, teams from the National Center for Toxicology Research that may have a unique lens into how to efficiently overcome early barriers, teams from OOPD that may face additional challenges adjudicating new classifications or designations. And teams on programs that involve clinical holds and CRLs, including those that were resolved successfully and those that led to the termination of the program, and teams that reviewed successful programs that represent different applications of tailored regulatory approaches.

(00:08:26):

In addition to the stated outcomes, we urge that you plan engagement that will address how desired changes can best be accomplished, specifying what is best suited for formal rulemaking, guidance documents, and pilot programs, and what is more appropriate for less formal actions, and whether

existing meeting structures can support the new framework recommendations or whether new mechanisms for patient and nonprofit organizations are needed to engage with the agency.

(00:08:55):

And finally, we encourage FDA to engage with an open mind and not impose artificial constraints on the potential outcomes. For example, should it become clear that additional authorities and amendments to the statute be necessary to achieve the desired outcome? While much can be achieved under existing authorities, we do not want to preclude such activity, particularly if necessary to achieve significant progress. Again, thank you for your leadership.

Susan C. Winckler (00:09:19):

Thank you. Our next comment will be from Caryn Alagno, Tammy Anderson, and then Ron Bartek. For our in-person commenters, there is a timer right in front of you. Commenter Alagno, please proceed.

Caryn Alagno (00:09:33):

Thank you. In a moment on the slide, you'll see a photo of my son Davidson. He's baseball obsessed. He's a pitcher and a first baseman, but not for long because Davidson is going blind. My name's Caryn Alagno and I'm the founder of the NPHP1 Family Foundation. As of today, we've built, tested, and are currently manufacturing a gene therapy that can stop Davidson's vision loss.

(00:09:58):

And our plan is to make our drug product available to other families with the same condition for free. Davidson's going blind because he's missing the NPHP1 gene. In the US, about one in a million people are missing that gene. Its primary phenotype is renal and I actually donated a kidney to him in 2020. However, 6% to 10% of that one in a million will also develop retinal dystrophy.

(00:10:20):

So, rough math says that's 35 people in the US. Davidson's condition is so super ultra-nano rare that it's the picture of a disease of no commercial interest. And we talk about what we're doing as drug assembly, not drug discovery. We're building on existing science. The biology looks good. The pathway to getting this to patients is where you come in.

(00:10:39):

Thank you for your commitment to creating this new framework. It meets a pressing need today and one that's only going to continue to grow because as diagnostics get better, as science advances and as information about emerging therapies becomes more broadly accessible, you're going to have more families and more patient groups coming to you, not as pharmaceutical companies interacting with their regulators, but citizens interacting with their government.

(00:11:01):

And that's good. It means more treatments and it means more patients treated. It means more programs here. Three suggestions I would offer to you as you make this new framework a reality. Number one, move faster than we do. Progressive diseases require progressive thinking, so please move quickly to turn your policies into practice and to make those practices standard.

(00:11:23):

Some drug development questions are ones that only you can offer or answer. So, consider offering interactions that don't require massive data packages, waiting 60 to 75 days for an interaction or using limited resources to hire FDA consultants. And number three, recognize the history that you're making.

(00:11:40):

A generation ago, transplant medicine with my family has benefited from was cutting-edge next-gen science and now it's standard of care. And if we all do our jobs right, gene therapy, ASOs, and other groundbreaking treatments are going to be routine in the future. And those with the most to gain from them are the patients and families that you're hearing from today who are right now told that nothing can be done. We are changing the course of our loved ones' lives and we want you present at the victory party...

Susan C. Winckler (00:12:08):

Our next comment will be from Tammy Anderson. Our queue is Ron Bartek, Kara Berasi, and Jyoti Bharadwaj. Commenter Anderson, please proceed.

Tammy Anderson (00:12:18):

I'm Tammy Anderson, executive director of Wake Up Narcolepsy, a national nonprofit patient advocacy organization advancing awareness, education and research towards more treatments, and ultimately a cure. A recent US study estimated approximately 182,000 people diagnosed with narcolepsy. Behind that number are people struggling to stay in school, sustain employment, raise children, and maintain relationships.

(00:12:44):

While existing treatments provide important benefits, significant unmet needs remain for people living with narcolepsy. As the FDA develops its rare disease framework, we urge you to prioritize three areas. First, make patient-centered evidence central to treatment, development, and evaluation. Involve patients early while trial designs and outcomes are taking shape and at meaningful milestones throughout development.

(00:13:08):

Expand clinical trial eligibility to increase patient participation and improve data collection representative of a more diverse patient population. Ensure that outcomes include real life improvements as well as symptom management. Patients need to know that treatments will help them learn, work, care for their families, and participate in their lives.

(00:13:28):

Second, strengthen research and treatment options for children with narcolepsy. Research indicates that more than half of patients report symptoms beginning before age 18. For many, this lifelong disorder begins while they are still developing academically, socially, and emotionally. Children cannot recover these formative years later. Encourage scientifically appropriate pediatric studies, age-appropriate formulations, and outcomes that reflect children's lives.

(00:13:56):

Families and clinicians need evidence to guide treatment during childhood, not only after patients reach adulthood. Third, address evidence gaps surrounding pregnancy and maternal and infant health. Women managing narcolepsy need better information when planning pregnancy, weighing treatment decisions and navigating postpartum care.

(00:14:17):

Support stronger evidence and coordinated post-marketing data collection, including academic industry consortiums, and multi-sponsored registries. Patient experience, childhood development, and

reproductive health must be deliberate throughout the development. As we conclude, we ask the FDA to make these needs explicit in the framework and carry them into implementation. Thank you.

Susan C. Winckler (00:14:42):

Thank you. Our next comment will be from Ron Bartek. In the queue we have Kara Berasi, Jyoti Bharadwaj, and Mackenzie Bloom. Commenter Bartek, please proceed.

Ron Bartek (00:14:53):

Hello, I'm Ron Bartek of the Friedreich's Ataxia Research Alliance here to report that we are truly enthusiastic about the framework, the right thing to do at the right time, and the current process has been too slow, too many CRLs, too many denials, too much inconsistency, too little dialogue.

(00:15:13):

Much of this has stemmed from prior chaotic leadership, staff reductions, and lack of collaboration across the agency. Current leadership is redressing those first two and the framework is suitably well-designed to redress the third. We must act quickly to provide the hub and the initiative, the resources, staff, and support they need to succeed for us all.

(00:15:36):

We are especially enthused about three aspects of the framework. First, the internal collaboration needed to provide rare disease expertise to all reviews, including in biostatistics fit for purpose for rare diseases, yielding far more consistency and predictability. We are confident that with the hub's leadership, the structure best suited for optimizing this collaboration will be developed quickly and well. Second, the commitment to ensuring all reviewers bolster their knowledge of specific diseases by engaging with patients and external experts. So, becoming familiar with rapid scientific advancements and with the patients so eager to benefit from them. This will be important in individual programs and with multiple programs in broadly applicable fields such as delivery mechanisms in cell and gene therapy.

(00:16:26):

Third, the systematic review of existing guidance documents and potentially issuance of new or revised guidance. One such draft guidance and dire need of revision is ethical considerations for clinical investigations involving children. It was issued four years ago and must be updated urgently to reflect the very positive evolution and regulatory thinking clearly manifest in the pediatric inclusion round table in July of 2024, and reinforced in the second such round table this past May so children with rare diseases can gain access to safe, effective therapies at the best time for them.

(00:17:05):

This update will be effective too in aligning the IRB community and the FDA on key issues such as the prospect of direct benefit. In sum, we are extremely enthusiastic about the framework, committed to helping you put it into practice quickly and confident it will enable our finding the way to yes together in addressing the unmet needs...

Susan C. Winckler (00:17:27):

Our next comment will be from Kara Berasi. In the queue we have Jyoti Bharadwaj, Mackenzie Bloom, and Tanya Brown. Commenter Berasi, please proceed.

Kara Berasi (00:17:37):

Hi, I'm Kara Berasi with Haystack Project and I want to thank you for today. We think three things are foundational to the success of this initiative. The first is that reviewers with good hearts and with strong scientific backgrounds who are trying to lean in on rare, they must know that every new leader and administration has their backs. To us, that means fighting for regulation and a statute. Second is patient and expert engagement. This should happen once reviewers understand the challenges with determining a study design, the endpoints, and must look at the nuances of the rare disease in front of them to determine what's needed. How do we design a process that calls for fluidity with a certain amount of structure?

(00:18:21):

And the third is documentation. Reviewers must document in the legal record what they learned from patients and experts and how it informed endpoints and study design. There will be challenges with figuring out how to include those things. We understand that, but patients and experts will be able to continually improve on what they provide and reviewers can continually improve on how they use it.

(00:18:47):

And there are other challenges. There will be concerns for protecting sponsor confidentiality, proprietary paperwork, conflicts of interest among experts to name a few, but there are too many lives at stake to let those things get in the way and we must solve for them. And as a rare disease mom, I add one more, and that's urgency. I wear a bracelet that has three letters on it for Christopher, Emmett, and Ruby, three of my friend's children who have died from the same disease my son has.

(00:19:16):

We failed these children and others who are in this room today, but I don't want to add any more letters to this bracelet, and I brought one for each of you. And I know it may sound silly, but it helps keep me accountable and focused on true north and hopefully for you serves as a reminder as who's at the heart of this initiative that you are all undertaking. Let's be partners in this. Thank you.

Susan C. Winckler (00:19:46):

Our next commenter is Jyoti Bharadwaj. In the queue we have Mackenzie Bloom, Tanya Brown, and William Brown. Commentor Bharadwaj, please proceed.

Jyoti Bharadwaj (00:19:57):

Good afternoon everyone. Thank you for this opportunity for us to be over here. I'm the parent, one of the parent of a patient with a rare disease. He's my son, Ayan. He has Duchenne muscular dystrophy. Within this particular disease, there is just not one mutation but multiple.

(00:20:13):

So, within a rare disease, we have multiple ultra-rare diseases too. We fund and coordinate an individualized program for him, a U7 snRNA exon skipping construct tested in patient derived iPSCs muscle cells carrying his exact mutation. The white paper commits to fit for its purpose evidence. I would like to ask what that means in practice for one child because for us, the obstacle is not the trial design.

(00:20:38):

It is the preclinical package required before we can begin and a lack of clear answer on who is eligible. I would also note that FDA has already approved four exon skipping products for Duchenne 51, 53, 45, with the same mechanism. My questions are about making that part repeatable, not about creating a

new one. For an N is equal to one, enough new few gene therapy are non-human primate studies necessary?

(00:21:09):

Which questions can patient derived iPSC models answer, and what is the minimum in vivo package needed for biodistribution and immunogenicity where a near identical construct has already been cleared and can its preclinical package be referenced rather than repeated?

(00:21:27):

For the clinical arm, are modification to the immune management protocol for better conditioning allowed? Can extensive immune modulation techniques be adapted to suit individual patients? Are virus-like particles for systemic delivery allowed for DMD? What preclinical studies are necessary? Are GLP animal studies required or is non-GLP data acceptable? Can gene editing or exon-skipping therapies be given to patients who have had prior AV therapy? Yes.

(00:22:01):

But the next question is, many boys have already received AV product and without an answer, it is a permanent exclusion. We have published approaches like plasmapheresis, B-cell depletion, and others, which, if any, would FDA accept? I thank you for this opportunity and I would look forward to getting an answer on this. Thank you.

Susan C. Winckler (00:22:28):

Thank you. Our next comment will be from Mackenzie Bloom. In the queue, we have Tanya Brown, William Brown, Mindy Cameron. Commenter Bloom, please proceed.

Mackenzie Bloom (00:22:38):

Good afternoon. I am Dr. Mackenzie Bloom and I am an associate in the Office of Government Affairs at St. Jude Children's Research Hospital, and I am pleased to deliver this comment on behalf of our institution. Since our doors opened in 1962, St. Jude has been committed to leading the way the world understands, treats, and defeats life-threatening pediatric illnesses.

(00:22:58):

Through our work supporting the development of therapies for children with rare and ultra-rare diseases, including gene-targeted and other innovative therapeutic approaches, we have had extensive interactions with the FDA. From our perspective, the FDA has demonstrated a strong commitment to supplying research institutions and non-commercial clinical development programs with regulatory pathways, opportunities for engagement, and review processes that have been generally very responsive, collaborative, and appropriately tailored to the unique challenges of rare disease research. These efforts have significantly contributed to advancing therapeutic development for rare pediatric conditions where traditional development models are often not feasible due to small patient populations, limited natural history data, and urgent unmet medical need. At the same time, continued refinement of the rare disease framework could strengthen the ecosystem for rare disease innovation.

(00:23:53):

From a pediatric perspective, ongoing dialogue regarding the regulatory expectations for ultra- rare diseases, novel trial designs, endpoint selection, natural history data utilization, individualized and gene-targeted therapies and scalable approaches for both academic and non-commercial developers would be particularly valuable.

(00:24:16):

Continued collaboration among FDA, patients, caregivers, academic research institutions, and industry sponsors will ensure that regulatory approaches remain scientifically rigorous while allowing necessary adaptability for treatments targeting small vulnerable patient populations. When new frameworks, models, or guidance have been introduced by the FDA in the past, there is often significant enthusiasm from stakeholders, but we have observed that some momentum fades when it comes time to put these promising approaches into practice.

(00:24:48):

Difficulties seem to arise in aligning these new mechanisms across the agency, and we are hopeful that this new framework can be efficiently implemented FDA-wide to avoid confusion for stakeholders. Overall, St. Jude thanks the FDA for its ongoing commitment to rare disease innovation and hopes to partner on continued efforts to expand and refine frameworks to support children affected by rare disease.

Susan C. Winckler (00:25:12):

Next comment will be from Tanya Brown. Then in the queue, we have William Brown, Mindy Cameron, and Meg Didier. Commenter Brown. First Commenter Brown, please proceed.

Tanya Brown (00:25:24):

My name is Dr. Tanya Brown and I am the Scientific Director for TESS Research Foundation, a nonprofit organization focused on driving research for the ultra-rare neurological disorder SLC13A5 citrate transporter disorder or SLC13A5 epilepsy. When I joined TESS six years ago, our goal was to have our community be clinical-trial ready.

(00:25:46):

The goal has shifted. We now need to be ready to bring promising therapies from nonclinical models to commercialization. TESS is the sponsor for a current phase one, two gene therapy trial, the first clinical trial investigating a drug specifically developed for this patient population. We are so thrilled to report that the first patient has officially received the first ever investigational gene therapy for SLC13A5 epilepsy.

(00:26:13):

We are deeply grateful to the FDA for its ongoing engagement with TESS and for the flexibility it has shown in working with our small nonprofit-led program to reach this milestone. Our hope is that FDA's continuing commitment to addressing the needs of rare disease patients will help other rare disease foundations develop treatments and sponsor first-in-human trials.

(00:26:35):

Our experience as sponsor has highlighted multiple challenges for ultra-rare drug development, including the significant financial burden and lack of reliable funding sources to ensure a promising drug candidate can move from in vitro models to commercialization as quickly as possible.

(00:26:52):

Securing reliable, sufficient funding is an ongoing challenge for the sustainability of our drug development program. We offer four suggestions for ways in which the framework creates an opportunity for addressing this ongoing challenge for rare disease drug development. One, create economic incentives that encourage sustained involvement and partnership from commercial entities.

(00:27:13):

Two, work with peer agencies such as NIH to create opportunities for reliable funding sources for rare disease drug development. Three, consider reviewing and tailoring FDA's guidance on charging for investigational drugs under an IND for the rare disease context to allow for greater cost sharing in connection with clinical trial participation where appropriate.

(00:27:34):

And four, consider flexibility associated with the sequencing between the award of a priority review voucher and the need to meet certain CMC requirements given the significant capital investment the latter demands. Thank you for your time today. I look forward to continued collaboration with all partners.

Susan C. Winckler (00:27:52):

Thank you. Our next comment will be from William Brown. In the queue, we have Mindy Cameron, Meg Didier, and Nasha Fitter. Commenter Brown, please proceed.

William Brown (00:28:03):

Good afternoon. My name's Bill Brown. I'm a public school teacher and father of five from Rochester, New York. On the screen in hopefully just a second, you'll see a picture of my daughter, Nova. Page four of the framework describes rare diseases with global populations in the low hundreds or fewer. Nova is that page four child.

(00:28:23):

She has INPP5K congenital muscular dystrophy. In the six years since her diagnosis, we have never met another person with her subtype. Right now at the University of Iowa Wellstone Center, Nova's the only child potentially in the world enrolled in a natural history study for INPP5K.

(00:28:41):

Last Friday at the FDA's patient voice and drug development meeting, Dr. Michelle Campbell recalled a boy from Cure CMD's 2022 meeting whose greatest hope was simply keeping the use of his fingers to drive his wheelchair. Looking at Nova on our school track, you can see why this hits home. In INPP5K, cognition stable while muscle weakness is progressive. First point, as page seven outlines, we need meaningful measures of progress. For Nova, treatment success isn't necessarily walking unassisted, it's stabilization and preservation of what she has now. It's keeping that upper limb strength to steer her chair, protect her breathing, having the stamina for a full day of school. Please embed families at every review milestone to protect that daily independence. Second, enforce reasonably attainable evidence from pages seven and eight. When placebo trials are impossible, reviewers must accept longitudinal natural history registries, non-invasive biomarkers like muscle ultrasound and caregiver reported outcomes while making external disease experts a mandatory structural feature of review.

(00:29:50):

And third, lock in that cross-center consistency highlighted on page nine. Codify this flexibility uniformly across CDER and CBER, so predictability never depends on which division draws the application. Thank you for putting CMD in the FDA's vocabulary and for giving kids like Nova a fighting chance of treatment.

(00:30:12):

It gives us hope that I really thought was impossible up until now. If anyone has any questions for me or leads, track me down. I don't really have any connections here and I'd love to chat. Thank you.

Susan C. Winckler (00:30:24):

Thank you. Our next comment will be from Mindy Cameron. In the queue, we have Meg Didier, Nasha Fitter and Maria Apostolaros.

Mindy Cameron (00:30:36):

Hi, I'm Mindy Cameron, another mother of a person living with Duchenne muscular dystrophy and an advocate for the neuromuscular and rare disease community. In my role as a patient advocate advisor for the Duchenne Consortium at C-Path, I realize our community research and care provider community is fortunate to have a dedicated program at C-Path that relies on sharing and standardizing data to address the challenges that we have encountered over decades of drug development in muscular dystrophy.

(00:31:07):

Hard-earned research participation data can do a lot more when it is shared. I also appreciate the regulatory adaptability that has facilitated significant gains in treatment options and life expectancy for many members of the Duchenne and neuromuscular disease community. However, as you can see by the numbers on the slide, we obviously have also experienced many challenges that the rare disease framework should address.

(00:31:34):

Prioritization of the establishment of fit for purpose evidentiary standards for rare disease by providing clear and consistent guidance across FDA divisions on how external controls and natural history data, biomarkers, endpoints, and confirmatory evidence are evaluated.

(00:31:52):

Patients, families, and patient organizations invest precious resources into the development of these tools, yet the high burden of things like long placebo controlled trials too often persist. It's great to hear about how the FDA is planning on to incorporate the experiences of patients and caregivers early on.

(00:32:11):

One thing that I do recommend that you include is how to approach combination therapies. We are entering into this era in Duchenne now where we have multiple therapies approved in a very short succession and we have patients rushing in to try them all in combination and we haven't quite figured out how to monitor that, and do trials in that and know when the right time to add an additional therapy could be.

(00:32:37):

So, I think that's one area that we could really look at. And of course my phone went dead and I can't remember anything else I was going to say, but I really appreciate this. I think we're at the very brink of something super historic. I think everybody in this room nodding their heads, we all feel it. I was just [inaudible 00:32:58]. The excitement and the electricity in the room was something I've never experienced and I've been doing this for a very long time. So I appreciate being here and let's go.

Susan C. Winckler (00:33:10):

Thank you. Our next comment will be from Meg Didier. Then in the queue, we have Nasha Fitter, Maria Apostolaros, and our first virtual commenter will come from Barb Ballard.

Meg Didier (00:33:24):

Good afternoon. My name is Meg Didier. I'm one of approximately 30,000 patients in the United States living with single ventricle heart disease. And today I represent Sisters by Heart. Single ventricle is a

congenital heart disease with progressive decline that can lead to multi-organ failure. Maintenance is key for our community. As patients, we are often asked to share our experiences, but not always recognized for the knowledge and expertise we can contribute. We offer three recommendations.

(00:33:48):

First, establish a standardized patient-informed assessment of evidence attainability from the very beginning. At key development milestones, FDA should document how scientific limitations, recruitment feasibility and patient burden inform what evidence is reasonably attainable. Patient organizations should have a defined opportunity to contribute feasibility information, helping distinguish between evidence that is theoretically attainable and evidence that can be realistically generated.

(00:34:13):

Second, establish a consistent approach for when evaluating complimentary evidence when interpreting clinical trial results. FDA should define how independently generated patient experience research, including patient-informed natural history can help assess the clinical relevance of observed treatment effects. This should include circumstances where primary endpoints are not met and the clinical relevance of other findings remain uncertain with clear expectations for evaluating methodological quality, relevance, and limitations.

(00:34:40):

Third, establish a patient-initiated regulatory science feedback pathway in which we're proposing to call a type P meeting for type patient. Building on existent mechanisms, patient organizations could submit structured disease-specific research proposals and receive question specific written FDA feedback on methodological considerations and potential regulatory applications. These discussions could occur independently for disease level questions or jointly with therapeutic developers to address shared scientific challenges and evidence gaps.

(00:35:09):

If patient organizations understand what good looks like, we can collaborate more effectively with industry to generate and accelerate rare disease development. We are not asking FDA to lower evidentiary standards, we're asking for a framework that enables a rare disease ecosystem to work together to meet them. Thank you.

Susan C. Winckler (00:35:26):

Thank you. Our next comment will be from Nasha Fitter, then Maria Apostolaros. And in our virtual queue, we have Barb Ballard and Jason Begalk. Commenter Fitter, please proceed.

Nasha Fitter (00:35:41):

Okay. Hello. I am Nasha Fitter, mom to Amara who has FOXG1 syndrome. I co-founded the FOXG1 Research Foundation and I'm also a co-founder at Citizen Health, the company that built our natural history data set.

(00:35:56):

Your white paper says natural history data in rare disease is often sparse or non-existent. For us, it was non-existent, so we built it ourselves from patient medical records. Our clinical advisors all pushed back. There was no regulatory guidance for it and they want predictability. A traditional natural history study takes years and millions of dollars and families drop out because the burden is too high. Instead, in under six months, we collected the complete medical records of more than 100 children with FOXG1,

nearly 1, 000 patient years of history. The data shaped our endpoints and became the external control for a single open label trial. You accepted us into RDF. Thank you.

(00:36:41):

In August, we dosed the first patient in the world with a gene therapy for FOXG1 syndrome. I have three asks. First, name medical records and other real world data as evidence in the guidance. Publish the standard upfront, pre-specified analyses, source verified records, audit trails, and matching on the factors that drive severity. We built to that standard from day one. Make it the rule. As Kareem McHale said, give a clear guidance. And Dr. Davis, as you said, this is the predictability that sponsors need.

(00:37:15):

Second, set practical manufacturing requirements for ultra-rare therapies that are proportionate to their scale. They can cost more than a small biotech or patient foundation can raise, which stalls programs or ends them. We need a framework that still demonstrates quality and consistency, but fits the patient numbers and financial realities. Post-approval commitments could be one solution.

(00:37:38):

Third, write this guidance for patient advocacy groups as sponsors, not only drug companies. The FOXG1 Research Foundation sponsors our trial. There is no pharma partner. In ultra rare diseases, more programs will look like ours because no one else is coming. Build the framework for us as well. Thank you.

Susan C. Winckler (00:37:59):

Thank you. Our next comment will be from Maria Apostolaros. Then we will turn to a set of virtual commenters beginning with Barb Ballard, Jason Begalk and Kat Bryant Knudson. Commenter Apostolaros, please proceed.

Maria Apostolaros (00:38:14):

Good afternoon. My name is Maria Apostolaros and I'm a deputy vice president in science and regulatory advocacy at the Pharmaceutical Research and Manufacturers of America or PhRMA. PhRMA represents the nation's leading innovative biopharmaceutical companies which have invested more than $900 billion over the past decade in developing new medicines, including for rare diseases. Thank you for convening this meeting and the opportunity to provide public comment.

(00:38:41):

As FDA focuses on rare disease drug development and review, PhRMA recommends three priorities, the patient voice, innovative evidence generation methods and fit-for-purpose data sources and regulatory flexibility through clear, predictable risk-based approaches. Patient perspectives are essential to understanding unmet medical need, disease severity and disease progression. We encourage FDA to work with sponsors to incorporate patient experience into benefit risk assessments and the development of clinically meaningful endpoints.

(00:39:13):

Rare disease development is uniquely challenging because patient populations are small and dispersed. FDA should support innovative clinical trial approaches, including adaptive designs, Bayesian methodologies and master protocols, as well as surrogate endpoints, clinical outcome assessments and biomarkers. Fit-for-purpose use of natural history studies, patient registries, external controls, real world data and real world evidence can strengthen development while avoiding infeasible requirements and unnecessary patient burden. FDA can and has exercised regulatory flexibility in reviewing rare

disease drugs. The agency should apply that flexibility predictably and consistently using the full range of criteria and its regulations and guidance.

(00:39:57):

FDA's existing statutory and regulatory authority is fit-for-purpose. Continued guidance explaining how the agency will use that authority would provide greater clarity and reduce regulatory uncertainty. Guidance should be clear, consistent, transparent and patient centered. It should leverage external expertise, apply risk-based approaches and account for disease severity, unmet medical need and the feasibility of trials in small patients. Rare disease also present unique chemistry manufacturing and controls challenges, particularly for cell and gene therapies with limited patient samples. Fit-for-purpose, risk-based CMC expectations will be critical. PhRMA looks forward to submitting comments to the docket. Thank you.

Susan C. Winckler (00:40:40):

Thank you. As we turn to our virtual commenter, the first commenter will be Barb Ballard followed by Jason Begalk, Kat Bryant Knudson and Hassan Denisi. Commenter Ballard, please proceed.

Barb Ballard (00:40:57):

Thank you. My name is Barb Ballard. I'm the president of the SCID Foundation where I advocate for patients with Severe Combined Immune Deficiency, also called SCID. I'm also the mother of a son with X-linked SCID. My son passed away in 2019 at the age of 25 after three bone marrow transplants. Although his stem cells had been collected in anticipation of gene therapy, he died before he could receive his corrected cells because he could not access the therapy in time.

(00:41:27):

Untreated, SCID is fatal in early childhood. While standard treatments such as bone marrow transplants have saved countless lives, they do not guarantee a cure or freedom from lifelong complications. SCID families have learned to educate themselves about complex treatments and their risks. We understand that gene therapy is not a cure all, but we have seen its potential to offer healthier and longer lives. We are not asking for lower safety standards. We are asking for realistic timely pathways to access. For ADA SCID, a gene therapy protocol has successfully treated more than 50 children in the US and UK, yet patients in the US today cannot access it. Regulatory and manufacturing hurdles remain. Similar therapies for Artemis SCID and X-linked SCID are limited to single institutions with no clear path to broader availability. Meanwhile, we watch for the next generation platforms coming on the horizon. We ask the FDA to establish clear yet flexible pathways that tailor evidence requirements to each rare disease, support scientifically sound and risk-managed manufacturing approaches, and include patient advocates early in decisions affecting development, approval and access. Please measure success not only by rigorous review, but also by whether patients can receive safe and effective therapies, work with patients and stakeholders to address barriers throughout the path from development to patient. A therapy that cannot reach patients is an incomplete success. Thank you for the opportunity to share the perspective of the SCID community.

Susan C. Winckler (00:43:10):

Thank you. Our next comment will be from Jason Begalk. I'll note Commenter Begalk, if you are in the virtual meeting, please raise your hand so that we can promote you to panelist. The queue then is Kat Bryant Knudson, Hassan Denisi, and Lindsay Ellington. Commenter Begalk, I do not see you present. So we will turn to Kat Bryant Knudson. Commenter Knudson, please proceed.

Kat Bryant Knudson (00:43:39):

Hi, my name is Kat Bryant Knudson. Thank you for allowing me to be here. I am the founder of The Speak Foundation and I also live with limb-girdle muscular dystrophy or LGMD. LGMD represents more than 30 genetically distinct forms of muscular dystrophy that cause progressive and often severe disability and in some subtypes lead to respiratory and cardiac failure and early death.

(00:44:07):

I would like to emphasize three priorities today. We must recognize the contributions patients have already made to research. Across our community, patients have participated in multiple natural history studies traveling long distances and undergoing invasive procedures. One patient I know has participated in five natural history studies before the age of 18. The SPEAK Foundation was to lead an effort regarding natural history studies as we have not been able to have an external control arm even with all the sacrifices made by our patients to participate. We need regulatory clarity on how existing natural history data can be standardized and fit-for-purpose. Our ultra rare community is too small to support traditional placebo controlled trials. Second, drug development must be viable for every rare disease population, not just a fortunate few. All ages, stages and subtypes matter. We encourage the FDA to follow through on its statement to explore and champion the use of cutting edge science, novel methods and innovative statistical approaches. We strongly urge FDA to help in our efforts to have basket trials so that more forms of LGMD can have access to potential treatments. And third, patients must have a meaningful role in shaping regulatory science. I strongly support FDA's proposal to engage patients early and include clearly defined milestones for the patient voice. I would extend this encourage the FDA to establish a formal rare patient innovation council. Within the implementation of this framework, this will help elevate the voice of the patient and hear from patients who are undergoing all of this. We get firsthand seats, unfortunately, when drug development works and when it doesn't. Thank you so much to the FDA and Reagan-Udall.

Susan C. Winckler (00:46:10):

Thank you. Our next comment will be from Hassan Denisi. In the queue we have Kimberly DeMicko, Lindsay Ellington and Lana Escamilla. Commenter Denisi, please proceed. Commenter Denisi, please proceed. We'll now move to commenter Lindsay Ellington. In our queue, we have Lana Escamilla, James Flint, and E'Lissa Flores. So commenter Ellington, please proceed.

Eric Coleman (00:46:50):

Hello. Yeah, good afternoon. My name is Eric Coleman. I'm filling in for Lindsay Ellington. I'm the proud parent of a six-year-old child with maple syrup urine disease who went undiagnosed for 19 months and consequently suffered permanent brain damage as a result. For MSCD families, life is measured in milligrams. An ordinary childhood virus can trigger a crisis in which leucine builds up and poisons the brain, causing swelling, coma, or permanent damage. Today, the only options are lifelong prescription diet or a liver transplant.

(00:47:26):

A one-time gene therapy has already restored metabolic control in MSCD mice and in a calf. What stands between the children is a clear regulatory path. This is further emphasized that in 2013, a study found that higher rates of attention mood and cognitive problems in MSCD than in their peers even after a liver transplant, which these broad milestones that test their attention, mood and cognitive problems are consistently missed.

(00:47:58):

I'm asking the framework for three things. First, name the endpoint now. Tell the developers whether keeping blood leucine in range while eating more natural protein can support approval. For PKU, a similar amino acid disorder, FDA approved a drug in 2007 based on lowering blood phenylalanine. MECD needs that same clarity before anyone invests.

(00:48:23):

Second, make flexibility predictable. With so few patients, natural history and registry data are the realistic comparison. Commit to accepting them in writing early and hold it when review teams change. Third, measure what families see, build attention, executive function and visual motor measures into trials as supporting evidence designed with MECD families and clinicians so a small trial isn't just only by blunt milestone. Data tells you the prevalence of the disease. [inaudible 00:48:52] tell you of the urgency. Please build this framework for the first MECD therapy that fixes the root cause reaches children while can still protect their brains. Thank you.

Susan C. Winckler (00:49:02):

Thank you, colleague of Commenter Ellington. Our next comment will be from Lana Escamilla. In the queue we have James Flint, E'Lissa Flores, and [inaudible 00:49:13] Earl Green. Commenter Escamilla, please proceed.

Lana Escamilla (00:49:17):

I am alive today because of experimental drug tetrathiomolybdate, referred to as TM going forward. 26 years ago, I went into fulminant liver failure, I was diagnosed with Wilson disease and placed on the liver transplant list. Neurological symptoms quickly followed. Tremors, dystonia, slurring of speech, the inability to read or write are just a few. I could no longer care for myself and even worse, I could no longer care for my young son. I participated in a clinical trial shortly after I was diagnosed with an experimental form of TM. Within a few months, my neurological symptoms significantly improved and I was able to return to college, eventually going on to graduate from law school. My liver disease also improved and I was removed from the liver transplant list. Today I'm a practicing attorney.

(00:50:01):

Five years ago, I enrolled in a second clinical trial of a newer form of TM called ALXN-1840. I did not have negative side effects like my current standard of care, so adherence was much easier. Unfortunately, in 2023, after regulatory discussion, the original sponsor discontinued the program. I was devastated. No safety concern drove that decision. Our community was given help when Monopar Therapeutics bought the licensing rights to ALXN-1840, and recently the FDA authorized Monopar to submit its new drug application on a rolling basis. It shows what is possible when the agency stays open to the evidence a small population can produce. That's why this framework matters, and I'd like to make three points.

(00:50:45):

First, fit-for-purpose evidence must reflect what is at stake. In a deadly progressive disease where many patients still worsen on current therapy, especially neurologically, the evidence bar should account for the cost of having no new option at all. A positive pivotal trial in a small population deserves a clear path forward.

(00:51:04):

Second, patients must be at the table when risk and benefits are weighed. We understand the risk of an investigational drug and we understand the risk of liver failure, transplant, and irreversible brain damage. Our tolerance for uncertainty is different, and the FDA should formally hear our tolerance before a program ends, not after.

(00:51:23):

Third, sponsors and patients need consistency and predictability. ALXN-1840 lost years between a successful phase three trial and a filing. A predictable framework means the next promising therapy won't need a second chance to reach patients. I am living proof of what one rare disease drug can do, and I'm grateful this one has a second chance. Please build a framework where the next patient doesn't have to wait for one. Thank you.

Susan C. Winckler (00:51:49):

Thank you. Our next comment will be from James Flint. However, if you would like to provide comment, please accept the promotion to panelist. Then our queue is E'Lissa Flores, Raphael Hebert, and then we will turn to our return to in-person comment with Courtney Backhop. Commenter Flint, if you're present, please proceed.

James Flint (00:52:10):

Great. Thank you for the opportunity to speak. My name is James Flint. I am a cancer surgeon, a rare cancer researcher, and a scientific advisor for the Aveni Foundation, a foundation focused on gene therapy or a novel gene therapy for rare sarcoma cancer. As we appreciate the comments of the previous presenters, and I have three specific things to note that may be important as we move forward with today's goals.

(00:52:41):

Number one, protecting against predatory manufacturing. I think this was brought up earlier. A promising drug can be identified, but especially for small companies or small manufacturers or small sponsors, the cost of that can be overbearing and predatory manufacturing is a problem. So perhaps considering trusted FDA manufacturers or selected manufacturers for these rare diseases where we can go to and have reliable manufacturing processes, CMC processes that aren't going to be extraordinarily skyrocketing as the cost of trying to manufacture these. And also, as was mentioned earlier, financial aid or reduced submission guidelines for small sponsors or investigators so that we can afford the cost of drug development and manufacturing. Secondary, and especially for cancer in particular, the need for expedited review and provisional approval after phase one safety and efficacy trials is going to be super important. It's really difficult, especially in rare cancer where patients are dying before they can get adequate treatment or we have sufficient follow-up data to get that data out there. So if we can get provisional approval and do a concurrent phase three, for example, we can open the floodgates for access for these rare drugs and these rare cancers and get more people treated at multiple sites instead of limiting clinical trial sites to one or a few sites where patients don't always have access to.

(00:54:15):

And then number three, standardizing the templates for documentation and statistical submission. It's sometimes very difficult to know exactly what documents are required or what statistical analyses are required and where to find that on the website. So as we move forward with the framework, just being very specific about which documentation is necessary, where do we find that, and how do we standardize that across the board for all rare diseases? Thank you.

Susan C. Winckler (00:54:37):

Thank you. Our next comment will be from E'Lissa Flores. Then in our queue, we have Raphael Hebert and in person, Courtney Backhop and Pamela Gavin. Commenter Flores, please proceed.

E'Lissa Flores (00:54:51):

Hi, thank you for the opportunity to provide biotechnology innovation organization's perspective on behalf of our industry members. We would like to highlight a few key priority areas for FDA's consideration, including fit-for-purpose evidence feasible for rare disease patients. This includes using the totality of available evidence, including biomarkers, real-world evidence, and natural history studies while maintaining scientific standards within existing statute. Hand-in-hand is fit-for-purpose CMC, which could be a bottleneck for some sponsors, so applying risk-based approaches while maintaining product quality standards. The next is innovation into practice. So this is advancing FDA's considerations and methods that they have previously announced at public meetings or workshops and pilots and use those into routine regulatory practice and use and use those learnings to update existing or finalizing guidances.

(00:55:52):

The next one goes hand in hand with the first. So this is early and throughout FDA sponsor alignment, so aligning early on pre- IND issues, what evidence is acceptable, endpoints, trial design and CMC, and also remaining uncertainties is critical.

(00:56:09):

Another essential consideration is patient input early and throughout. So we would like FDA to really clarify how the patient experience and their preferences inform their decision-making across the review cycle.

(00:56:25):

And the last one is really the overarching theme for success here, can the FDA leverage the hub cross-center learnings and internal expertise as well as external expertise and apply that consistently agency-wide, I think will be key to the success.

(00:56:47):

And overall, BIO sees this framework as an opportunity to translate the fit-for-purpose practices into consistent practice and greater predictability, early alignment, patient input, and appropriate consideration of uncertainty while maintaining FDA scientific standards. And BIO looks forward to submitting our detailed comments to the docket and continuing our engagement with the FDA. Thank you.

Susan C. Winckler (00:57:12):

Thank you, Commenter Flores. Our next comment will be from Raphael Hebert. Then we will return to the in-person comment with Courtney Backup, Pamela Gavin, and Charlie Gayer. Commenter Hebert, please proceed.

Raphael Hebert (00:57:41):

Thank you for this opportunity and for recognizing that rare diseases require a fit-for-purpose approach to drug development and review. I am living with ALS, a fatal, rapidly progressive disease with few treatment options. I was diagnosed in 2024 and have lost my ability to speak. Today, you are hearing my cloned voice. For most people with ALS, life expectancy is just two to five years from diagnosis. Time is not an abstract consideration, and while rare diseases differ, many families share this urgency.

(00:58:16):

On behalf of I AM ALS, we welcome this initiative and offer three priorities. First, make fit-for-purpose evidence a reality. Conventional trial requirements can exclude people with ALS as their disease

advances. We encourage FDA to engage with sponsors and experts early to align on suitable endpoints, standards for conditional approvals, biomarkers, innovative trial designs, natural history data, expanded access programs data, and other credible approaches. In a progressive disease slowing decline or preserving function can be a meaningful benefit. We are not asking for weaker science, but rigorous evidence suited to the disease and realistically attainable.

(00:59:03):

Second, ensure consistency, transparency, and reviewer accountability. The framework must be applied consistently from FDA leadership to individual review teams and across divisions. We encourage clear guidance, reviewer training, meaningful oversight, and public reporting on implementation. Accountability means a fair and predictable process, not pressure to approve a drug.

(00:59:28):

Third, move from listening to patients to learning from them. We are not regulatory scientists, but we know which losses matter, what risk we may accept, and which trial requirements make participation impossible. Include patients and caregivers early, make participation accessible, and explain how their input shape decisions. I AM ALS looks forward to working with FDA and the broader rare disease community as this framework is developed and implemented. We will expand on these recommendations with supporting examples in written comments by December 11th. Thank you.

Susan C. Winckler (01:00:06):

Thank you, Commenter Hebert. We'll return to in-person comment and hear first from Courtney Bockhop. Commenter Bockhop, please proceed.

Courtney Bockhop (01:00:17):

Good afternoon. Good afternoon. I'm Courtney Bockhop. I'm the community services associate at the National Ataxia Foundation. Thank you for the opportunity to provide a public comment today. The National Ataxia Foundation serves people affected by ataxia across the United States. Ataxia refers to a group of rare neurodegenerative diseases often characterized by damage to the cerebellum, leading to severe effects, including poor balance, incoordination, loss of the ability to swallow and speak, and premature death. We do celebrate that there are now two FDA approved treatments for two types of ataxia with an approval just recently for ataxia-telangiectasia. However, we recognize that two is far too few for the over 100 known forms of ataxia, especially given that there are no cures for any form.

(01:01:11):

With many potential treatments in the development pipeline, we feel the urgency to get this new foundation for rare disease reviews right. Therefore, we are heartened to see that this framework has such a commitment to clarity and consistency, even as there is an emphasis placed on the use of adaptive fit-for-purpose trial designs and statistical methods. We are grateful to know that FDA has been listening to this community as this framework does include many of our priorities.

(01:01:38):

We urge FDA to incorporate meeting opportunities with patients and patient groups into the typical review process. Industry plays a key role, but ideas can easily get lost in translation, forgotten, or downplayed when relayed by third parties. Meeting directly with patients, caregivers, and others in the advocacy community is essential to getting the most accurate picture of each disease. Advisory committee meetings provide a fantastic opportunity for patients and experts to give input into reviews. We hope FDA will continue to schedule more ad coms and not come to definite conclusions before those meetings are held.

(01:02:17):

However, we encourage FDA to also gather this crucial input directly from experts and patients earlier in the review process to inform trial design decisions and proper endpoint selection. In addition, we call on FDA to document the input it receives during meetings with patients and industry and explain how this input tangibly impacts review decisions. This will help us provide FDA with the best information possible. Documentation will also acknowledged of rare diseases, which is another stated goal of the framework. Thank you and we look forward to continuing to work with you.

Susan C. Winckler (01:02:56):

Thank you, Commenter Bockhop, and we will correct The audiovisual glitch at the beginning of your remarks in the posting. Our next comment will be from Pamela Gavin. In the queue, we have Charlie Gayer, Christine Green, and John Hagstrom. Commentary Gavin, please proceed.

Pamela Gavin (01:03:13):

Good afternoon and thank you to the FDA leadership and Reagan-Udall Foundation for convening this important discussion. I'm Pam Gavin with the National Organization for Rare Disorders. NORD excitedly welcomes FDA's fit-for-purpose Rare Disease Framework initiative, and its recognition that rare disease development requires regulatory approaches grounded in the circumstances of each disease.

(01:03:35):

Fit-for-purpose does not mean a lower standard of evidence. People living with rare diseases deserve the same rigorous standards of safety and effectiveness as anyone else, but scientific rigor does not require identical study designs, endpoints, or evidentiary approaches across diseases with vastly different characteristics and patient populations. The challenge is to make scientifically appropriate approaches predictable rather than exceptional. The opportunity now is to translate FDA's considerable experience into clear, durable, regulatory policies that developers can rely upon and reviewers can apply consistently. That requires consistent advice across review divisions, continuity when personnels change, and clear explanations when regulatory expectations evolve so that learning continues. It also requires a strong FDA workforce with the expertise and resources to evaluate novel trial designs, real world evidence, and emerging scientific methods, drawing on external disease specific experts when appropriate. And it means engaging people living with rare diseases early enough to influence development strategies with greater transparency about how their input informs decisions. So again, learning continues. We encourage FDA to establish a phased approach, identify what can be implemented under existing authorities while pursuing guidance or rulemaking where needed, so progress can begin as a durable framework is developed as patients have very little time to wait. NORD looks forward to submitting detailed written comments and working with FDA and the rare disease community to translate this initiative into lasting improvements. Thank you so much.

Susan C. Winckler (01:05:30):

Thank you. Our next comment will be from Charlie Gayer. In our queue, we have Christine Green, John Hagstrom, and Jessica Haywood. Commenter Gayer, please proceed.

Charlie Gayer (01:05:43):

Thank you. Good afternoon. I'm Charlie Gayer, CEO of BioCryst Pharmaceuticals. For nearly two decades, we have focused on developing medicines for people living with rare diseases. Thank you to the FDA and the Reagan-Udall Foundation. Our message is simple, scientific rigor without flexibility can stifle innovation. Rare disease development should meet high evidentiary standards, but generating reliable

evidence requires an approach that reflects the realities of each disease and patient population. In rare diseases with few or no targeted treatments, disease prevalence can understate actual prevalence. Without targeted therapies, physicians may be less likely to pursue a difficult diagnosis. The result can be a self-reinforcing cycle. Few diagnosed patients, few experienced clinicians, and few trial centers. Patients are often widely dispersed, travel can be burdensome, and placebo controlled trials may be difficult to enroll, sustain, or justify, especially when symptoms are serious or disease progression matters. Applying conventional templates without sufficient flexibility can slow or even prevent rigorous evidence generation and innovation. We also ask that patients with rare diseases be seen as small and precious populations. Their willingness to enroll, travel, interrupt work or family life, and accept uncertainty and treatment burdens, should help define what is feasible and ethical and shape endpoints, duration, comparators, visit schedules, and use of external or natural history data.

(01:07:27):

Finally, sponsors need earlier substantive FDA dialogue on development strategy and trial design even before clinical data exists. Early alignment can clarify persuasive evidence, prevent avoidable delays, and conserve patient population. A fit-for-purpose framework should not lower the bar. It should provide the flexibility needed to help sponsors, patients, investigators, and the FDA build the strongest evidence that each rare disease can realistically support, with the goal of helping patients sooner. Thank you.

Susan C. Winckler (01:08:04):

Thank you. Our next comment will be from Christine Green. In the queue, we have Jon Hagstrom, Jessica Haywood, and Lauren Holder. Commenter Green, please proceed.

Christine Green (01:08:16):

Airway obstruction, seizures, and respiratory failure. Right now, those are my daughter Everly's biggest threats to life. I've seen my daughter turn blue and almost die, more times than I can keep track. I'm developing treatment for her and her FRIZZLE friends, not because I want her to be a gymnast, but because I just want her to swallow, breathe, and hold her head up. Anything but the current suffering she experiences, because that is a meaningful endpoint to her and us. I'm Chrissy Green, co-founder and president of Finding Hope for FRIZZLE. FRIZZLE is an ultra-rare disease that causes children by the age of two to regress and lose all their abilities. Thank you USFDA for the time to speak today. I'd like to remind the FDA that lives like my daughter are at stake now. And although we will cheer on the framework, we need internal agency changes to be implemented now.

(01:09:08):

We know there are rare disease groups currently in pre-IND and IND process, and their programs absolutely deserve the implementation of proposed changes even now. Increased FDA communication can be implemented now to allow meaningful dialogue and shared problem solving. Early communication of evolving agency level expectations can be done now without requiring formal meetings before small programs commit precious time and scarce resources. Expert input can be incorporated and valued now when a rare disease program includes it with a submission. The right criteria for variants of uncertain significance can be accepted now through allowing rigorous expert clinical assessment. I'd like to invite FDA leadership to look at the FRIZZLE program and use it as a case study when developing the framework. We are a parent led organization that runs and funds the whole thing ourselves. We don't have a pharmaceutical partner. We're just parents desperate to get our kids treatment as soon as possible.

(01:10:06):

We would be a great case study to look back and review what it was like for our small, ultra-rare, life-threatening disease, to bring a novel treatment to the FDA, with expert advising and limited resources, because more family groups are coming behind us and this process must be right sized for rare, not to change standards, but to save lives now. Thank you.

Susan C. Winckler (01:10:30):

Thank you. Our next comment will be from Jon Hagstrom. In the queue, we have Jessica Haywood, Lauren Holder and Mike Hugo. Commenter Hagstrom, please proceed.

Jon Hagstrom (01:10:43):

Thank you. I'm Jon Hagstrom. I'm here representing the patient community that has Alpha-1 antitrypsin deficiency, or as we simply say Alpha-1. I'm the board chair of the Alpha-1 Foundation and an Alpha-1 patient myself. Alpha-1 is a monogenetic condition that can cause lung or liver damage. And in my case, it was lung damage and I had a bilateral lung transplant 10 years ago. First of all, I want to thank the agency for this effort. Reading your framework document was very encouraging. Your understanding of the problem is spot on. I'm probably not the only patient advocate here that read that framework and thought, Wow, they have been reading our letters. AATD is a perfect example of what I would call the middle case that this framework really must address. Too big for last September's ultra-rare evidence principles, but too small for conventional trials. My asks come from AATD, but I made sure that they're generalizable to a whole bunch of rare diseases.

(01:11:38):

So, first of all, reviewers have to accept realistic endpoints, ones that can actually be recruited and measured, given the realities of the patient population. I choose the word reviewers intentionally. Too often we've seen agency leaders accept our evidence as to why a higher precision endpoint such as CT densitometry for lung disease is appropriate only for that understanding never to reach the reviewer of the actual protocols. This framework's commitment to reviewer training and consistency has to close that gap.

(01:12:08):

Second, therapies that correct the underlying molecular defect, warrant a different evidentiary approach than those that are well downstream of the cause. And so, in AATD, restoring functional AAT in my body, including its normal response to inflammation, is that correction, right? That should be eligible as a primary endpoint supporting approval, without requiring years of observation of irreversible organ damage. Finally, well-managed registries and natural history studies should be part of the evidentiary base, including as external controls, so that placebo arms in late stage rare disease trials can be avoided wherever possible.

(01:12:48):

As a patient, it is demoralizing to join a study where the definition of success is half of you get demonstrably and permanently sicker. Your framework document says all the right things. It really does. But I'm confident I speak for many in the rare disease community when I say, we will judge it not by the guidance that comes out and put on the website, we'll judge it by what happens in the subsequent protocol reviews and ultimately getting these treatments in the hands of patients. Thank you very much.

Susan C. Winckler (01:13:14):

Thank you. Our next comment will be from Jessica Haywood. In the queue, we have Lauren Holder, Mike Hugo and Matthew Kan. Commenter Haywood, please proceed.

Jessica Haywood (01:13:26):

Good afternoon. My name is Jessica Haywood and I'm here on behalf of Cure Sanfilippo Foundation. We're excited about this new framework that has the potential to help so many. Last month, FDA approved Fayuvi, the first ever treatment for Sanfilippo syndrome. While we celebrate this incredible milestone, it took over a decade of clinical development to reach approval. For children with Sanfilippo type A, whose average lifespan is 15 years, that is nearly a lifetime. My 10-year-old niece, Sadie, has waited her entire life for this treatment and has lost so much in that time. So, here are a few suggestions to help speed up drug development.

(01:14:03):

Make direct engagement with patient organizations a structured component of development and review. While FDA provides opportunities for patients to share information, a gap remains between listening to patients and engaging with them as scientific partners. As we first asked during the FDA round table in June, establish a Type P scientific meeting for qualified patient organizations to engage FDA review teams independently of sponsors.

(01:14:29):

Patient groups increasingly fund and design natural history studies, registries, biomarkers and outcome measures. We need predictable access to scientific feedback, including non-binding written summaries before development starts. We would also like to see FDA expand and increase use of the patient representative program during development and review. On fit-for-purpose review, we ask the agency to make stage appropriate endpoints a standard part of early development planning. In Sanfilippo and other ultra-rare neurodegenerative diseases, cognition may capture benefit in early disease, while preserving walking or swallowing may be more meaningful and measurable later. We ask reviewers to proactively and consistently consider multi-domain measures and multiple alternative primary endpoints when scientifically appropriate with patient input. We would also like to see the rare disease endpoint advancement pilot expanded beyond its current capacity of three proposals a year. Allow patient groups to initiate these conversations as well. Lastly, knowledge sharing is critical to increasing consistency and predictability.

(01:15:31):

Make scientific and regulatory learnings more easily accessible. The LEADER 3D case studies are a great start, but expand this to SIEPR. Also develop an internal and external FDA library that preserves scientific reasoning, explains persuasive evidence and clarifies what approaches might or might not be appropriate to different diseases. This would reduce barriers and improve efficiency for all stakeholders. Thank you for your time and we're excited to continue this conversation.

Susan C. Winckler (01:15:58):

Thank you. Our next comment is from Lauren Holder. In the queue, we have Mike Hugo, Matthew Kan and Sharon King. Commenter Holder, please proceed.

Lauren Holder (01:16:09):

Thanks. Good afternoon and thank you for the opportunity to speak today. My name is Lauren Holder. I am a Huntington's disease patient, clinical trial participant and longtime patient advocate. I've watched HD take my grandfather, my father and far too many of my friends. And now after nearly 20 years fighting for change to the future of this disease, I'm beginning to feel it take pieces of me too. For me, disease progression is no longer something I fear for my future, it's something I'm experiencing in my present. I shared this because I need you to understand what regulatory delays look like from the other

side of the table. I welcome the FDA's new rare disease framework and I'm genuinely encouraged by the commitment to finding better pathways for rare disease treatments. But regulatory flexibility cannot simply exist on paper. It must be consistently applied in practice.

(01:17:05):

First, we need clear pathways for natural history data, innovative trial designs and fit-for-purpose endpoints. Second, regulatory expectations must be consistent. When they change, patients suffer the consequences. We deserve transparency and accountability. Third, patients must be meaningful partners throughout the regulatory process. Our lived experience is expertise. We understand meaningful benefit, acceptable risk, and what we stand to lose. The FDA must recognize that waiting carries risks too. For patients with progressive irreversible diseases like HD, waiting is not a neutral outcome. Every delay can mean another ability lost, another milestone missed, another piece of independence that may never return. The absence of treatment is not the absence of harm. I'm not asking the FDA to abandon scientific rigor. I'm asking you to recognize that uncertainty exists on both sides of the equation and perfection cannot become the enemy of progress. Please measure this framework's success not by the policies you publish, but by the barriers you remove and the time you save patients.

(01:18:15):

Regulatory frameworks can be revised and scientific questions revisited. But for rare disease patients, time isn't just something we're measuring, it's something we're actively losing and can never get back. So, let's not waste it. Thank you.

Susan C. Winckler (01:18:28):

Thank you. Our next comment is from Mike Hugo. In the queue, we have Matthew Kan, Sharon King and Mike Lehmicke. Commenter Hugo, please proceed.

Mike Hugo (01:18:41):

Hello, my name is Mike Hugo. I was diagnosed with glioblastoma April 2022, and survival usually is 12 to 15 months. I had standard of care, surgery, radiation, chemotherapy, joined a clinical trial and it was shortly shut down. I tried to get expanded access for several treatments, but my requests were all denied or ignored. FDA was not my obstacle. The problem was getting hospitals, doctors, and companies on board. To them, the expanded access program was red tape, extra work, extra costs, and administrative burden and perceived risk, with no upside or very little. I've done everything I could to survive these four and a half years. I wear this almost 24 hours a day. My diet, everything else, as tight as you can be. But my cancer came back. A few weeks ago, I just had brain surgery and I just flew up from Florida and made it up here, so if I mess up...

(01:19:52):

I'm seeking a dendritic cell vaccine, which I knew for four and a half years, I was going to want. I was prepared and I still can't get it. I am actually going to fly over to Europe after this to go get this technology that was developed and... Everything was developed in the United States, but because of the process and the time it takes, I have to go abroad. The median survival after regrowth is six to nine months. If I wait six to nine months for the approval process, I'm dead or I am severely handicapped.

(01:20:38):

So, I love your guys' commitment to making things better and faster. I would love to help you make that happen. So, please reach out to me and I've lived it. I've been in the industry for 20 years. Until you're

going through the paperwork and the process, there are things that you do not know, I do not know. And so, let me help you. And don't do placebos, especially for a terminal cancer patient. Thank you.

Susan C. Winckler (01:21:12):

Thank you. Our next comment is from Matthew Kan. In the queue, we have Sharon King, Mike Lehmicke and Mackenzie Liebowitz. Commenter Kan, please proceed.

Matthew Kan (01:21:29):

Hi, I'm Matthew Kan. I'm a pediatric immunologist and genome editor. I'm here representing the Innovative Genomics Institute and University of California, San Francisco. I take care of pediatric patients with inborn errors of immunity. These are monogenic diseases of which there are 508 genes. They represent 7% of rare disease and over 50,000 pathogenic variants. When the slide comes up, you'll see a representation of our 35 patients at UCSF that don't have an appropriate bone marrow donor, either matched or not. And to address this, we have made an Avenger style team, in the words of Fyodor Urnov, called the BEGIN Trial. It's a collaboration between UCSF and the Innovative Genomics Institute to leverage our learnings from what we did to help baby KJ for bespoke genome editing, for loss-of-function IEIs for 440 diseases. This is an institutionally approved IRB to do a really, really novel study.

(01:22:29):

Earlier in the summer, I admitted three patients with SCID as Barb Ballard just described to you. It's a horrible disease. Three patients, it's the same disease, but they all had three different genes, JAK1, RAG1, [inaudible 01:22:42] RAG1 and X-linked SCID. So, what's the barrier to therapy? We know from robust studies that these patients need to get transplanted in three months. The preclinical side, the editors, we can make that in six months. We have an amazing team that can do that. At the very end, cell manufacturer, we have a half billion dollar cell manufacturing suite. We can do this cell-to-vein in three weeks.

(01:23:06):

The backlog, regulatory. Each of these patients on a gene-specific IND would be their own barrier. It's a baby's, exactly baby size barrier, to getting all these patients through the pipeline. So, what are we asking? Please permit academic nonprofit sponsors, clinical syndrome INDs inclusive of multiple genes with common clinical endpoints. That's what's really going to get us through this.

(01:23:29):

The other point is about CGMP material. The one size fits all means that we're paying for 20 to a thousand times of what we need for one patient, and it takes many months. So, what we would like is, please, qualify platform and variant testing at the CDMO in master file level, rather than patient specific materials and incentivize small scale production. Thank you so much.

Susan C. Winckler (01:23:51):

Thank you. Our next comment will be from Sharon King, then Mike Lehmicke and Mackenzie Liebowitz. Commenter King, please proceed.

Sharon King (01:24:02):

Thank you. Good afternoon. I'm Sharon King, chief operating officer of the National MPS Society with 20 years of experience in the rare disease community. I raised a child with Batten disease, a life-limiting condition with no available treatment. Holding on to hope, I co-founded Taylor's Tale in 2006, catalyzing drug development for CLN1 disease. That experience drives everything that I do. In the MPS community,

families joined clinical trials that became approved therapies the first 23 years ago and totaling seven today. Many of those children are adults now speaking for themselves, but MPS is relentless and those participants need more.

(01:24:52):

A next generation therapy that reaches the brain, lowered than now accepted biomarker heparin sulfate by more than 90%, yet half of our syndromes still have no therapy and no one has a cure. We bring more than two decades of natural history data, a patient-owned registry planned for all forms of MPS and ML2 and three and adults who know what matters.

(01:25:19):

Three ask. First, do not leave adults behind. Both of this year's new approvals are for pediatric patients. Fit-for-purpose must include adults in evidence plans, confirmatory studies and on the label. Second, honor the evidence that our families and patients have shared, count natural history and registry data, discuss biomarkers pre-IND consistently. Third, use our experts. These are individuals surviving into adulthood because of life-saving therapies. They can contribute to clinical trial, design and help choose endpoints that matter. They can articulate pain sources and levels and specific syndrome impact on daily functioning and quality of life. Bring their knowledge to the table early. The MPS community is your case study for fit-for-purpose.

(01:26:16):

My daughter died in 2018. She didn't have a treatment to improve her life. I continue to hold on to hope. Through the rare disease framework, we can change the trajectory for children and adults living with rare diseases. I know we can do this. Thank you.

Susan C. Winckler (01:26:37):

Thank you. Our next comment will be from Mike Lehmicke. In the queue, we have Mackenzie Liebowitz and Michael Pacold, and then we will turn to our virtual presenters again with Angie Howell. Commenter Lehmicke, please proceed.

Mike Lehmicke (01:26:53):

Thank you. A downside to my name is having to follow Sharon. I am the senior vice president of scientific affairs at ARM. Thank you to Reagan-Udall and FDA for allowing me the opportunity to speak today. ARM is the leading international advocacy organization, championing the benefits of engineered cell therapies and gene therapies for patients, healthcare systems and society. I will comment today on considerations related to four principles in the framework. First, fit-for-purpose review of rare disease therapies. It is important that evidentiary standards and clinical trial designs in particular are fit-for-purpose for rare diseases, where the patient populations are small, unmet need is high and the ideal treatment window may be narrow. It is often the case that in these situations that randomized trials are difficult or impossible to run, and from a scientific standpoint, may not be capable of providing evidence that the treatment works.

(01:27:44):

In fact, 75% of engineered cell therapies and gene therapies approved by FDA, used single-arm trials. There are scientifically valid ways to control for bias in the context of a single-arm trial. Certainly there are cases where randomized trials are more appropriate, but each case should be weighed in a light of the realities of executing the trial. Randomized trials should not be the default. Second, consistency and predictability of FDA's regulatory requirements. FDA should strive to maintain alignment with the sponsor and should ensure consistency between review teams. The guidance that a sponsor is given

should be consistent throughout the review process. New information may lead to the need for changes. These changes should be discussed with the sponsor and documented with leadership sign-off. When two or more sponsors are pursuing an approval for the same disease at the same time, the evidentiary standard should be the same. Third, FDA engagement with external parties.

(01:28:33):

As we've heard, evidentiary standards, including clinical endpoints, should be informed by the patient voice and disease expert opinion. This needs to happen very early in the process. FDA should seek specific feedback relevant to the disease and drug in question. Every patient's experience is meaningful and we should strive to account for this.

(01:28:54):

Last but not least, CMC. These requirements should be applied using a risk-based approach. This can be done by applying prior knowledge and platform principles to accelerate development. ARM has worked with FDA on these concepts and we have shared details about how to operationalize these principles, most recently in our playbook for applying platform principles to gene editing. I hope that these concepts have resonated with you. ARM looks forward to continuing to work with FDA and the entire rare disease community towards our shared goal of advancing this rare disease framework. Thank you.

Susan C. Winckler (01:29:25):

Thank you. Our next comment will be from Mackenzie Liebowitz. In our queue, we have Michael Pacold and then turning to the virtual queue, Angie Howell and Amit Khanna. Commenter Liebowitz, please proceed.

Mackenzie Liebowitz (01:29:38):

Good afternoon. My name is Mackenzie Liebowitz. I bring to this framework experiences as a life sciences researcher, a public health professional, a board certified patient advocate, and most importantly, a multi-rare disease patient. Because of that, I frequently don't qualify for clinical research due to stringent I/E criteria and inflexible options for rare disease patients. People have called me resilient my whole life, but what other choice do I have? So when I started helping other patients navigating all of these systems, I named my team the Tenacious Advocacy Consulting Team, because we are the TAC team you send in to ensure patient voices are always represented in the room and always listened to. My husband, Erin, drove me here today. In clinical research, the participants who usually stay have an errand of some kind. We also have to support the support. As a patient, I spent more than 24 years searching for answers and recently six years appealing for treatment my doctor said was necessary, but wasn't on label for my conditions.

(01:30:39):

As a researcher, I see that trust determines who enrolls and who is still there one year later. In a 20 person rare disease trial, one person leaving means 5% of your data leaves too. As a public health professional, I also look at who's missing. Most patients who reach this agency are already connected to a rare disease advocacy organization. The white paper mentions embedding the patient voice at clearly defined milestones, so I'm asking the FDA to get predictable and consistent by writing them into regulation at the following. When we are learning, understanding the disease in question, at pre-IND, pivotal design, during the trial, FDA review, and post-approval. At each one, we should invite patients and caregivers while the decision is actually still open, including people outside of organized advocacy groups. And then we need to ask, listen, implement, and close the loop in writing. Then apply those milestones the same way across every review division and both centers.

(01:31:47):

After each one, publish a plain language summary of what patients said and what it changed. That's what actually being heard looks like, and there's nothing for us without us. I'm going to be submitting written comments and would welcome a seat at the patient round tables. Thank you.

Susan C. Winckler (01:32:04):

Thank you. Our next comment will be from Michael Pacold, and then we'll turn to a set of virtual commenters, Angie Howell, Amit Khanna, and Tim Klein. Commenter Pacold, please proceed.

Michael Pacold (01:32:17):

All right. Thank you very much to the FDA and also to the Reagan-Udall Institute for allowing me to speak. I'm a physician scientist at NYU Langone and particularly interested in an ultra-rare disease whose etiology our lab discovered. We actually discovered a new disease called HPDL deficiency. We discovered the cause of this and in recently published paper treated the first patient with this, an eight-year-old child, who was able to walk about 10 meters and about almost three years now after treatment with the therapy discovered in our lab is now hiking over six miles. This is meaningful progress that can actually be initiated at the academic level. From an academic standpoint, we are very, very excited about treatments, about this framework, particularly the consistency and the applicability of clinical trial design and expertise from ultra-rare disease and from rare disease experts to other areas of expertise within the FDA.

(01:33:20):

I'm particularly interested in the incorporation of novel sources of natural history data. Natural history is for us is, particularly in a novel rare disease, a limiting factor at times. And so, developing novel methods for actually looking at patient data that's either been previously gathered or that we can extrapolate from cross-sectional data, would be extraordinarily helpful in bringing treatments for this disease to fruition. We're also particularly interested in incorporating the lessons learned from single patient INDs. As we have published this work, we started to hear from these patients. There may be only 200 of them in the States, 2000 worldwide. It looks like there are probably a few more than that. And so, incorporating the data from single patient INDs, particularly responses and toxicity in these endpoints, would be a valuable, of incredible use to us in this framework.

(01:34:12):

I'm looking forward to working with the FDA and with the Reagan-Udall Institute on this framework. I'm grateful for the opportunity to present. You can see the decline in spastic paraplegia rating scale in this patient in the first eight months, but that does not capture the ability of a patient who previously could run, to run again. Thank you very much for the opportunity. Looking forward to contributing as best I can.

Susan C. Winckler (01:34:35):

Thank you. We'll turn to our virtual stage. Our first commenter will be Angie Howell in our queue, Amit Khanna, Tim Klein, and David Leepert. Commenter Howell, please proceed.

Angie Howell (01:34:49):

Good afternoon. My name is Angie Howell and I'm here today as both a registered nurse and the mother of a 19-year-old daughter with ALS. Last year, it was discovered purely by accident that my daughter Jade carries an ultra-rare de novo FUS mutation associated with an aggressive form of juvenile

ALS. That discovery may be what saves Jade's life, because now we have Ulefnersen, also known as jacifusen, which was developed because of Jaci Hermstad, a pioneer in the fight for FUS-ALS treatment. Jaci once said, "There's no hope. It's either you die or you die." Jaci unfortunately passed at the age of 26 from FUS-ALS. Her identical twin sister, Alex, died at 17. So did so many others, just teenagers like Catherine at 16 and Haley at 17. Four young women, four future stolen, three families forever changed. Though Jade was only recently diagnosed with very early onset FUS-ALS, she has almost No noticeable functional loss despite changing biomarkers and neurological testing.

(01:36:06):

Without that accidental discovery, the falls, the bruises, the fatigue, and the weakness would be attributed to a clumsy teenager, while irreversible damage was occurring inside her body. I'm here now to ask the FDA for two things. First, create a framework for early and appropriate genetic identification of familial and de novo mutations through newborn or childhood screening, especially those with promising or research supported treatment. Second, simplify and streamline existing expanded access pathways, reduce unnecessary administrative barriers and make processes easier and faster to navigate.

(01:36:52):

I'm not asking you for guarantees and I'm not asking you for promises. I'm asking for early identification, expeditious early treatment, and something Jaci, Alex, Katherine, Haley, and so many others didn't get, hope for thousands upon thousands of tomorrows. Thank you FDA, the Hermstad family, Dr. Neil Shneider, Ionis and Otsuka for giving patients like my daughter that hope with Ulefnersen.

Susan C. Winckler (01:37:24):

Thank you. Our next comment will be from Amit Khanna. Then in our queue, we have Tim Klein, David Leepert and Marianne Meskus. Commenter Khanna, please proceed.

Amit Khanna (01:37:37):

Good afternoon and thank you to the FDA and the Reagan-Udall Foundation for the opportunity to contribute to this important initiative. My name is Amit Khanna and I represent Yashraj Biotechnology, a life science company based in Mumbai, India, focused on fit-for-purpose NAM model development in rare diseases. In many rare diseases, one of the fundamental challenge is the lack of relevant preclinical models that adequately captures human disease biology. When disease mechanism are poorly understood and patient populations are extremely small, generating the evidence need to understand disease and development, effective treatment becomes particularly challenging. We believe that human relevant new approach methodologies, particularly patient-derived induced pluripotent stem cell or iPSC model can help address these gaps.

(01:38:31):

We have three recommendations for FDA. First, explicitly incorporate NAM into the rare disease framework. Patient derived iPSC model can help investigate disease mechanism study, disease specific biology, and evaluate potential treatment responses. The FDA should clarify how scientifically justified evidence from these models can compliment clinical, genetic, natural history and other evidence, particularly where conventional approaches are constrained by a small patient population. Second, establish clear fit-for-purpose expectation for evaluating these models. Guidance on model characterization, reproducibility validation, and context of use together with early regulatory engagement would help researcher and a sponsor understand how NAM-generated evidence may contribute to drug development and regulatory decisions. This would encourage innovation while maintaining rigorous standard of safety and effectiveness. Third ask is, strengthened international

collaboration and patient representation in rare disease research. Patients are geographically dispersed and individual countries may have access to only a small number of affected individual. Coordinated international efforts are needed to support access to diverse patient population and develop disease model that captures meaningful genetic and clinical variations. Yashraj works with a network of more than 2,200...

Susan C. Winckler (01:40:10):

Thank you. Our next comment will be from Tim Kline. Then we will hear from David Liepert, Mary Anne Meskis, and Amanda Moore. Commenter Kline, please proceed.

Tim Kline (01:40:24):

Good afternoon. I'm Tim Kline, head of regulatory and compliance at Aadi Bioscience, a Kaken company. We're thankful for the FDA and this initiative and committing to fit-for-purpose evidence for rare diseases. The white paper is right that the FDA's tools are already flexible. The challenge is using them consistently. Our message is simple. Fit-for-purpose evidence should be applied the same way in every review division from pre-IND through post-approval. And this is based on two experiences that we have as a company. One is, we market a product for a rare type of cancer. And the second is, we are developing a therapy for a rare disease where it affects the pediatric population. And so this is certainly a matter that we want to be a partner with the FDA on. And so we have four asks of the agency. One, bring rare cancers in. The white paper says that OCE, Oncology Center of Excellence, will be engaged where relevant.

(01:41:38):

We ask that rare tumors be covered explicitly within the same fit-for-purpose standards. Second, agree on evidence sources upfront. We applaud the agency in all they've been doing with many guidances issued on this matter for different types of opportunities to be flexible. But specifically, we'd like to see more written alignment on external controls, acceptance of ex-US natural history data, and more Bayesian borrowing. That alignment shouldn't wait until review time. Third, make post-approval obligations feasible. When a confirmatory trial can't give sponsors clear alternatives, the obligations become a barrier to access. And four, for CMC, we support risk-based CMC review and inspections for the small batch manufacturing typical of orphan products. And finally in close, we will be providing detailed comments to the docket and we thank the agency for providing an opportunity to comment.

Susan C. Winckler (01:42:52):

Thank you. Our next comment will be from David Liepert. Then in the queue we have Mary Anne Meskis, Amanda Moore, and Hetanshi Naik. Commenter Moore, I'd ask you to respond to the prompt to be promoted to panelist. Commenter Liepert, please proceed.

David Liepert (01:43:10):

Good afternoon all. I'm Dr. David Liepert, founder of My Next Health. We build a phone-based instrument that records a person's own symptoms in two serial camera-derived readings tracking objective metrics of cellular and systemic physiology with clear expectations stated before each remeasurement. It is positioned as a general wellness product and we hold no application and we ask for no recognition of any product. But the white paper says two things I want to address directly, that natural history in rare disease is "frequently sparse or non-existent and that many rare diseases lack reliable fit-for-purpose biomarkers or clinical outcome assessments". For a rare condition with few patients, the only natural history that can be characterized in time to matter is that individual person's

own, and it exists usefully only if it is recorded consistently. The plausible mechanism framework already asks for that record, a prior course, the patient has their own control, and post-approval evidence on metrics agreed in advance.

(01:44:14):

So under topic one, my recommendation is one sentence, that a sponsor may meet those expectations with a pre-specified within-person series collected on a digital health technology and a clinical outcome assessment, both built to guidance the FDA has already issued. The FDA already names both halves. A sensor-derived physiologic measure is a digital health technology under the 2023 guidance. A patient's own symptom record is a patient reported outcome, a clinical outcome assessment under PFDD guidance four. Three properties make two one record. Change implications are clearly stated and understood before remeasurement. A stable baseline and repetition come before a change is read and the dimensions of an assessment are reported separately, never averaged. Meanwhile, under topic three, that a patient who re-scores the same symptoms on the same instrument at the same cadence is not giving testimony.

(01:45:13):

They are supplying evidence. The framework should say what makes that record admissible and should name instrument developers as a stakeholder because those properties are built in before any sponsor uses them. One record pre-specified once serves the investigation, the confirmation and the post-approval obligation. Thank you.

Susan C. Winckler (01:45:33):

Thank you. Our next comment will be from Mary Anne Meskis. In the queue we have Amanda Moore, Hetanshi Naik, and Miro Pastrnak. Commentor Meskis, please proceed.

Mary Anne Meskis (01:45:45):

Thank you for the opportunity to speak today. I'm Mary Anne Meskis, CEO of the Dravet Syndrome Foundation and the parent of an adult son living with Dravet syndrome, which is a developmental and epileptic encephalopathy. We're very excited about this new framework and I wanted to highlight the three areas where our organization feels that the outcomes of this framework could have the greatest impact on drug development and ultimately the lives of those living with rare diseases. First, how can we realize the promise of natural history data to reduce the burden of placebo and sham arms? Patient groups often lead efforts to gather natural history data. This is a large financial investment and places a large participation burden on patients and families. Control arms for many advanced experimental therapeutics are incredibly burdensome on patients. Sham arms and prolonged study periods raise significant ethical questions, particularly in individuals experiencing significant medical burdens with life-risking symptoms.

(01:46:40):

We must find common ground between rigor, urgency and humanity in the scientific approach to designing rare disease trials. Clear guidance is needed not only on success stories, but on what might make a data set incompatible for use as a comparator to the therapeutic arm of a study.

(01:46:57):

Second, the patient voice should be a regular touchpoint, not just a checkbox. Patient voices need to be incorporated in proactive and formalized ways throughout the drug development process. Representation of the patient voice during regulatory considerations for a therapeutic product should not be dependent on the relationship and decisions of the sponsor alone. While PFDD meetings are

important, they may not align with developmental timelines and may lack formal follow-up mechanisms. Additionally, externally led PFDD meetings depend heavily on the resources of the patient groups, which can create further disparities for small and under-resourced patient communities. The FDA should engage the patient community and incorporate the patient voice throughout the development timeline of each product.

(01:47:41):

And finally, benchmarks are necessary for reflection. 95% of rare diseases still lack an approved therapy and many of the 5% that do have an approved therapy still have significant levels of disease burden. So how do we know or how are we measuring when the new framework is successful? And my key takeaway today is that in developing this framework, we must always be asking, what are the consequences for patients if a treatment is not approved and how can we identify pathways that enable approval while appropriately managing risk? Thank you.

Susan C. Winckler (01:48:12):

Thank you. Our next comment will be from Amanda Moore. In the queue, we have Hetanshi Naik, Miro Pastrnak, and Sandra Smieszek. Commentor Smieszek, please accept the promotion to panelist to provide your comment. Commentor Moore, please proceed.

Amanda Moore (01:48:29):

Thank you. My name is Amanda Moore. I'm the founder of Appendicure, a patient-led nonprofit for people with appendix cancer, including pseudomyxoma peritonei. It's a mouthful. My husband was diagnosed with appendix cancer and that's how I got here. So I'm asking a couple of things, but one thing particularly, let cancer patients into trials the way cancer drugs are actually built in 2026. So modern cancer drugs target mutations. Clinical trials still sort patients by where the tumor started. Many of our tumors carry KRAS or GNAS mutations, but our patients are shut out of targeted trials because the tumor started in the appendix, not the colon or the pancreas. Same mutation, different organ, no trial. So for most of our patients, that leaves one main option, a surgery that can last up to 18 hours and has literally changed very little in 35 years. I know three women today, same diagnosis, same mutation.

(01:49:31):

One got into a trial built for pancreatic cancer by luck. She's living her life again, living the dream. Two other women are on chemo waiting to get into that same trial. So here is our big idea. In 2017, Congress made sure children with cancer were not left behind. When a new drug targets a mutation that matters in childhood cancer, the company has to plan for children early, but that law didn't take into effect until 2020, three years. Our patients don't have three years. Do the same for rare cancers. If there's a scientific reason to leave us out, the sponsor should have to say why. Give rare cancers the same fit-for-purpose flexibility you give rare diseases in writing so it's predictable for sponsors and consistent for patients in every division. Here is what success looks like. A patient is diagnosed, her tumor is tested.

(01:50:25):

If she carries a mutation, a trial is targeting, she can enroll. Her data goes to Appendicure, our IRB reviewed global registry collected to standards the FDA sets up out front so it counts for the next patient. Nobody should have to fight their way into a trial. We built a trial finder that matches patients to trials by mutation. The data's there. It just has to be acted on. Please let our people in and bring patients and caregivers in early. Thank you so much.

Susan C. Winckler (01:50:55):

Thank you. Our next comment will be from Hetanshi Naik. In the queue we have Miro Pastrnak, Sandra Smieszek, and Devyn Smith. Commenter Naik, please proceed.

Hetanshi Naik (01:51:08):

Thank you very much for the opportunity to speak today. I'm a genetic counselor and clinical researcher who's been working in rare diseases for 16 years. I've been involved in many clinical trials and I'm on the board of the United Porphyrias Association, and I'm speaking from this experience. So as it relates to fit-for-purpose review, others have suggested this as well, but there should be a mechanism to allow patient advocacy groups and researchers to get input from the agency on natural history study design. You've heard that a lot of patient advocacy groups are leading this work to build registries and collect natural history data, and it would be incredibly valuable to get input on assessments and valuations from the agency prior to a product being evaluated.

(01:51:55):

It's critical that the framework allows for evidence generation scaled by rare disease prevalence. What you can collect in 5 or 10 patients for an ultra-rare condition is very different than what you can collect in 200 patients, but that clinical trial design needs to be done very carefully with input from the patient community. There should also be adaptive validation approaches that are incorporated into the framework for clinical outcome assessments in particular. Standards can maintain rigor, but they should be flexible by what's possible in the different patient communities. So where necessary qualitative evidence should substitute for quantitative when sample sizes are limited, looking at things like face validity from clinical experts and patient advocates can be sufficient. And then again, as you've heard from others, there's individual patient data and case series that should be incorporated along with real world evidence. As it relates to consistency, risk tolerance should be assessed by the community and early in the process. Those value judgments should be calibrated to individual communities in particular.

(01:53:06):

And again, as you've heard from others, the engagement with the community should be early and frequent and passive listening sessions are not sufficient for these rare diseases. Reviewers need to have an in-depth understanding of the nuances of the condition and that can only happen with active engagement across the process. Thank you for the opportunity again, and I look forward to submitting more information online.

Susan C. Winckler (01:53:33):

Thank you. Our next comment will be from Miro Pastrnak. Then our queue is Sandra Smieszek, Devyn Smith, and Charlene Son Rigby. Commentor Pastrnak, please proceed.

Miro Pastrnak (01:53:47):

Hi, good afternoon. I'm Miro Pastrnak, chief strategy officer at Rare Disease Research, a site network running over 30 active rare disease trials and an organizer of the Rare Trials Summit. On September 14th, the Accelerate Rare Working Group, about 35 leaders from industry, patient advocacy, CROs, and academia met at the summit to answer some of the same questions this framework addresses, and so I'm sharing our findings. Take a disease with 40 known patients, a conventional two-arm trial is usually impossible, and like many speakers today, we find that the flexibility exists, but what's missing is predictability. And so our recommendations map onto your four focus areas.

(01:54:38):

First, fit-for-purpose review. Make the whole body of evidence, not just a single trial, the unit of proof before collecting more data, sponsor and FDA should agree on a plan, what matters to patients, what's already known, what evidence fills the gaps, and what counts as success or failure. We ask the FDA to help set those standards. Two, predictability. Publish the rules for reusing evidence, what a developer with a characterized platform must repeat and what it doesn't. And separate three decisions, treating the first patient approval and continued access. Each needs its own bar with a post-approval learning plan agreed upfront.

(01:55:18):

Three, engagement. Ask patients and families what change matters and how much uncertainty they'll accept. Diseases differ, families differ, and the review should reflect that range. And four, first patient evidence and CMC. Apply known or shown. For each question, the developer shows the answer for this product or shows it's already known. For one, patient therapies, explore authorizing a standard backbone with agreed limits on the patient specific part. None of this lowers the bar. Where randomization is feasible and ethical, use it. Our ask is to test these ideas with us in two or three time limited case studies. Thank you. We'll submit full comments to the [inaudible 01:56:10].

Susan C. Winckler (01:56:11):

Our next comment will be from Sandra Smieszek. Then our queue includes Devyn Smith, Charlene Son Rigby, and we'll return to in-person comment with Allison Martin. Commentor Smieszek, please proceed.

Sandra Smieszek (01:56:24):

Thank you for this opportunity to speak. Thank you for organizing this very important discussion. Vanda is currently developing an antisense oligonucleotide for Charcot-Marie-Tooth type 2S, a rare axonal neuropathy caused by variants in a gene called IGHMBP2. The disease is genetically heterogeneous, as much as can possibly be. Patients carry private variants and few share the same mutation. We designed an exon skipping ASO antisense oligonucleotide for a single patient and then of one at the time, only one identified candidate existed around the world. The program is now a year into clinical dosing and we are seeing meaningful clinical improvement. Since then, we have been contacted by hundreds of families, many carry variants that fall within the mutational hotspot. We have now delineated and a substantial number are amenable to axon skipping ASOs that share the same gene target, the same mechanism of action, the same backbone chemistry, and the same clinical endpoints as the one already in the clinic. This is the situation, a platform approach we designed for. This is what we believe developing each of these as a separate small molecule style program would mean repeating the same non-clinical and manufacturing work that takes a very, very long time, a time that these patients do not have. Many do not simply have the time to wait to commence such treatment. We welcome this opportunity and we are committed to work with the agency on their platform framework for this program, including agreement in advance to evidentiary expectations and on prior information that can be carried from one construct to another. We believe that this is what will take to make a huge change in these individualized therapy and make them workable, and we look forward to the collaboration with the FDA. We appreciate your time. Thank you.

Susan C. Winckler (01:58:23):

From Devyn Smith. Then in our queue, we have Charlene Son Rigby and in person, we'll turn to Allison Martin, Jewell Martin, and Tracy Mayne. Commenter Smith, please proceed.

Devyn Smith (01:58:36):

Thank you. Thank you very much for the time and for this important work. I'm Devyn Smith, I wear multiple hats, CEO of Arbor Bio, board member of the Alliance for Regenerative Medicine, and also someone with many family members who are rare disease sufferers. Arbor Bio is a clinical stage gene editing company focused on rare diseases in both liver and in the CNS. In the CNS, we're focused on using novel AAV capsids to actually deliver gene editing therapies into the brain with our first therapy target in ALS. We appreciate the efforts to create this framework, to accelerate getting these treatments to patients. We believe that platform technologies like gene editing can be used to potentially treat many of these rare diseases. I do want to call out and thank all the comments from the patients and caregivers. They illustrate why we need to create this framework as the need is tremendous.

(01:59:34):

I see five opportunities here, or comments. So first, as many have said, we need patient and KOL input throughout the drug development process, including as early as IND submission. It's critical to have that input. Second, the requirement for placebo controlled trials. We heard this in a recent pre-IND last week on a rare disease opportunity that we're pursuing. It costs tremendous amount, it costs time, it costs money, and the benefit is pretty minimal. There's so much natural history data from any of these diseases we've heard about. Let's use that data.

(02:00:14):

Third, ensuring that prior guidelines and guidances, like the gene editing platform guidelines, plausible mechanism guidelines align with these rare disease approaches. As a company that crosses all of these guidances, having a uniform and consistent guidance is going to be really important for us. Consistent advice. Recently, we've had a couple of interactions with programs discussed at the FDA and received different feedback on how to deal with all the off targets, which is challenging for a company to not have a single agreed approach.

(02:00:48):

And then finally, CMC, making it fit-for-purpose. It is extremely expensive in both time and money. That is one of the biggest costs for getting these therapies to patients. Thank you very much.

Susan C. Winckler (02:01:03):

Thank you. Our next comment will be from Charlene Son Rigby. Then we'll return to the room and we will hear from Allison Martin, Jewell Martin, and Tracy Mayne. Commenter Son Rigby, please proceed.

Charlene Son Rigby (02:01:17):

Thank you. I am Charlene Son Rigby, CEO of Global Genes. We are a patient advocacy organization that works across the more than 10,000 rare diseases. I'm also the parent of a child who is living with STXBP1- related disorder, a very severe, very rare neurodevelopmental condition, and I co-founded the STXBP1 Foundation. I am very enthusiastic about this initiative and the time is now. We need a regulatory framework for rare disease that makes it more viable, not just commercially viable, but frankly, financially viable and predictably navigable. And that navigation needs to happen for both industry, academia, and as we've heard multiple times today, patient advocacy group sponsors. We need to also take into account very small patient populations and patient heterogeneity.

(02:02:11):

I have three points. First, patient input. Patient input early and through the regulatory process and review process is crucial. I've heard from people at the FDA that they encourage sponsors to include

patients in meetings with the agency, but it rarely happens. Encouragement is not enough, especially if patients and patient advocates don't have defined roles and if there isn't clear definition on how the input is going to impact the process. So patient input needs to be incorporated in a consistent and visible way. We need to define the outcomes out upfront and have them at specific milestones. And importantly, we also need to take efforts to not create more steps and lengthen already long timelines.

(02:03:04):

Second point, outcome measures and endpoints. Communities invest millions of dollars and years of efforts in validating and developing natural history data so that...

(02:03:18):

Sorry, is my video having problems?

Susan C. Winckler (02:03:21):

We can hear you and see you. Please proceed.

Charlene Son Rigby (02:03:22):

Okay, great. Communities invest all this money and then they may learn late in the process that something needs to be adjusted or restructured and they have to start over. The FDA can lower the likelihood of this happening by giving earlier and proactive guidance. This is critical for small populations. I know I'm at time. Thank you for your leadership in...

Susan C. Winckler (02:03:47):

Now we lost the feed. We'll turn to... Thank you and we will turn to our first in-person comment from Allison Martin. In the queue, we have Jewell Martin, Tracy Mayne, and Reenie McCarthy. Commenter Martin, first one, please proceed.

Allison Martin (02:04:02):

Hi, I'm Allison Martin, Director of Regulatory Science and Policy from Sanofi. Thank you for the opportunity today. Sanofi has been committed to advancing rare disease drug development for over 40 years, bring deep scientific expertise and a steadfast focus on improving the lives of patients and families affected by these conditions. We applaud the agency for recognizing that while great progress has been made in rare disease drug development and regulation, more can and should be done to bring safe and effective treatments to patients more efficiently. We appreciate FDA's thoughtful approach to the challenges of many rare disease programs and recognize that the agency is leveraging its experience and learnings in developing the framework to strengthen consistency. Even so, sponsors may still encounter varying interpretations of what constitutes sufficient evidence across centers, divisions, and therapeutic areas. We welcome the agency's efforts to improve predictability and acceptance of fit-for-purposes approaches and in review decisions, particularly in how clinical benefit and meaningful treatment effect are evaluated.

(02:05:06):

Excuse me. As the framework takes shape, we recommend the FDA more explicitly encourage regulatory decision-making based on totality of evidence rather than statistical significance alone. While P values provide important information, they represent only one component of the evidentiary package, particularly when small sample sizes can limit statistical power. For example, FDA could further endorse Bayesian approaches that quantitatively integrate data beyond the clinical trials such as observational and mechanistic studies, patient preference research, and registries that could capture a more holistic

measure of benefit and support actionable assessment of a treatment's effect. Sanofi is also pleased to see the framework will include considerations for CMC and we look forward to providing recommendations through the public docket. Finally, incorporating the patient and caregiver voice throughout product development is of critical importance, and we are happy to see that it's a primary focus in the framework. For many rare diseases where treatments are not curative, the impact on daily functioning, independent symptom burden, and quality of life may represent the most meaningful benefit and are often not fully captured by traditional clinical measures alone.

(02:06:20):

Early in engagement with patients and caregivers is essential to ensuring development programs focus on what matters most to those living with the disease. In closing, we're highly supportive of FDA's initiative to develop this new framework and we welcome the opportunity to participate in future activities and [inaudible 02:06:36]-

Susan C. Winckler (02:06:35):

Thank you. Our next comment will be from Jewell Martin. In the queue, we have Tracy Mayne, Reenie McCarthy, and Paul Melmeyer. Commenter Martin, please proceed.

Jewell Martin (02:06:46):

Hi, my name is Jewel Martin. On behalf of BioMarin Pharmaceutical, thank you for the opportunity to contribute our perspective. For nearly three decades, BioMarin has been committed to developing transformative therapies for people living with rare genetically defined diseases with significant unmet need. That experience gives us a practical perspective on both the promise and challenges of tailoring regulatory approaches to the realities of rare disease drug development. FDA's white paper brings renewed focus to several important regulatory principles that have evolved over time with an opportunity to have their potential more fully realized in practice. Regulatory adaptability has long contributed to the approval of important rare disease medicines. Similarly, patient voice and patient-focused drug development have been priorities for many years. The opportunity now is to make these concepts predictable, durable, and operational in practice.

(02:07:44):

Rare disease sponsors make consequential development decisions years before an application reaches FDA, relying on regulatory advice about endpoints, trial design, evidence generation and other issues, yet sponsors can later encounter regulatory skepticism and some variation of, "We recognize the principle, but it does not apply in this case." When those differences are difficult to anticipate, regulatory adaptability becomes difficult to rely upon. That is why we are particularly encouraged by FDA's focus on fit-for-purpose evidentiary expectations, consistency and predictability, reviewer training, and alignment across review organizations. Success should ultimately be measured by whether we see clear evidence that sponsors and patients are expecting greater consistency in actual regulatory advice and decisions.

(02:08:36):

We also strongly support more systematic incorporation of patient input. Patient partnership has always been central to BioMarin's work. The next step is to make the influence of patient experience data more visible in regulatory decision making. FDA should communicate how patient input informs endpoint selection, meaningful clinical benefit and benefit risk assessments. In conclusion, the promise of this initiative is to close the gap between regulatory adaptability and principle and regulatory adaptability in

practice. That requires timely, iterative communication, rolling reviews, predictable application, meaningful incorporation of patient voice and transparency [inaudible 02:09:19]-

Susan C. Winckler (02:09:20):

Thank you. Our next comment will be from Tracy Mayne. In the queue, we have Reenie McCarthy, Jason Menzo, and Allison Mintz. Commentor Mayne, please proceed.

Tracy Mayne (02:09:30):

My name is Dr. Tracy Mayne. I'm Senior Vice President of Regulatory and Life Sciences Research at Slipstream Life Sciences. The innovations you've talked about today could be saving hundreds of thousands of lives, but they won't, not unless the review teams adopt these innovations. What I'm about to tell you is not meant to impugn anybody, but to help you understand what's happening as of two weeks ago, there are 11 to 15,000 glioblastoma patients diagnosed every year. 35 to 50% of them will be dead within a year of diagnosis. Multiple studies in our own work show that there are only about 1,000 trial eligible patients in the US each year. Competing for those patients, 38 trials looking to recruit 6,600 patients. You can do the math. As you heard, two of the trials have been stopped because they could not enroll patients.

(02:10:20):

An incredibly promising phase 2 product with mortality benefit and an approved trial has not begun in 6 years. And I can tell you why, because nobody is going to fund a rare disease trial that's going to take 10 years to read out. There have been no innovations in two decades. The last drug approved does not decrease mortality in the two thirds of patients with unmethylated disease. We went to the FDA and we said, "We'd like to do an external control trial." We were told point-blank, "The only valid trial is a randomized controlled trial," period, no discussion. The tropes they gave us... Sorry, there was a slide with this. They said, "Well, real world data can never rule out unmeasured bias." A randomized placebo controlled trial can't rule out unmeasured bias. There are 10 FDA guidances that tell industry, how do you address these issues? So you follow them. Every single rule, you pre-register the fit-for-purpose study on clinicaltrials.com. You give them the clinical study report.

(02:11:22):

You get to a type C meeting, they wouldn't even read it. The solution is, you have to mandate the adoption of these existing and future guidances. If you don't do that, they're not going to flow through to the divisions. It's critical. Put members of real world evidence and rare disease on the review teams. Their job being to ensure that those teams are educated and that they adopt and implement the guidances that are out there. You could be saving hundreds of thousands of lives. Please require the adoption of the guidances. Thank you.

Susan C. Winckler (02:12:00):

Thank you. Our next comment will be from Reenie McCarthy. In the queue, we have Paul Melmeyer, Jason Menzo and Allison Mintz. Commenter McCarthy, please proceed.

Reenie McCarthy (02:12:11):

Thank you, that's hard to follow. Good afternoon, I'm Reenie McCarthy, CEO of Mighty Therapeutics, with two recommendations from developing Forzinity for Barth Syndrome, an ultra-rare mitochondrial disease affecting just 150 known individuals in the US, where we partnered closely with patients for over a decade to embed their voice. First, severity of symptoms can vary by age and rare genetic diseases.

Establish a presumption that children have the same underlying disease as adults and implement a practical approach for evidence generation in ultra-rare pediatric populations. I'm sharing a plea from Kate McCurdy, Chair of the Barth Syndrome Foundation, who lost her son to that disease, in solidarity with the 17 members of the Mitochondrial Disease Advocacy Coalition. Please do not forget our children.

(02:13:03):

In genetic mitochondrial disease, children are most often vulnerable to abrupt and devastating bioenergetic crises, all too frequently leading to sudden death. Do not assume that the fragility of these children suggest that they are living with a different disease, requiring distinct development efforts which are even more infeasible in a further segmented population. Do consider ways to expedite access to novel therapies to children as soon as your risk analysis permits. They don't have time to wait and expanded access is a pretty imperfect solution. Second, back to me, identify intermediate clinical endpoints as tools for fit-for-purpose review and train reviewers on their utility. Most of the more than 300 rare mitochondrial diseases have no validated biomarkers or surrogate endpoints, which has precluded accelerated approval and access to pathways like RDEP and plausible mechanism. Last year's accelerated approval of Forzinity for muscle weakness in older kids and adults with Barth syndrome was based on an intermediate clinical endpoint. The approach could enhance development and expedite access for other rare mitochondrial diseases. We appreciate the patient centricity FDA demonstrated in our review by approving on an intermediate clinical endpoint and post-marketing by green lighting a common sense approach to couple PK modeling with extrapolation of efficacy, hopefully speeding access to some of the kids who are outside our label. We'd like to see these approaches standardized across ultra-rare programs in the framework. Thank you for inviting me to comment.

Susan C. Winckler (02:14:41):

Thank you. Our next comment is from Paul Melmeyer. In the queue we have Jason Menzo, Allison Mintz and Samarendra Mohanty. Commenter Melmeyer, please proceed.

Paul Melmeyer (02:14:51):

Thank you very much and thank you for the opportunity to speak to you today. I am Paul Melmeyer. I'm with the Muscular Dystrophy Association and we serve the neuromuscular disease community in a variety of ways, including advocating for the accelerated development of more and better therapies. Neuromuscular diseases are complex, heterogeneously and irreversibly progressive and are sometimes severe, yet other times slowly progressive over many years, and most are considered ultra-rare. Each of these features makes developing new treatments for neuromuscular diseases incredibly challenging and evaluating safety and effectiveness all the more difficult. This is why a new paradigm, a rare disease framework, could be critically important for our community.

(02:15:31):

I'll briefly touch on several topics for the framework to consider and we'll expound further in written comments. Neuromuscular diseases progress unevenly and sometimes slowly, making traditional clinical trials unlikely to capture a prospective therapy's true effectiveness. The framework should invest in paradigm shifting clinical, statistical and regulatory approaches to evaluating effectiveness in slowly and/or heterogeneously progressive rare diseases. The use of biomarker surrogate endpoints are critical for these same reasons, but very few are validated or FDA qualified. This framework should include FDA investments to generate, validate and qualify surrogate endpoints in progressive rare diseases with the reevaluation of the often unobtainably high bar for the FDA qualification program.

(02:16:17):

FDA cannot simply be an arbiter, it must be a partner and ideally a leader. The framework should invest in fit-for-disease approaches that could feature tailored regulatory pathways, evidentiary requirements, clinical trial structures, statistical approaches and more that fit the disease in question rather than the disease needing to fit arbitrary and unrealistically strict standards. This includes more robust and progressive use of patient generated data to inform benefit risk evaluations tailored to the disease.

(02:16:47):

This framework should include a dramatic expansion of the use of platform technologies, particularly in ultra-rare and NFU diseases and allow for multiple NDA/BLA approvals across genetic subtypes of a rare disease without recreating the wheel each time. Flexibilities on nonclinical, clinical and CMC requirements for NFU diseases developed by nonprofit and academic developers must be considered to unlock development pathways in NFU treatments. We urge the FDA to move forward as quickly as possible. We'll say it once more, time is muscle. Thank you so much for the opportunity to speak.

Susan C. Winckler (02:17:22):

Thank you. Our next comment will be from Jason Menzo. Our queue is Allison Mintz, Samarendra Mohanty and Edward Neilan. Commenter Menzo, please proceed.

Jason Menzo (02:17:32):

Well, thank you very much. My name is Jason Menzo and I'm the CEO at the Foundation Fighting Blindness. I'd like to ask you to imagine an eight year old boy named Alex. Alex has trouble seeing at night. In fact, his parents won't let him go out trick or treating the Saturday because they're afraid that he's going to fall and get hurt. You see, Alex was born with a genetic condition that is slowly taking away his sight and without treatment he will eventually go blind. But here's the amazing thing about science. Today we can identify the exact genetic mutation that is responsible for Alex's condition. And with advances in gene therapy and other technologies, researchers are developing a treatment today. That's great news, right? So what's the problem? Well, let's say there are 200 people in the United States with Alex's exact genetic mutation, all of whom could benefit from the same treatment.

(02:18:33):

We're seeing extraordinary progress and heroic efforts with innovative n-of-1 and NFQ approaches for individualized treatment, but these models weren't really designed for populations of 200 patients. And at the same time, 200 patients are too few to make traditional commercial drug development economically viable. So despite the scientific progress, Alex and patients like him are being left behind. At the Foundation Fighting Blindness, we've invested nearly $1 billion in research to develop treatments and cures. And today our Uni-Rare natural history study currently follows approximately 1,500 people with blinding diseases caused by rarely mutated genes.

(02:19:18):

If we don't figure this out, all that time, money and effort would be wasted, not to mention the patients who will continue to wait. So we're asking the FDA for three things. First, establish a predictable approval pathway for therapies targeting genetically defined populations of fewer than 1,000 patients where commercial viability doesn't exist. Second, allow relevant safety manufacturing and platform evidence to carry forward across regulatory... I'm sorry, across related therapies. And third and most importantly, ensure that these pathways include serious slowly progressing diseases with evidence requirements and clinical endpoints that reflect how they actually progress and that matter to patients. The Foundation Fighting Blindness-

Susan C. Winckler (02:20:07):

Thank you, thank you. Our next comment will be from Allison Mintz. In the queue we have Samarendra Mohanty, Edward Neilan and Jackie O'Neil. Commenter Mintz, please proceed.

Allison Mintz (02:20:18):

Good afternoon. My name is Allison Mintz and I'm a patient living with cavernous malformation, specifically a genetic form of the disease called CCM. Cavernous malformations are leaky blood vessels found in the capillaries. They can hemorrhage in the brain or spinal column and they could cause such things as strokes, paralysis, seizures or headaches. I myself live with seizures. The problem with cavernous malformation, similar to many rare diseases, is that it is one of the 95% of rare diseases that do not have a treatment or cure. As a result, you can only get spinal surgery or brain surgery. This is one of the things that I am asking, is that once organizations or studies show proof of safety, then perhaps allow people to provide the drug to the patient population.

(02:21:33):

It's not as if the people researching this drug are playing 52 card pickup. They are building a house of cards, carefully built in order to help the potential population who may need the drug. It takes a very long time to build an efficacy study, oftentimes many years. Patients cannot wait necessarily for this time. A secondary ask is that CMS and the FDA work together to allow patients to have these drugs covered, because oftentimes patients cannot afford these drugs. Patients cannot always wait. I myself am lucky, but at any point in time I might become paralyzed again or need another urgent surgery. Please consider allowing patients to get drugs once safety is proven. Thank you very much.

Susan C. Winckler (02:22:47):

Thank you, Commenter Mintz. Our next comment will be from Samarendra Mohanty. In the queue, we have Edward Neilan, Jackie O'Neil and Sierra Phillips. Commenter Mohanty, please proceed.

Samarendra Mohanty (02:22:59):

Good afternoon. I'm Samar Mohanty, Chief Scientific Officer of Nanoscope. I'll make two points. First, the arithmetic of heterogeneity. Several group of diseases such as inherited retinal dystrophies caused by mutation in more than 300 genes, more than 8,000 mutations under one gene, one disease and one product model sponsor builds a complete program with pivotal trial with a population to address few hundred to thousand patients, then repeats all of it again. So most of the genotypes will never support independent development program because there are very few patients that are being affected by few mutations. So the majority of patients are not underserved by accident, they're excluded by the structure of the model itself.

(02:23:46):

The gene agnostic and disease diagnostic approaches which are coming up with new science invert that premise. For example, supplementing with the option molecule to the surviving retinal neurons, one can restore vision with a single active substance that can address many disease which are genetically distinct but converge on same endpoint of loss of option molecule or the photo receptors. The science here is settled, the development and regulatory consequences are not. Where the loss of molecule and the mechanism of action is identical across indication, prior knowledge should carry forward almost in full, but the boundaries of acceptable leveraging of prior knowledge in safety and efficacy and the evidentiary burden that's required for a second indication are yet to have settled guidance.

(02:24:36):

Further, how an endpoint is validated in one disease lacking that molecule will be transferred to another disease is also answered program by program. Can a composite endpoint be used, taking into account heterogeneity of rare diseases while considering product evaluation for many disease, and many disease that is affected by commonality of lesser lack of option? Second, this is where I ask agency to look. There are a lot of guidance, but retina is just an extension of the brain. In the CNS space, there is a precedence which we can directly draw and apply to retina space. For example, applying intermediate clinical endpoints, surrogate endpoints and using natural history and using open level extension trial to expand into this disease. With that, I will thank you and I think my time is up, but I'll say draft guidance that will provide cross-functional prior knowledge leveraging across indication.

Susan C. Winckler (02:25:32):

Thank you. Our next comment will be from Edward Neilan. In the queue we have Jackie O'Neil, Sierra Phillips and Trey Putnam. Commenter Neilan, please proceed.

Edward Neilan (02:25:43):

All right. Thank you, Susan, and hello, everyone. I'm Ed Neilan. I'm a molecular biologist, a pediatrician and a medical geneticist, and I recently assumed the role of Head of the Pediatric and Rare Disease Center of Excellence at IQVIA. In that role, I have the privilege of leading a multidisciplinary group of experts who provide strategic guidance on the design and execution of many rare disease trials every year, so I find that very exciting. Prior to joining IQVIA, among other roles, I served sequentially as President of the Medical Staff at Boston Children's Hospital, as Head of Global Medical Affairs for Rare Neurogenetic Diseases at Sanofi Genzyme. And recently it was my honor to serve as the Chief Medical and Scientific Officer at NORD. Overall, I have 25 years of experience developing rare disease drugs and have worked on at least six programs that got new FDA approvals.

(02:26:43):

I guess my point in part is that IQVIA as a whole has much more experience than that. And in this context, we appreciate the need and IQVIA as a company, up to our executive leadership is excited and thankful for FDA's committing to build this improved framework for rare disease drug development and regulatory review that is fit for purpose for small populations. Over the past 10 years, IQVIA, which is the world's largest CRO, has helped sponsors to conduct more than 500 rare disease trials, enrolling more than 52,000 patients in 96 countries, but still that's of course, not enough.

(02:27:23):

As you've heard already from others, the unmet medical needs and rare diseases are huge and patients urgently need safe and effective new treatments and new clinical development paths tailored to what evidence is both meaningful and reasonably obtainable. Sponsors do need, as was discussed earlier, clarity and predictability from FDA to justify and to invest further in rare disease drug development. However, as Kareem indicated earlier in his comments towards the beginning of this meeting, that predictability can't come solely or even primarily from past precedent, but rather these new regulatory approaches and the framework must evolve alongside the rapidly advancing science. At IQVIA, we have seen sponsors who aspire to apply innovative approaches, who then hesitated or reverted to more traditional common disease-like designs-

Susan C. Winckler (02:28:17):

Thank you. We'll turn to our next commenter, who is Jackie O'Neil. In the queue, we have Sierra Phillips, Trey Putnam, and then we will turn to our virtual session again with Liza Squires. Commenter O'Neil, please proceed.

Jackie O'Neil (02:28:32):

Thank you. I'm speaking to you today as a patient with connective tissue disorder, luckily someone who has 17 years chemistry experience in innovative pharmaceutical development. I welcome the agency's renewed focus and wish to suggest opportunities to help allow approval of affordable new treatments through expanded indications for approved drugs and also repurposing promising therapies. Patients are already accepting risks through off-label use and expanded access programs, yet existing regulatory requirements often make new approvals economically impractical, particularly for affordable treatments. I'm experiencing this personally.

(02:29:12):

Low-dose naltrexone, a drug first approved by the agency in 1984, helps me enormously. Yet, without indication specific approval, patients face barriers to access even when there are years of published evidence and clinical experience. An opportunity exists here to leverage published studies, past investigator initiated trials and real world clinical evidence to demonstrate efficacy for new indications without requiring development programs that are disproportionate to the populations they would help. I encourage the agency to consider four particular opportunities. One, allow evidence of effectiveness to be demonstrated by a combination of targeted studies that supplement true gaps in current evidence, thus conserving resources and expenses. Second, establish a more economically viable regulatory pathway that recognizes the limited incentives for developing affordable new drugs and expanding indications where current pathways are not viable.

(02:30:14):

Third, apply a risk-based review approach that more appropriately weighs the damages of inaction. We've heard moving... For example, moving CMC validations to post-marketing requirements is an opportunity perhaps to better balance risk and pre-approval investment by sponsors. Finally, create a robust reporting structure and/or platform for data capture. This could provide a unique opportunity to collect a lot more data from patients who are already accepting risk and taking therapies for their indication. I'm not suggesting lowering standards of efficacy or safety. I'm asking to use the best possible evidence, capture data already being generated and to focus studies on the risks that truly remain to help us bring promising treatments to patients waiting for them.

Susan C. Winckler (02:31:06):

Thank you. Our next comment will be from Sierra Phillips. In the queue, we have Trey Putnam and in the virtual queue, Liza Squires, Michael Templin and Stephen Thompson. Commenter Phillips, please proceed.

Sierra Phillips (02:31:17):

Hello, my name is Sierra Phillips and hopefully you'll see here in a few seconds that I am blessed to be the mother of five-year-old twins, Charlotte and Jack. I'm also the founder of the Warsaw Breakage Syndrome Foundation. Jack is one of fewer than 20 patients in the United States living with Warsaw breakage syndrome with less than 50 documented cases worldwide. We have no approved treatment, we have no disease specific registry, we have no natural history study, we have no lab working to advance a treatment candidate. I have a background in human and muscular genetics, I work in clinical research. I help other foundations pursue treatments for their communities, yet I still carry immense guilt for not having been able to do this for Jack. No parent should have to carry the absence of a treatment as a personal failure. I want to change Jack's future while still being able to be present for the only childhood he and Charlotte will have.

(02:32:09):

FDA, you have seen firsthand what families, many of whom are in this room and have joined us virtually today, have accomplished. They've developed therapies, they've founded biotechs, they've funded and led extraordinary research programs. Build on what these achievements have brought to us and your own progress in the rare disease drug development by addressing three gaps that leave children like Jack without a clear path. First, help families without a sponsor or research program build evidence that the FDA can use before treatment candidate exists or IND enabling work even begins. Through the Rare Disease Innovation Hub, please provide a named contact, scientific guidance, clear regulatory expectations and written next steps.

(02:32:52):

Second, help us define meaningful outcomes and prioritize evidence, identify scientifically sound studies and methods for data collection that are realistic and achievable for our patient numbers and our resources, including alternatives when traditional and conventional trials are not feasible. Third, define when and how families and disease experts will help the FDA interpret evidence during development and review for very small populations with limited natural history data. Include small family-led groups in designing the support. Report annually, how many communities move from no development program to a credible path that is aligned with the FDA's scientific and regulatory expectations. While we work to build that path, Jack is losing time, time we will not get back. As you heard, time is muscle. In the neurodevelopmental world, we say time is brain, so please make sure this framework reaches him, too. Thank you.

Susan C. Winckler (02:33:47):

Thank you. Our next comment will be from Trey Putnam and then we'll turn to virtual. I would ask Commenter Squires, Thompson and Tompkins to please accept your promotion to panelists so that we can hear you. Commenter Putnam, please proceed.

Trey Putnam (02:34:03):

Thank you for this opportunity to speak. I'm Trey Putnam. I'm here today, representing Elpida Therapeutics, a nonprofit working to bring treatments to patients and families facing ultra-rare diseases. Many of these diseases have less than 100 patients worldwide. Specifically, we would like to see the FDA establish clear, proportionate regulatory approach for therapies serving ultra-rare patient populations, particularly gene therapies whose manufacturing development costs make sustained commercial investment quite difficult. For diseases affecting up to 100 diagnosed patients in the United States, demonstrating clear and measurable evidence of clinical benefit may be scientifically or practically infeasible.

(02:34:51):

Many genetic diseases only have recently been identified, leaving limited or non-existent natural history data, validated biomarkers or suitable clinical endpoints. In some cases, a single study involving 10 or fewer patients represents the maximum feasible clinical evidence, particularly for nonprofit organizations and foundations with limited resources. When traditional efficacy requirements cannot be reasonably met, FDA should establish a conditional approval pathway that considers an acceptable safety profile, biological plausibility, early indications of potential benefit and real world observations, including physician assessments and caregiver reported changes.

(02:35:38):

Similar to the humanitarian device exemption framework, such a pathway could permit controlled patient access while requiring continued collection of safety and efficacy data to support full approval. Clinical flexibility must be matched with a fit-for-purpose feasible manufacturing pathway. Those expectations should permit scientifically justified alternatives to conventional CMC, including process validation programs and conducting process validation PPQ post-approval as a post-approval commitment. There's regulatory precedence for this in small molecule and well-characterized biologics. FDA should establish transparent eligibility criteria for this approach, considering both the size of the treatment eligible population and barriers to commercial sustainability. Thank you.

Susan C. Winckler (02:36:36):

Thank you. To the audience, we have five virtual commenters and 10 in-person commenters. So if you're watching the clock, that means we're going to go to about 5:10. I expect that because I allowed you to applaud, you will stay until 5:10, please. Our first in-person commenter in this queue is Liza Squires. Liza, please turn on your camera. And then in the queue, we have Michael Templin, Steven Thompson and Sarah Tompkins. Commenter Squires, please proceed.

Liza Squires (02:37:09):

Good afternoon. I am Liza Squires, Chief Medical Officer at Neuren Pharmaceuticals. Neuren focuses on a range of rare monogenetic neurodevelopmental disorders that affect small patient populations and can have a devastating impact on patients and families. Even within similar indications, different approaches are necessary to execute a viable clinical trial. This depends heavily on available patient numbers, the degree of heterogeneity and the fragility of patients. To address these unique challenges, flexible evidence-based regulatory approaches are essential to achieve an accurate efficacy evaluation. Crucially, this flexibility does not mean lowering of rigorous safety standards, but rather adopting how we capture meaningful clinical evidence.

(02:38:10):

Neuren welcomes this rare disease framework initiative, which in our view, should consider the following principles. For a particular indication, basic clinical trial endpoint and substantial evidence requirements should be the same for all participants across biologicals and non-biologicals. The requirement should be tailored to the indication, which means that they may be different in different indications [inaudible 02:38:48] trials such as patient [inaudible 02:38:50] their own control or natural history comparator studies may be necessary and effective in some indications.

(02:38:59):

For a particular indication, consideration of trial design and primary efficacy endpoints are connected and a traditional trial design may be possible using one endpoint, but not possible if another endpoint is required to be used. Regulatory flexibility around the use and validation of fit-for-purpose disease specific endpoints that accommodate heterogeneity in symptoms should be encouraged. By building a clear and reliable framework, the FDA has a historic opportunity. This may transform what used to be seen as too risky into a powerful incentive that encourages companies to-

Susan C. Winckler (02:39:44):

Thank you. Our next comment will be from Michael Templin. In the queue, we have Stephen Thompson, Sarah Tompkins and Matthew Zyrus. Commenter Zyrus, please accept the promotion to panelist. Commenter Templin, please proceed.

Michael Templin (02:40:01):

Thank you for the opportunity today to talk. As we've heard many times, rare disease drug development requires a highly tailored approach. While the conversation often centers around early discovery, efforts to speed cures to patients should not overlook the role of non-clinical CROs in accelerating drug development and ensuring patient safety. As we've heard many times today, rare diseases present unique scientific and translational challenges. This includes limited understanding of disease biology, small and yet heterogeneous patient populations and diverse disease mechanism. This creates a complex landscape that is often compounded by the lack of established non-clinical development pathways.

(02:40:46):

A successful strategy relies on integration of in vitro and in vivo studies. In vitro models, including patient-derived cells and other novel platforms, can better characterize disease mechanisms, demonstrate target engagement and generate critical proof of concept and proof of benefit data. These approaches are particularly valuable when a traditional model will not adequately reflect a complex disease biology. At the same time, in vivo studies remain essential for assuring patient safety. Animal models provide insight into whole body responses that cannot be fully captured in isolated systems. Thus, questions related to bio distribution and safety may require in vivo studies.

(02:41:30):

It is together that in vitro and in vivo evidence forms the foundation for clinical translation and decision making. The non-clinical CRO is more than just a testing provider. Experienced CROs can develop fit-for-purpose disease models, design integrated pharmacology and toxicology programs and provide expertise in biomarker and translational science. This allows for informed decisions while reducing developmental risk and avoiding costly delays. This is why a framework for rare disease development should consider the essential role for nonclinical CROs. Ultimately, combining innovative in vitro approaches with robust in vivo studies through tailored nonclinical strategies accelerates and improves the likelihood of delivering much needed therapies to rare disease patients. Thank you for your time.

Susan C. Winckler (02:42:23):

Thank you. Our next comment will be from Steven Thompson. In the queue, Sarah Tompkins, Matthew Zyrus, and then returning to in-person, Nicole Reich. Commenter Thompson, please proceed.

Steven Thompson (02:42:37):

Good afternoon and thank you to FDA and the Reagan-Udall Foundation for this opportunity. My name is Steve Thompson, Founder, Chief Architect of INTEKNIQUE. I spent more than three decades working across regulated life sciences, quality systems and technology. I commend FDA for recognizing that rare disease development requires scientific approaches tailored to patients and the evidence that can be realistically obtained. I'd like to offer a perspective on what happens as that evidence evolves. In rare disease research, evidence may come from patients, clinicians, laboratories, research institutions and sponsors often working across organizational boundaries and evidence doesn't stand still. New information emerges, scientific assumptions change, new technologies and methods are introduced. Decisions made yesterday may need to be reconsidered tomorrow.

(02:43:27):

So how do we continuously assure that decisions and actions remain appropriate as the evidence changes? And how do we leverage flexibility without sacrificing consistency? At INTEKNIQUE, we explore this through three connected concepts. First, computable governance. That's making the rules, responsibilities and decision authority explicit through enough to be consistently applied across systems

and organization. Second, behavioral assurance. That's establishing whether people, processes and increasingly intelligent technologies are fit-for-purpose and act within their authorized responsibilities.

(02:44:06):

And third, continuous assurance, using new evidence and changing conditions to determine when prior decisions must be reassessed, escalated or corrected. For FDA's consideration, I suggest that rare disease framework address not only what evidence is sufficient at a particular milestone, but also how that evidence, the decisions based upon it and their consequences remain subject to appropriate oversight throughout development. The need to introduce additional regulatory burden or mandate particular technology is not necessary. The objective is not simply to document that the decisions were made, the objective is to maintain confidence that decisions and actions remain justified as circumstances changes. For rare disease patients and families, that continuity matters. Thank you.

Susan C. Winckler (02:45:01):

Thank you. Our next comment will be from Sarah Tompkins, then Matthew Zirwas, and in-person Nichole Riek and Yoko Rosenbaum. Commenter Tompkins, please proceed.

Sarah Tompkins (02:45:11):

Thank you. My name is Sarah Tompkins. I'm an Ehlers-Danlos syndrome and rare disease patient advocate with the Northwest Rare Disease Coalition and Connective Strength. Thank you for the opportunity to comment. I want to thank the FDA for centering the patient voice in the Rare Disease Framework. For rare disease and EDS patients, natural history data and patient-reported outcomes are essential to define meaningful endpoints and accelerate therapeutic development.

(02:45:36):

However, when a single patient organization owns and controls registries and historical data sets and unintentionally limits who participates and who can access the data regulators and independent researchers need. I ask with the rare disease framework that FDA consider requiring or incentivizing registry practices that ensure equitable access, independent validation and multi-stakeholder stewardship, specifically requiring public data access plans with timelines, favor multi-steward or federated governance that includes US patient representatives, mandate transparency about recruitment, consent and metadata, require diversity transport reporting, and support expedited access and funding for US rare disease patients and patient nonprofit organizations to participate and engage in the patient-focused drug development.

(02:46:24):

If the rare disease framework is to produce fit for purpose pathways and meaningful endpoints, the lived experiences of all rare disease patients, caregivers, and families, including EDS patients, must be accessible, verifiable, and included early and often in the process. Thank you for this opportunity to comment. I will submit to the [inaudible 02:46:44] comment and I'm eager and grateful to continue participation and learn more how patients can be involved. Thank you.

Susan C. Winckler (02:46:51):

Thank you. Our next virtual comment will be Matthew Zirwas, and then we will turn to in-person Nichole Riek, Yoko Rosenbaum and Anthony Saleh. Commenter Zirwas, please proceed. Commenter Zirwas.

Matthew Zirwas (02:47:15):

Sorry, I was muted. You would think after all this time.

Susan C. Winckler (02:47:18):

Yep, please proceed.

Matthew Zirwas (02:47:20):

So hi, I'm Matt Zirwas. I'm a dermatologist and clinical trial investigator. And you might wonder why a dermatologist is on here, and it's because dermatology has more rare diseases than literally any other specialty. And so I've taken care of more rare disease patients than I could ever, ever count. And the thing is, we've got really great treatments for a lot of them, but we're not allowed to use them. So we've got case series, case reports, pretty big databases actually showing that some of the blockbuster drugs out there work, drugs that have thousands and thousands of patients that have been through clinical trials.

(02:47:58):

So we know they're generally very safe, but we can't use them because insurance denies them under the guise of experimental and the companies can't provide the drugs off-label, so nothing. And so I've had lots of conversations with pharma about why they don't do something and why they don't study them and get indications.

(02:48:17):

And it's basically, number one, the trial is hard. So patients are few, they're scattered and they won't accept placebo. So FDA can make rules to fix all of this next month. So cap the trial at 0.1% of the estimated US patient population, floor of 10 patients. Don't really use historical controls, have it be add-on trials. So standard of care plus or minus placebo. If you're on placebo, you cross over, become your own control.

(02:48:45):

Number two, there's no economic incentive. Even if they get the drug approved, a couple thousand more patients doesn't matter to these companies. So give them some extension of the exclusivity across the board that's proportional to how big the unmet need is. Doesn't have to be long. Two weeks of longer exclusivity would matter to these companies. And then most important though is fear of the label. So they are worried that if there's a new adverse event that shows up in this study, it's going to contaminate the label for the blockbuster indication, and that is a disaster.

(02:49:19):

And that's actually the easiest one to fix. So put a new thing in the label, a box that says that this side effect only applies to this indication because if the side effect didn't show up in 5,000 phase three trial patients and it shows up in a trial of 10 rare disease patients, it's not the drug. It is either just a random thing that happened or it's a specific drug disease interaction, but by having it contaminate...

Susan C. Winckler (02:49:49):

Thank you so much, Commenter Zirwas. Turning in person, we'll turn to Commenter Riek, then to Rosenbaum, Saleh and Savoie. Please proceed.

Nichole Riek (02:50:00):

Good afternoon. My name's Nichole Riek and I'm the Vice President of Regulatory Affairs for Integrated DNA Technologies in Aldevron. First off, I want to applaud FDA's willingness to really think boldly about rare and ultra-rare diseases. When the patient population may be only a handful of individuals, we need

a regulatory model designed for that reality. We've seen that firsthand with baby KJ and the heroics that went into supporting that timeline.

(02:50:25):

So integrated DNA technologies in Aldevron working with Acuitas helped enable his personalized CRISPR therapy. IDT provided the guide RNA and the off-target safety work while Aldevron manufactured the mRNA in the final drug product and Acuitas manufactured a lipid nanoparticle. That experience showed us what's possible, but it also showed us something really important. We need to make this repeatable. These therapies are going to come from clinicians and investigators working closely with specialized manufacturers and CDMOs.

(02:50:57):

The patient specific sequence may change, but much of the manufacturing, the analytics, the technology that sits behind them and the quality system is going to remain the same. And that really brings me to where FDA can really help. FDA's platform technology designation program is an important step, but it doesn't work so well when a specialized manufacturer is building platform knowledge across multiple clinicians, institutions and sponsors.

(02:51:25):

So how do we leverage what we already know? How do we focus new evidence on what change and what creates risk for a patient population rather than regenerating evidence for what hasn't changed? Again, this isn't about lowering the standard. It's about applying the standard intelligently. The same thinking needs to also extend to inspections. A platform-based pre-market approach also needs an aligned risk-based inspection strategy. Otherwise, we create flexibility on the front end only to return to a product-by-product model on the back end. Baby KJ demonstrated what's possible through close collaboration among regulators, clinicians, researchers, and manufacturers. FDA can now build on this model by enabling qualified platforms to be validated once and leveraged across individual therapies, focusing subsequent reviews on what's new or what's different. Validate the platform once, accelerate every therapy after. Danaher calls on FDA to convene a stakeholder forum to develop this framework and a practical path forward. We stand ready to contribute our expertise in our-

Susan C. Winckler (02:52:32):

Thank you. Our next comment will be from Yoko Rosenbaum, followed by Anthony Saleh, Hillary Savoie and Trisha Shivas. Commenter Rosenbaum, please proceed.

Yoko Rosenbaum (02:52:43):

Thank you for the opportunity to provide comments on FDA's Rare Disease Framework Initiative. My name is Yoko Rosenbaum and I represent the Rare Disease Company Coalition, an organization that represents biopharmaceutical companies dedicated to discovering, developing, and delivering treatments for patients living with a rare disease.

(02:53:01):

As FDA recognizes, rare disease companies face unique challenges in developing drugs for rare diseases. In order to identify potential solutions to address these challenges and improve regulatory efficiency and predictability, RDCC commissioned research to examine FDA's regulatory approach to rare disease drug development and review. The data we collected reflects a regulatory environment in transition and the announcement of this initiative comes at a critical time.

(02:53:27):

The output of our research efforts, which will be released in just a few weeks, are well aligned with the principles outlined in FDA's white paper. We agree that greater regulatory clarity, consistency and predictability are essential to fostering innovation, attracting investment, and accelerating the development of therapies for rare disease patients.

(02:53:45):

Providing opportunities for patients and families to have earlier and more direct engagement with FDA will help ensure that regulatory decisions are informed by the scientific evidence and the priorities of the patients most directly affected. Similarly, we support opportunities for scientific exchange with scientific and clinical experts to ensure product reviews are fully informed by disease context. A totality of evidence approach to regulatory review should be central to FDA's approach, preserving rigorous evidentiary standards while appropriately accounting for the realities of rare disease drug development.

(02:54:18):

FDA can and should consider the full body of relevant evidence. A truly fit-for-purpose approach should also examine whether preclinical manufacturing and early clinical requirements are appropriately calibrated to the risks and objectives of first-in-human rare disease studies to ensure meaningful scientific dialogue between sponsors and FDA and to facilitate early US clinical development. We are immensely grateful for FDA's leadership on this initiative and the framework represents an important step forward.

(02:54:46):

Its ultimate success will depend on how effectively its principles are translated into regulatory practice across review divisions and at all levels of the agency. RDCC stands ready to support FDA in the weeks and months ahead to ensure that the concepts and improvements described under the framework become a reality. Thank you again.

Susan C. Winckler (02:55:06):

Thank you. Our next comment will be from Anthony Saleh and then Hillary Savoy, Tricia Shivas and Amy Simon. Commenter Saleh, please proceed.

Anthony Saleh (02:55:16):

Hello, thank you. I come to you with three different roles today. First, I'm a patient with facial facioscapulohumeral muscular dystrophy, a mouthful. Thanks to Gregory Mendel, I'm also a parent of a patient with FSHD. I was also an NIH-trained scientist in developing oligonucleotide therapy, and I come to you as a CEO of a pharmaceutical company that's developed a platform to deliver RNA therapy to muscle to correct these underlying mutations.

(02:55:45):

We have a treatment for FSHD that we hope goes into the clinic next year. And then we've also decided to apply that technology to another more severe neuromuscular disease, central nuclear myopathy. That's a disease that affects mostly children, about half of patients that are born with that disease die before age two. As a patient and an executive in a pharmaceutical company, I am so excited about what has happened at FDA over the last few years, seeing the severe life-threatening disease guidance, the plausible mechanism guidance and the rare disease framework that we're talking about today really could change the feasibility of bringing these drugs forward for patients.

(02:56:27):

And I really look forward to collaborating with regulators to see our therapies and therapies of other companies come forward. There are three things I know would be incredibly impactful and I want to hit on that are in this guidance and hopefully we can apply.

(02:56:44):

So the first is phase appropriate CMC and GOP toxicity. Every dollar we reduce our preclinical development increases the chance we can raise enough money from a variety of groups to bring that drug into humans and test that underlying hypothesis that that RNA therapy can work. Second is, if we understand the disease mechanism, having as much guidance as possible around using that disease mechanism and biomarkers associated with that as evidence. For muscle diseases in particular, it takes a long time for muscle tissue and for physical changes to happen in a patient. There are very few examples of observed neuromuscular muscle function endpoints being provable in rare muscle diseases.

(02:57:36):

Having accelerated approval based on mechanistic data is critical. Lastly, having better defined pathways for including the most severely affected patients. There have been over a dozen clinical trials in FSHD...

Susan C. Winckler (02:57:51):

Thank you. Our next comment will be from Hillary Savoie, then we have Teresa Shivas, Amy Simon and Michelle Sloan. Commenter Savoie, please proceed.

Hillary Savoie (02:58:01):

Good afternoon. I'm Hillary Savoie and I'm here today after all of these wonderful comments to focus on something very particular, accountability as a central focus for the framework. We all know that patient input is absolutely essential. We know this. However, the reality of the drug development ecosystem is that it struggles to incorporate qualitative expertise that does not fit neatly into spreadsheets, especially when it's not required. I'm a rare disease mom, an advocate, a nonprofit founder, former biotech head of advocacy, and current drug development and advocacy consultant. I've spent 15 years of my life learning the perspectives of families, advocates, researchers, drug developers, and translating and negotiating between them, which is not always easy. In that time, I have seen the absolute best of intentions sometimes turn into box-ticking exercises, like patient input requirements that have advocates spending hours providing really, really meaningful feedback that development teams and operation teams are literally not positioned to act upon.

(02:59:16):

And I've seen the opposite, how strategic patient input in really unexpected rooms, rooms we don't belong in supposedly yield... Like in conversations about early CMC decisions yield fundamentally improved viability for programs. Without clear structures and requirements for translating this patient knowledge into decisions, the framework could risk institutionalizing performative patient engagement.

(02:59:47):

But what we need is fit-for-purpose, strategic substantive impact. So how do we get there? We build it by explicitly creating accountability. Instead of three points, I'm going to offer three questions. One, who is responsible for ensuring that patient expertise actually influences development decisions at the right times? Two, what are the obligations for documenting when patient input was sought, how it was used and when it was overlooked? Three, how can FDA enable meaningful multi-stakeholder dialogue, including providing rare disease specific compliance guidance so that necessary safeguards aren't out-sized into unnecessary barriers...

Susan C. Winckler (03:00:34):

Thank you. Our next comment will be from commenter Shivas with Amy Simon, Michelle Sloan and Elaine Towle in the queue and you're at the best part of the alphabet. All right. Commenter Shivas, please proceed.

Trisha Shivas (03:00:49):

Thank you so much for the opportunity and your commitment to the rare disease framework. I'm Tricia Shivas and I represent the Foundation for Sarcoidosis Research. Sarcoidosis is a rare inflammatory disease that can impact any organ of the body. Sarcoidosis is a snowflake disease because no two patients look the same and it is a flaring condition and it makes endpoint development and measurement particularly challenging.

(03:01:15):

In previous conversations with FDA reviewers, we have been told that inclusions of patients with multiple manifestations of the disease in drug development generates noise in the data, and it is imperative that we evolve our definition to what good data is for particular patients. Heterogeneity requires innovative statistics. Building drug development that is responsive to heterogeneity is the only true path for a drug design in diseases like sarcoidosis. We need to start with the disease and build from there. True patient-centered drug development must consider improvement in quality of life measure use.

(03:01:57):

Current use of healthcare quality measures in drug development rely on unrealistic validation standards requiring reevaluation and measures commonly used in clinical care and in research, and that those validated measures are not considered to be valid in this disease.

(03:02:14):

Treatments that show improvement in quality of life are highly desirable for patients. As you consider a new framework, please prioritize identifying ways to include quality of life in meaningful ways for patients in those communities. The externally led patient-focused drug development process has been pivotal in advancing the FDA's understanding of rare diseases.

(03:02:39):

However, how that data are used is still a mystery to many of us. We would like to ask for more transparency around how you are using patient feedback and patient information, and find mechanisms for reporting that back to the community directly. We want to have patient expert voices in the IND and review processes. The rare framework is a beacon of hope for the rare disease community. I hope you heard that here today, but we do need to be very careful to engage the patients directly, make sure that their voices are being heard and think about that future. Thank you so much.

Susan C. Winckler (03:03:14):

Thank you. Our next comment will be from Amy Simon, then Michelle Sloan, Elaine Toll, and James Valentine. Commenter Simon.

Amy Simon (03:03:22):

Good afternoon. I'm Amy Simon. Medical Officer at Beam Therapeutics where we're developing gene editing medicines for patients living with rare diseases, including sickle cell disease and alpha-1 antitrypsin deficiency or alpha-1. We strongly support FDA's commitment to fit-for-purpose evidence.

(03:03:40):

Our central recommendation is the framework translate flexibility into predictable and innovative regulatory pathways, particularly for genetic medicines with large objective biological effects directly linked to disease causation. First, efficacy should be measured where the therapy acts. Gene- editing addresses disease at its root cause. In our ALPHA-1 trial, we see large, rapid, and consistent increases in functional M-AAT protein along with decreases in mutant Z-AAT, yet clinical outcomes such as preventing further lung damage can take years to measure.

(03:04:17):

We ask FDA to clarify when durable correction of a causal defect coupled with a large well-understood biomarker response can provide primary evidence of effectiveness with longer term clinical outcomes confirmed after approval.

(03:04:31):

The duration of the primary efficacy assessment should follow the biology. For a one-time therapy with a rapid stable response, that could mean six months rather than 12. Second, endpoints validated in large populations may not fit rare diseases. FEV1 is widely used in COPD, but in Alpha-1, they have a distinct clinical course and substantial lung damage is evident on CT while FEV1 remains normal.

(03:04:56):

A layered approach could include serum alpha-1, CT lung densitometry, FEV1 as a longer term outcome. We ask for a predictable patient-informed pathway to qualify endpoints that reflect rare disease biology. Third, we should avoid placebo when it is not needed. When treatment effects are large and objective and the disease is progressive and irreversible, external controls can provide a meaningful alternative. Clear standards for their use and access to high quality placebo data sets from prior trials could reduce unnecessary placebo exposure and make rare disease development more efficient.

(03:05:32):

The opportunity is to make these approaches predictable, not exceptional. Evidence matched to mechanism, endpoints matched to disease, and trial designs matched to rare populations. We appreciate FDA's leadership and look forward to working together so the incredible scientific progress we have heard about today can translate to what matters most, giving patients the opportunity to move beyond their disease and get on with their lives. Thank you.

Susan C. Winckler (03:05:56):

Thank you. Our next comment will be from Michelle Sloan and then Elaine Towle, James Valentine, Monica Weldon. Commenter Sloan, please proceed.

Michelle Sloan (03:06:07):

Good afternoon. My name is Michelle Sloan. I'm CEO and Co-founder of the Foundation to Fight H-ABC, and mother of Eloise who lives with H-ABC, a rare progressive neurological disease caused by changes in the TUBB4A gene. TUBB4A-related leukodystrophy is a heterogeneous condition with broad clinical spectrum affecting approximately 300 known patients worldwide. Several children have received this ASO through an individual protocol and applications have been submitted for many more. I'm asking a broad question as it relates to individual patient protocol treatments.

(03:06:47):

How can the FDA help advance treatment from this point in such a scenario? Could the FDA identify an FDA aligned pathway for using experience in patients to support treatment for more eligible patients

while continuing to build evidence and protect safety? What evidence and safeguards would be needed? Could the pathway include enrollment under a shared protocol, independent safety oversight, common outcome measures and planned FDA review points as evidence accumulates?

(03:07:17):

The goal would be to advance treatment for all eligible patients, not only the few who can access these individual protocols. Yesterday's draft guidance on individual genome editing products concerns a different modality, but offers a useful example of FDA proposing how product variation could be evaluated in advance. I hope the FDA will consider what similarly clear modality specific guidance would look like for ASOs.

(03:07:43):

I'd also like to touch on two other unrelated matters that affecting our community. Natural history data is very essential for a trial as we know, but when it's managed and institutionally held through NIH funding or partial NIH funding, it's very difficult to access without paying an exorbitant amount. We would ask the FDA to work with the NIH and institutions on timely affordable access that protects privacy and fairly credits these researchers, but families should not have to repeat data collection because existing information is inaccessible.

(03:08:19):

And lastly, clinical trials for pediatric onset conditions should include older adults, and children and adults. Many have waited the longest and have as much need, if not greater, for potentially lifesaving treatments. Turning 18 or 21 does not end a childhood onset disease. Trials should accommodate different disease stages and use outcomes that can...

Susan C. Winckler (03:08:40):

Thank you. Our next comment is from Elaine Towle, and then we'll hear from James Valentine and Monica Weldon. Commenter Towle.

Elaine Towle (03:08:48):

Thank you for the opportunity to provide input on the framework initiative. My name is Elaine Towle and I'm speaking on behalf of the Prader-Willi Syndrome Association USA, and I'm also mom to a 40-year- old man living with Prader-Willi syndrome. Prader-Willi Syndrome, or PWS, is a complex multi-system genetic disorder whose impact cannot be measured through a single symptom or clinical endpoint. Individuals with PWS experience metabolic, behavioral, neurological, endocrine, and developmental challenges that profoundly affect health, independence, and quality of life.

(03:09:26):

Our community has participated actively in presenting the patient voice through our ELP FDD meeting, our voice of the patient report, and ongoing engagement with the FDA. These efforts have helped communicate the lived experiences of individuals with PWS and their families. However, collecting patient experience data is only the first step. The greater challenge is ensuring that those insights meaningfully influence clinical trial design, endpoint selection, and benefit risk assessments. Rare disease communities face unique barriers to drug development, small patient populations, diverse symptoms, and changing disease manifestations across the lifespan can make traditional trial approaches difficult. Translating patient prioritized outcomes into validated clinical endpoints is also a challenge. We encourage FDA to adopt scientifically rigorous, yet flexible evidentiary expectations that reflect these realities. Specifically, we urge FDA to recognize patient identified outcomes, provide

clearer guidance on the use of natural history data and real-world evidence, and support innovative trial designs that generate credible evidence in small populations.

(03:10:47):

We also encourage greater coordination across FDA review divisions for multi-system conditions like PWS, treatment benefits may extend beyond a single indication. Finally, patient engagement should be integrated throughout drug development and regulatory review. The patient voice should not simply inform the process. It should help shape the evidence we collect, the outcomes we measure, and the decisions we make. Thank you for your commitment to advancing rare disease drug development. We look forward to working with you.

Susan C. Winckler (03:11:21):

Thank you. Our next comment is from James Valentine, and then Monica Weldon is ready to go. Commenter Valentine, please proceed.

James Valentine (03:11:30):

Thank you, Susan. Good evening now. I'm James Valentine, a director at Hyman, Phelps & McNamara. Our firm has been involved in roughly one third of all of the orphan new chemical entity approvals, half of all non-oncology accelerated approvals, and about two thirds of all externally led patient-focused drug development meetings, which is why we feel a responsibility to share our insights here. We strongly endorse the framework's broad scope to address every stage of development with goals of opening more first-in-human INDs for rare diseases here in the US, to making approval decisions more predictable since the barriers we see appear start at the beginning of a program as often as at the end.

(03:12:17):

We also believe the framework must recognize that rarity is a continuum, not a set of categories. While a disease affecting tens of patients may seem to present more acute challenges than one affecting 1,000, 10, 000, or even 200,000, the challenges across that continuum are often more alike than different, and a few diseases can provide a proving ground for novel approaches and create pathways to be applied more broadly.

(03:12:48):

When operationalizing the framework, we need to change the narrative that opens FDA sponsor meetings. And I'm in three such meetings this week alone across different divisions, and too often the starting point that we hear is that the standard is same for rare and prevalent conditions. That's true as a legal matter, but it doesn't facilitate a fit-for-purpose discussion. It's the presumption that reviewers are asked to work from, and as a consequence, FDA puts the traditional path on the table and then the onus shifts to the sponsor to argue for deviating often over multiple meetings. We should share in that responsibility for a tailored approach, whether that be questioning the feasibility of an RCT or the classic 0.5 alpha level, or earlier on of whether a conventional NOAL-based margin aligns with patient risk tolerance. The first question should always be, what framework is fit for this purpose?

(03:13:49):

Today is just the start. We plan to publish a series of FDA law blog posts culminating a docket submission. Dr. McHale, you asked us to aim big and we will. Thank you.

Susan C. Winckler (03:14:00):

Thank you. And closing out our public comment process, we will turn to Commenter Weldon. Commenter Weldon, please proceed.

Monica Weldon (03:14:08):

I thank you for having me here today. I'm Monica Weldon. I'm the mother of the sixth child diagnosed with SYNGAP1 in the world in 2012. I founded the first research organization in the world for its condition in 2014. Over 10 years, it built the foundation for a US clinical trial now pending IND approval because more data is needed. I also work in national defense for the last two and a half years inside and outside government building business frameworks, models for industry.

(03:14:39):

At the Defense Department, I proposed a priority review voucher for national security and recommended a domestic API manufacturing facility. I helped craft the Promising Pathways Act 2.0 introduced in 2024. National defense and rare disease have similar challenges. They all have moving targets. So I speak today in my personal capacity. First, use data that already exists. The FDA should summarize patient-focused drug development reports by class for small sponsors and turn them into pre-specified secondary endpoints in one registry that serves as a natural history, external control, and confirmation.

(03:15:19):

We backed our SYNGAP report top quality of life impacts with our own natural history study data. The benefits, small sponsors save money and have missed primary endpoints no longer wasting a trial. Second, build the promising pathway into FDA rules, time limited conditional approval for rare progressive diseases. The benefit, earlier access confirmed by the registry. Third, tell sponsors what is enough. Review past trials for missed endpoints, then publish a minimum evidence package by disease class and a written response on evidence gaps with set time, within a set time. The benefit, the sponsors stop guessing. Fourth, convene a consortium for small rare disease sponsors as defense does. Neutral manager, low barriers, shared problems stated upfront, add independence test and firewalls from large companies. Teach patient communities how to build data packages. The benefit, a level-playing field for small sponsors so they can compete and patient data gets fair value.

(03:16:27):

Start each as a pilot, two to three diseases, 24 months, and a comprehensive proposal I have prepared for the FDA right here that I will be putting in the docket for your consideration. I thank you again for-

Susan C. Winckler (03:16:41):

And thank you. So with that, let's thank our more than 75 public commenters who we were able to hear from today. What I've learned is that when you give the rare disease community two minutes and 30 seconds, they will take two minutes and 29. And so thank you all. I appreciate your patience. Thank you all for your extraordinary contributions. The recording slide and transcript will be at reaganudall.org next week. Thank you so much and take care.