Drug Repurposing: Considerations for Selection Criteria and Prioritization

Hybrid Public Meeting
Wednesday, August 5, 2026 | 10:30 am – 5 pm (*eastern*)

Transcript – Public Comment

Public Comment

Susan C. Winckler:

So this is the time where I have to do a fair amount of logistical explaining. So I think that's the word. We have choreography. That is the appropriate way to describe this. So as we said in the meeting announcements for this meeting, [00:00:30] we had put out a notice and said, if you're interested in providing public comment, please raise your hand. A number of individuals raised their hand and I'm pleased to say that we were able to accommodate all who raised their hand and then responded to our offer to speak today. So we are organizing the public comment by topic, and we will begin by hearing from those of you who requested topic number one. As a reminder, topic number one is what are [00:01:00] examples of successful prioritization approaches from other programs or jurisdictions that could be adapted? So here's what's going to happen.

We are going to hear from our virtual speakers first. I'm going to give a rolling list of three to give you advanced notice that you will be up for public comment. That tells you you should hear your name twice before I call on you to present your remarks. So as we turn to those who are dialing in virtually, I will call on [00:01:30] each of you in alphabetical order by last name with one exception where we had someone who needs to go later in the queue. So we didn't mess up the alphabet. It was an intentional adjustment. As I introduce each commenter, I will list the next three commenters in the queue. And so with that, let me just give a heads-up to the first three who are in the queue while I continue my instructions. The first three in the queue are Andrea DiCarlo-Cohen, Linda Feinstein, and Barbara Goodman.

[00:02:00] When I first announce your name, that's your queue to look for the Zoom prompt to become a panelist if you are not already. The second time you hear your name, turn on your camera and prepare to unmute your microphone. When the speaker before you completes their remarks, unmute your microphone and wait for my introduction. Our producers will bring you on screen and you have up to two and a half minutes to comment. If you do not begin speaking within 10 seconds of my turning the virtual stage to you, we'll move to the next [00:02:30] commenter. And if time allows, we'll come back to you at the end of the section's virtual commenters. To help you with time management, there is a countdown clock that will display on screen showing the time you have remaining. I will also come back on screen when you have about 15 seconds left. And at the two and a half minute mark, we will end your audiovisual support and move to the next public commenter.

Our in the room commenters will use the podium on the stage opposite me. When you hear your name the first time, make [00:03:00] your way to the front of the room by the wall and a member of our team will help you navigate to the stage when it's your turn.

Public Comment

Topic 1: What are examples of successful prioritization approaches from other programs or jurisdictions that could be adapted?

Susan C. Winckler:

So with that, we are just about ready to begin. As a reminder, no one from the foundation or any of the speakers, we're not responding to the comments. We all have our listening ears on. This is the listening part of the meeting. And so if we are ready to begin, a reminder, this is topic number one. And our first three, Andrea DiCarlo-Cohen, Linda Feinstein, [00:03:30] and Barbara Goodman are in the queue. Do we have commenter DiCarlo-Cohen ready?

Andrea DiCarlo-Cohen:

Yes, I'm here.

Susan C. Winckler:

Excellent. Please proceed.

Andrea DiCarlo-Cohen:

Thank you, and good afternoon. My name is Andrea DiCarlo, and I'm the Director of the Department of Health and Human Services Radiation and Nuclear Medical Countermeasures Program, a funding agency within the NIAID NIH. Since 2004, the program has used a deliberate product for purposing strategy to strengthen national medical preparedness for radiation emergencies, [00:04:00] such as nuclear power plant accident or attack, dirty bomb, or detonation of an improvised nuclear device. Rather than relying solely on the development of new drugs, we've prioritized funding research on FDA-approved medical products that already have well-characterized safety profiles and could be repurposed for post-exposure treatment of radiation-related injuries. In doing so, it's possible to reduce the cost and time to licensure of a product for a new indication, and physician familiarity with these products will make them more confident about prescribing them during a radiation incident. [00:04:30] The program held a meeting on this topic in 2017, and the publication and link are shown on the slide.

This approach has produced many tangible results. Since 2015, multiple products, both branded and generic, each of which had their unique challenges, have been approved to stockpile and treat potentially lethal radiation-induced bone marrow injuries. There's also been an approval for radiation-induced skin injuries as shown on the slide. These products can now be deployed in a radiation emergency to save lives.

At the same time, the program continues to evaluate additional classes [00:05:00] of widely available medicines for efficacy against radiation injuries, including blood pressure medications like lisinopril and captopril, GLP-1 receptor agonists, statins, antibiotics, and oncology drugs like growth factors. This effort

creates a diversified pipeline that balances near-term implementation with longer-term innovation. Equally important are the prioritization principles that guided these successes. The program emphasizes engaging industry partners early, understanding the intended end users and operational settings from the outset, [00:05:30] and involving regulatory agencies throughout product development rather than only at the end.

These practices reduce development risks, accelerate regulatory review, and help ensure that selected products are practical for a real-world emergency response. These lessons are broadly applicable beyond radiation preparedness. Those seeking to prioritize limited resources could adopt a similar framework by focusing on products with existing evidence and established manufacturing capacity, engaging stakeholders early, and integrating regulatory considerations into decision- [00:06:00] making from the beginning. Together, these strategies provide a practical evidence-based model for efficiently translating scientific opportunities into deployable public health solutions. Thank you for the opportunity to speak today. Those completed my comments.

Susan C. Winckler:

Thank you. Our next public comment will be from Linda Feinstein. In the queue, I have Barbara Goodman, Jacqueline Perez, and then in the room we'll turn to Barbara Binzak Blumenfeld. But turning to the commenter right now, Linda Feinstein, if [00:06:30] you're with us, please come up on the screen and proceed to present.

Linda Feinstein:

Thank you very much. I'm Linda Feinstein, counsel at Dentons, representing the International Contrast Ultrasound Society, a grassroots nonprofit organization representing doctors, sonographers, scientists, and patients in 90 countries. Thank you very much for the opportunity to discuss the repurposing of ultrasound contrast agents, which are drugs that enhance diagnostic ultrasound scans. [00:07:00] Their use changes management and outcomes for patients suffering from cancers and diseases, including rare diseases throughout the body. At present, adult indications are limited to the heart and liver, but benefits are much broader because a single IV injection shows perfusion of all organs. Ultrasound contrast agents are ideal candidates for repurposing because safety is well established in clinical trials and scientific literature.

In addition, [00:07:30] clinical practice guidelines and experiences support uses throughout the body, and some patients have no other option for advanced imaging. For example, patients who are kidney impaired or pregnant may not be candidates for contrast CT or MR because those contrast agents can damage kidneys, cross the placenta, and present risk of gadolinium deposits in the brain.

We also think it's important to note that ultrasound contrast agents provide reliable [00:08:00] results in real time, so that reduces the need for downstream tests and procedures, which lowers costs and risks.

We also note that limiting use to the heart and liver is simply clinically illogical because if a radiologist, for example, examines the liver and spots a suspicious mass on the kidney or spleen, it just makes sense to move the transducer and follow disease.

We also note that ultrasound is more affordable [00:08:30] and more widely available than MR and CT. And for those reasons, ultrasound contrast agents are often used for whole body applications in Europe and elsewhere without raising safety concerns. Unfortunately, in the United States, we have an organ-specific approval process, and that can be cost prohibitive and burdensome. So we believe ultrasound contrast agents are low-hanging regulatory fruit and should be one of the first drugs considered for repurposing because they [00:09:00] are safe, they're affordable, and they have the potential for high impact on care and outcomes ...

Susan C. Winckler:

Thank you. We will now proceed in the queue. We have Barbara Goodman, Jacqueline Perez, and then Barbara Binzak Blumenfeld. We'll then turn to topic two where the first commenter in the queue is Olugbenga Ajulo. So let's turn now to Barbara Goodman. Please proceed.

Barbara Goodman:

Thank you for organizing [00:09:30] this important discussion today. I am Barbara Goodman, President and CEO of Cures Within Reach, a U.S.-based nonprofit testing repurposed therapies for unsolved diseases by funding trials to de-risk and catalyze follow-on funding, building clinical evidence required for the FDA or for off-label use. With over 20 years of success stories, Cures Within Reach supports the FDA's initial priority areas and recommends three additional ones. First, [00:10:00] given the complexities of Pediatric trials, children are often left out of initial drug approvals. Rare pediatric diseases have smaller patient populations with fewer commercial incentives. One of Cures Within Reach's first earliest successes is FDA-approved sirolimus for autoimmune lymphoproliferative syndrome. In 2004, Cures Within Reach funded successful trials at Children's Hospital of Philadelphia, leading to nearly $1 million from [00:10:30] the NIH for a larger trial after an 85% remission rate and several publications. Sirolimus is now considered a standard of care globally.

In 2023, the Swedish Medical Products Agency selected Cures Within Reach as the nonprofit lead and potential non-traditional sponsor of a label change for sirolimus and ALPS in Sweden's national repurposing pilot alongside of EMA's STAMP effort.

A second prioritization [00:11:00] approach is expanding neurology to include mental health, chronic pain, and traumatic brain injury. In 2022, Cures Within Reach funded a successful early trial at the University of New Mexico testing FDA-approved N-acetylcysteine to improve TBI outcomes. Positive results led to $3 million from the US DOD for further development.

Our third prioritization approach is refractory recurrent oncology after first and second-line treatments aren't enough. [00:11:30] In 2023, Cures Within Reach funded a successful trial at University of Pittsburgh testing FDA-approved interferon gamma in blood cancer patients relapsing after stem cell transplantation. This spurred 3.5 million in funding from the FDA for an ongoing multi-site trial. These are just examples from our portfolio. Earlier this year, we funded three ultra-rare, including DeSanto-Shinawi syndrome at Mayo Clinic.

Susan C. Winckler:

[00:12:00] Thank you. Our next commenter will be Jacqueline Perez. Then we'll turn to in-person comment from Barbara Binzak-Blumenfeld and then turn to topic two. Olugbenga Ajulo and William Fitzsimmons are in the queue. We'll turn now to Jacqueline Perez. Please proceed.

Jacqueline Perez:

Good afternoon. My name is Jacqueline Perez, Director of Clinical Research at ASCO on behalf of the American Society of Clinical Oncology and the Targeted Agent and Profiling Utilization [00:12:30] Registry Study Team, thank you for the opportunity to comment. The TAPUR study is a pragmatic, multi-basket, multicenter precision medicine trial launched in 2016, operating across 281 U.S. states and territories with 3,039 participants enrolled. The TAPUR study evaluates FDA-approved targeted anti-cancer drugs, prescribed off-label for patients with advanced cancers that harbor actionable genomic alterations. Since its inception, the TAPUR study has evaluated 27 treatments in over 230 [00:13:00] cohorts. We believe the TAPUR study is the largest oncology drug repurposing study ever conducted. Thus far, we have reported on 47 cohorts in various cancers, and our results have been cited in clinical practice guidelines such as the ASCO Guidelines and NCCN Colon Cancer Guidelines amongst others. Details [inaudible 00:13:17] published cohorts can be found by scanning the QR code on the screen.

To answer the question at hand, the TAPUR study's design shifts prioritization from cancers defined by anatomic location or histology to specific biomarker defined population [00:13:30] and uses pre-specified genomic inclusion and exclusion criteria to match patients to specific treatment options. That is matching a drug to a gene alteration regardless of tumor type or location. This approach could be employed in any therapeutic area where biologically or molecularly defined diseases could be treated with targeted therapeutics. TAPUR is a platform that allows evaluation of multiple drugs simultaneously, screening them for activity against any solid tumor that harbors the genomic target of the drug. [00:14:00] This allows for high efficiency in patient enrollment in that historically 70% of patients screened for TAPUR have found a drug match and enrolled.

To efficiently evaluate and prioritize treatments without exposing patients to ineffective therapies, we have used a [inaudible 00:14:15] two-stage design allowing early stopping for futility. The design is based on the assumptions that a 15% disease control rate is of no interest and a 35% disease control rate is sufficient to justify further study for the treatment in the cohort. Each cohort enrolls a minimum [00:14:30] of 10 patients and a maximum of 28 patients. This structured approach serves an excellent blueprint for other drug repurposing initiatives to officially identify early efficacy signals in a pragmatic clinical trial while minimizing risk and optimizing resource utilization. Thank you.

Susan C. Winckler:

Thank you. We'll now turn to in-person comment on this topic. And so we are going to hear from Barbara Binzak Blumenfeld. [00:15:00] Please proceed.

Barbara Binzak Blumenfeld:

Great, thank you. My name is Barbara Binzak Blumenfeld. I'm the leader of the FDA and Biotechnology Practice at Buchanan Ingersoll & Rooney. I'm also regulatory counsel to the Value Added Medicines Alliance or VAMA, a nonprofit representing stakeholders with interests in 505(b)(2) new drugs. And as a practical matter, repurposed drugs fall within the ambit of 505(b)(2). Thank you for this opportunity to

summarize the comments that VAMA submitted to FDA's [00:15:30] drug repurposing docket that focused on challenges and opportunities.

The first challenge for this sector is the R&D knowledge gap. Sponsors may identify a candidate drug for repurposing, but not be able to articulate its value add because they don't fully understand the patient population, the development time or the costs involved, or the intricacies of formulary placement and payer coverage. We recommend FDA create a development education partnership with entities such [00:16:00] as VAMA to educate sponsors early in the development process about the regulatory requirements so they can map their efforts to viable commercial pathways.

The second challenge is insufficient market exclusivity leading to investment risk. A (b)(2) new drug may be eligible for three years of market exclusivity, but this period may not be offset by the drug development or patent litigation costs or the extended timelines needed for market access. Investors may simply not [00:16:30] invest if they don't see a timely ROI. We recommend FDA explore optimizing existing incentives such as expanding the orphan drug designation criteria or exploring new exclusivity that will appropriately reward investment.

Finally, the third challenge is the reimbursement commoditization gap. Current payment and PBM structures have difficulty recognizing and distinguishing value-added medicines from other brand or generic drugs [00:17:00] leading to product confusion, payment denials or inappropriate product substitution. This can effectively penalize repurposed drug sponsors and investors. We recommend FDA collaborate with and seek the input of other stakeholders, including CMS and private payers to create a formal regulatory designation for repurposed drugs, such as a separate orange book listing that can help address this stakeholder confusion. We believe these actions [00:17:30] will be well worth the effort. Thank you.

Public Comment

Topic 2: What factors should organizations consider when selecting repurposing candidates, and how should these factors be prioritized in the decision-making process?

Susan C. Winckler:

Thank you. We are now going to turn to topic two. Let me give the cue for topic two. Olugbenga Ajulo, William Fitzsimmons, and Anna Hedden. So topic two as a reminder, what factors should organizations consider when selecting repurposing candidates and how should those factors be prioritized in the decision-making process? So I will turn first to our virtual commenters. Olugbenga [00:18:00] Ajulo, if you are with us, please turn on your camera and proceed.

We'll turn to our next commenter. So William Fitzsimmons will be next in the comment. Then in our rolling queue, we have Ana Hedden and Rachel Heilmann. William Fitzsimmons, if you're present with us, please turn on your camera and proceed.

William Fitzsimmons:

[00:18:30] Thank you very much. I'm Bill Fitzsimmons. I spent most of my career in the pharmaceutical industry at Astellas Pharma working in development and regulatory affairs and have focused on transplant immunosuppression and led the repurposing of program for tacrolimus for lung transplant using the RWE that was previously referred to in the session.

First, I want to start with the prioritization framework shown on the left of the slide. Most of these factors have been touched upon earlier, but I would stress [00:19:00] that we need to focus first and last and always on the priority of the patients, whether that's an unmet medical need, where there's no widely available therapies for treating the condition, or whether it's the issue of patient access where a drug may be available and even potentially commonly used with a lack of FDA approval and compendial listings often produce great impediments to patient access and reimbursement.

[00:19:30] And also in the middle, the potential public health impact. For instance, as we referred to, the development of new antivirals for hemorrhagic fever viruses where we have approved antivirals that are effective in animal models yet have not been approved for treating potential pandemics that would occur with hemorrhagic fever viruses in the future.

I would also want to stress that repurposing be focused also on transplant immunosuppression. [00:20:00] There hasn't been a new immunosuppressant approved in 15 plus years in the United States. Yet we have a very solid database using the SRTR, which captures data on every transplant of patients in the U.S. There's a high need for new immunosuppressants because of the toxicity, yet most of the innovation in immunosuppression has gone to allogeneic graft-versus-host disease after hematopoietic stem cell transplant or T-cell-mediated autoimmune [00:20:30] diseases. We've seen that using tacrolimus as an example for lung transplant, we can also leverage RWE to improve patient access where we saw Medicare Part D providers refusing coverage due to lack of approval. So I think that this is a key issue. Also, we've seen that lack of FDA approvals has resulted in inability to use that regimen in a control arm. So I would encourage that beyond the incentives mentioned, we consider things like priority review vouchers [00:21:00] that have been effective in other areas to incentivize companies.

Susan C. Winckler:

Thank you. Our next public comment will be from Ana Hedden. In the queue, we have Rachel Heilmann, Kimberly Juroviesky, and Sarah Philbin. Commenter Hedden, if you are present, please turn on your camera and proceed.

Ana Hedden:

Good afternoon. Good [00:21:30] afternoon. I'm Ana Hedden. I'm a two-time survivor of rare metastatic ovarian and endometrial cancers. And I'd like to offer a patient-centered framework for prioritizing drug repurposing candidates. Our highest priority should be criterion one, target high unmet need. Cancers with high lethality, rapid recurrence, rare histologies, and underinvestment. Ovarian cancer remains the deadliest gynecologic cancer [00:22:00] with two-thirds of patients diagnosed at advanced stage and approximately 80% recurrence rate. Endometrial cancer is increasing in both incidence and mortality and Black women experiencing a disproportionate mortality burden. When commercial pipelines overlook these under-researched and underfunded diseases, drug repurposing isn't simply an alternative. It can be a lifeline. I'm living this reality. My tumor subtype, mesonephric adenocarcinoma, [00:22:30] represents less than 1% of cases. After recurrence, there are virtually no tumor-specific

treatment options. Despite exhausting multiple lines of therapy, my journey reflects the reality faced on many rare tumor patients and families. When standard options are no longer available, drug repurposing may represent the next opportunity.

Criterion two, prioritize drugs with a distinct mechanism of action that can overcome treatment resistance [00:23:00] through a novel biological pathway.

Number three, prioritize candidates supporting by robust FDA-approved human safety data, accelerating development while maintaining regulatory rigor.

Finally, criteria four, prioritize mechanism over organ origin. Rare cancers often cannot support the large trials required for traditional developing pathways. Yet organ-specific labeling creates population inequity even when the biology is a match. [00:23:30] I experienced this firsthand with abemaciclib. Although prescribed based on my tumor biology, insurance initially denied coverage and I lost access to patient assistance because the label was written for breast cancer rather than underlying mechanism. My recommendation is this, prioritize drug repurposing through a mechanism-driven tissue agnostic framework that protects real-world patient access. Applying that framework, I respectfully ask the FDA [00:24:00] to prioritize Anktiva for rare ovarian ...

Susan C. Winckler:

Thank you. Our next commenter will be Rachel Heilmann. Then in the queue we have Kimberly Juroviesky, Sarah Philbin, and Muhammad Ahmed Qamar. Rachel Heilmann, if you are with us, please turn on your camera and proceed.

Rachel Heilmann:

Thank you so much for having me today. And a lot of what I've heard is very promising. And I think that for me [00:24:30] as a clinical pharmacist, I've been uniquely positioned to comment on many of these. And as a freshly minted business owner for repurposed pharmacy practice as helping patient advocacy organizations navigate the repurposed drug space, a founder myself, and ultimately as a mother who's watched her child die of a rare neurogenetic disorder, my priority is in this disease burden and unmet need category, [00:25:00] prioritizing serious rare neurogenetic disorders that have a really high care burden on families and affect quality of life for the individual, family and society. And 95% of them have no approved therapies. I think we really need to think about what greater flexibility for rare diseases and access to drug repurposing candidates are. I think about drug characterizations, including established safety profiles with pharmacokinetic applicability, [00:25:30] human evidence, whether that's large robust trials or case series, real-world evidence, [inaudible 00:25:36] CURE ID, et cetera, and mechanistic rationale, having strong biological plausibility in those rare neurogenetic disease or diseases to allow greater accessibility.

And finally, it's that accessibility and availability that I think is the greatest barrier and burden that needs to be overcome, which is whether that's access to prescribing, labeling, and [00:26:00] payer conundrums that we face. And how do we come together to help improve investment and lower the threshold, increase flexibility to access without sacrificing that quality? And I'm often struck by the Hippocratic Oath, which I have taken as a healthcare professional, which is to do no harm. I think we're in this position now where sometimes doing nothing is more harmful than doing something. And so my

ask today is [00:26:30] to come away with action items as how all of us come together to move progress forward in this space to provide opportunities for those who need it most, the patients, the families, and those who are suffering every day. Thank you.

Susan C. Winckler:

Thank you. Our next comment will be from Kimberly Juroviesky. In our queue, we have Sarah Philbin, Muhammad Ahmed Qamar, and Appu Rathinavelu. Commenter [00:27:00] Juroviesky, if you're present, please turn on your camera and proceed. We see you, please proceed.

Kimberly Juroviesky:

Hi, I'm President and founder of the Ketamine Task Force, a patient advocacy organization. On a weekly basis, we hear from patients seeking help for both chronic pain and mental health issues, and these patients are not asking for a miracle. The FDA needs a new inexpensive pathway to repurpose new uses for old generic drugs. When FDA decides which drugs to prioritize for repurposing, I believe they should begin with four questions. How urgent is the unmet need? How much do we know [00:27:30] about the drug? How serious and widespread is the condition? And what is the human cost of waiting? I would place the urgency of the unmet need first, followed by the strength of the evidence. Access delayed is access denied. An effective treatment still fails patients if the pathway never reaches them. Under that framework, ketamine deserves serious priority. Depression and chronic pain are felt in entire families. It can affect all aspects of daily living, independence, emergency room use, hospitalizations, and the ability to participate in everyday life.

For people living with chronic pain, [00:28:00] waiting is not a minor inconvenience. Symptoms can worsen, families can reach a breaking point, and patients can end up in a crisis or wind up committing suicide. Ketamine can act faster than currently approved drugs, and for some patients that difference can be lifesaving with a single treatment. We are also not starting from zero. Ketamine has been used in medicine for more than 50 years and for more than 25 years for mental health. It shows over a 50% reduction in chronic pain, a 70% reduction in treatment-resistant depression, and a 95% reduction in [00:28:30] suicidal ideation and acute suicide attempts. There are decades of research on the safety and efficacy of ketamine, as well as pharmacology data, broad clinical experience, and a growing body of evidence that support its use in depression and chronic pain with minimal side effects.

Repurposing efforts need to go to [inaudible 00:28:47] to candidates where much of the foundational work has already been done. The problem is that the science has moved faster than the systems responsible for approval, coverage and access. Even when ketamine treatment is available, access often depends on where someone lives or whether they [00:29:00] can afford to pay out of pocket. Our request is straightforward. Prioritize ketamine for an expedited evidence-based repurposing pathway. Involve patients and experienced clinicians early and treat coverage and access as part of the plan. Approval without coverage is not meaningful access. A veteran in a rural community should not have fewer options than someone living near a major hospital. Patients should not have to reach a crisis point before receiving a treatment supported by evidence. We are not asking anyone to lower the scientific bar. We are asking you to use drug repurposing as it was intended. [00:29:30] Take a medicine we already know a great deal about and move it into a clearer, safer, more accessible pathway for those who need it. Thank you.

Susan C. Winckler:

Thank you. Our next comment will be from Sarah Philbin. In the queue, we have Muhammad Ahmed Qamar, Appu Rathinavelu, and John Rosa. Commenter Philbin, if you are present. Yes, please proceed.

Sarah Philbin:

Thank you. Good afternoon. I'm Sarah Philbin, Program Director of Translational Science at the Cerebral Palsy Foundation. Cerebral palsy is the most common [00:30:00] lifelong physical disability beginning in childhood. It impacts about a million Americans and more than 50 million people worldwide. And there is not one approved therapy that modifies the underlying condition. Not one. The Make Our Children Healthy Again strategy named drug repurposing a priority for childhood chronic disease. Cerebral palsy is exactly that. So how should the FDA choose what to prioritize? I'd offer four factors and cerebral palsy meets everyone.

First, [00:30:30] is the barrier scientific or economic? A prioritization exercise does the most good where the market has already decided not to act. If a compound is generic or near the end of exclusivity, nobody funds that trial no matter how good the biology looks.

Second, mechanistic convergence. Does the condition run through pathways that approved well-characterized drugs already hit, including neuroinflammation, oxidative stress, and myelination?

[00:31:00] Third, how long does the benefit last? A condition that starts in infancy and lasts 80 years returns far more per trial than the usual arithmetic credits. Plus, there are windows in early development where an intervention can change a trajectory instead of managing one.

Fourth, is there a community that can actually run the study? A candidate is only as good as the infrastructure behind it. Registries, natural history data, outcome [00:31:30] measures that mean something to families, investigators who are already networked, weight trial readiness explicitly. It's the difference between a promising list and an approved drug.

Cerebral palsy meets these factors. The science has moved. Injury, adaptation, and repair continue long after the initial brain injury. What hasn't moved is the commercial case. So two asks. Name cerebral palsy as a priority condition for repurposing [00:32:00] and use disease foundations like ours. We can bring you the registries, the trial networks, and the families. Thank you.

Susan C. Winckler:

Thank you. Our next comment will be from Muhammad Ahmed Qamar, followed by Appu Rathinavelu, John Rosa and Shane Wald Altman. Commenter Qamar, if you are present, please turn on your camera and proceed.

Muhammad Ahmed Qamar:

Thank you everyone. So [00:32:30] my comment is about a new perspective or a new aspect of off-label drug use when we talk about the drug repurposing. So we can start with what we already have in the market and those drugs which are used off-label, we can take them and then we can combine with the

real world safety data from the FDA databases like FAERS and FDA's Sentinel. And we come up with that data, analyze it, and then we can ask, [00:33:00] are we going to use this drug? Are we going to use this drug with the new indications? And for that, how companies can filter these candidates? They can start with ... There are four criteria.

They can start with unmet medical needs or whether this off-label use is a signal for treating any unmet needs and strength of evidence, what evidence it shows, like there is FDA's Sentinel and FAERS. We can [00:33:30] check that how these drugs are used in off-label settings.

Then what's the disease burden? Higher the disease burden, then there is a higher chances of formalization of this new therapy.

And then we can go with the public health impact. How big is the impact of this repurposing of this candidate? So it can go with the sponsors and the FDA corporations where companies share their utilization and the safety data from their sources like pharmacovigilance, and then request FDA [00:34:00] to provide input from their databases like Sentinel and FAERS, combine the data, review it, and advance with the 505(b)(2) applications or labeling supplements. And if the profile supports that formalization, then FDA can provide some incentives like expedited designations, enhanced meetings, early real-world evidence, and existing exclusivity.

Also, we have few examples from off-label use to real world indications, which [00:34:30] is metformin for PCOS and pre-diabetes, which is currently off-label use, GLP-1 agonist for PCOS. And historical, we have a success from off-label to our full indication for propranolol for infantile hemangiomas. So we can start with selecting off-label signal, combining it with the safety data from the FDA, and then converting into a high value experience labeled indication which can improve the excess [inaudible 00:34:56] characterization. Thank you.

Susan C. Winckler:

Thank you. Our [00:35:00] next comment will be from Appu Rathinavelu. Then John Rosa and Shane Wald Altman. We'll then turn to the commenters in the room. So Commenter Rathinavelu, if you're present, please proceed.

Appu Rathinavelu:

Thank you. Good afternoon, everyone. I'm Appu Rathinavelu, Director of the Rumbaugh-Goodwin Institute for Cancer Research of Nova Southeastern University, which is also part of the Barry and Judy Silverman College of Pharmacy in Florida. I'm a new kid [00:35:30] on the block in terms of drug repurposing research. Our team includes dedicated scientists and students. Today's webinar has provided a wealth of knowledge and information that might have otherwise could have taken a couple of years for me to accumulate. I would like to thank the organizers for providing this opportunity to participate and also offer my comments. It would be a wonderful idea if the foundation can also organize a seminar or a webinar for the researchers who have [00:36:00] approached IND or other stages of FDA approval for their recently repurposed drugs.

I also would like to mention and request a consideration for the scientific and regulatory community that the term repurposing is very broad and certainly is encompassing all necessary criteria for the

intended purpose. In order to have a better clarity, we are internally expanding the paradigm with the addition of the subtopic repositioning. As shown in [00:36:30] the slide, we are internally, as I mentioned, we are internally defining this. For example, a soccer player like Lamine Yamal can make a good football player when he's repositioned. But when we are talking about ... It's repurposed. When we are talking about repositioning, if a cancer drug is working very well for leukemia, we are trying to reposition that drug for treating solid tumors like neuroblastoma [00:37:00] and glioblastoma. This kind of approach can be target ... Biomarker-driven approach. For example, we are using epigenetic modifiers that are known to work very well for leukemia and other liquid cancers that are repurposed and repositioned for treating solid tumors.

We have seven patterns for new discoveries, but our drug repurposing program is new and we are looking for collaborations and support. I like the idea for creating a repurposing network, [00:37:30] and we would like to be part of that kind of network if it is created. And thank you once again for providing this opportunity, and we are welcoming for any future collaborations in this arena. Thank you.

Susan C. Winckler:

Thank you. Our next comment will be from John Rosa and then Shane Wald Altman. We'll then turn to commenters in the room, the first being Daniel Jacobson. But now we'll turn to Commenter Rosa. If you're present, please proceed.

John Rosa:

Thank [00:38:00] you, Dr. John Rosa. I'm President of Attune Biotech, a late stage biotech company that is actually in the process of utilizing a repurposed drug. When selecting candidates for drug repurposing, the obvious factors such as unmet need, strength of evidence, disease burden, public health impact are all important. But I'd encourage the agency to take a look at different category within that that's repurposing an already approved drug that's at a substantially [00:38:30] lower dose than previous, but creates an entire new mechanism of action to utilize in different things. So low-dose naltrexone is an example of that. Naltrexone was originally approved at 50 milligrams. Today there's an extensive publication, clinical literature evaluating low-dose naltrexone in dose ranges from 0.1 milligram to 10 milligrams across numerous chronic conditions. At those doses, the mechanism of action differs from conventional dose naltrexone. While the [00:39:00] parent molecule has an exceptional safety profile, a large systemic review of 118 clinical trials involving more than 21,000 participants found no increase in serious adverse events compared with placebo with clinically significant liver enzymes elevated only at 300 milligrams and above, which is 6 times the approved therapeutic dose.

So the challenge is not really science, it becomes economics. LDN is currently being prescribed for several conditions and widely through the VA [00:39:30] and DOD. Unfortunately, it is all through compound pharmacy because at a smaller milligram strength, that's where we end up. Most repurposed drugs can simply be prescribed off-label as an existing commercial product, but low-dose formulas cannot and most typically be prepared by compounding pharmacists creating variability in quality, reproducibility, and patient access. Companies willing to invest in developing FDA grade formulations, completing chemistry manufacturing and control requirements and manufacturing [00:40:00] under FDA oversight or pursuing regulatory approval are asked to assume millions of dollars in development costs, which is the quite obvious burden for what we've discussed today. Without a substantial commercial pathway, many of these therapies will remain outside of FDA regulation despite substantial evidence and the significance of public health. So I just would encourage to have private investment to maybe

have a pathway for commercialization to include something similar to orphan drug status where a company can [00:40:30] get a few years of ,,,

Susan C. Winckler:

Thank you. Our final comment virtual in this section will be from Shane Wald Altman. Then our in-person queue is Daniel Jacobson, Susan Lin, and Mariia Markitanova. We'll turn now to Commenter Wald Altman if you're present. Yes, please proceed. Let us set your timer. Yep. Sorry, go ahead.

Shane Wald Altman:

Thank you so much. Okay. I'm Shane Wald Altman. I'm the CTO and co-founder of QRGenetics. We build [00:41:00] QRGenAI, a platform that takes disease-causing genetic variant, model its virtual 3D effect on the protein to uncover the disease mechanism. And then we match that mechanism to an already approved drug. We've applied it across more over 180 different rare genetic disease cases. In 34 of them, physician acted on the platform recommendation and more than 20 patients have shown clinically meaningful outcomes. You ask what are [00:41:30] the factor? Let me answer with the results.

The factor that matters are the one that predicted them. Take one of our peer review cases, a real world evidence as you suggested before. ACTA-2 IL-179 syndrome, [inaudible 00:41:45] allele stroke in young children, no therapy. The platform uncovered the mechanism and matched it to sapropterin, a drug approved for PKU. We validated in patient cell in mouse model alongside Harvard and MGB, and then in a six-year-old [00:42:00] girl. Over 18 months, her disease stabilized with 0 treatment related adverse effect. That wasn't luck. It was selection. Three factor predicted it. One was mechanistic understanding. We knew why the drug corrected defect. It's not just correlation.

Second is existing approval. We inherited the FDA-approved safety and those and also [inaudible 00:42:23]. And a rare genetic disease where one variant gives an ambiguous readout. Proving it that one child candidate [00:42:30] means something bigger, that a drug that fixed a specific mechanism and the mechanism recur in common diseases. So the platform now find that same treatable mechanism across diseases affecting tens of millions with no therapy today where the same approved drug can treat it. That's how public health impact. Not as a market guess, but as a validated mechanism, you can count the patient behind it. We're pre-IND [00:43:00] on a 35 million people indication. So how should this prioritize factors?

First, mechanistic strengths. Second, it's existing safety. And the third one is genetic validity. Then unmet need and public health scale, which proven mechanism lets you measure instead of estimate it. This is how we made it repeatable and how we find the candidate worth prioritizing at scale.

Susan C. Winckler:

Thank you. We'll now turn to in-person comment. Our first [00:43:30] commenter is Daniel Jacobson. We'll then turn to Susan Lin, Mariia Markitanova, and Simon Vukelj. Commenter Jacobson. Yep. Please proceed. There will be.

Daniel Jacobson:

Okay. Hi, I'm a computational systems biologist, the Oak Ridge National Laboratory, where we're fortunate to have some of the world's largest supercomputers that we're actually applying for biology, and in this case, drug repurposing. We're building digital twins of the entire human system, cell type by cell type, tissue by [00:44:00] tissue, organ by organ, organ systems and whole body. That gives us unprecedented resolution into understanding the human system at really every omic layer. So we're using genomics and transcriptomics and epigenomics and proteomics and metabolomics, you name an omic, and we're probably using it into the phenomic space, including real world data from EHRs to define phenotypes and to utilize those phenotypes both for mechanistic understanding as well as for drug repurposing. This gives us what we were talking [00:44:30] about earlier in the day of multiple lines of evidence, both mechanistic evidence, biomarker evidence and biomarker targets for clinical trials, as well as real world data coming out of EHRs and several different large EHRs.

All told, this gives us the ability to develop mechanistic signatures for diseases, mechanistic signatures for all FDA-approved drugs, and then match them so that we have coverage of [00:45:00] diseases across drugs. And often multiple drugs have overlapping signatures. We can then prioritize those signatures based on mechanism, take them into machine learning boosted retrospective clinical trials and large EHRs to further prioritize candidates that can then, if they're a more common disease, go into randomized clinical trials with omics measurements feeding back into the system through so that we have predictive biomarkers of efficacy coming out of the system and further mechanistic [00:45:30] understanding of how the drug is actually acting.

If it's not a common disease, I.E. a rare disease, there are genic gene associations with 4,000 different random rare diseases. We can use those to generate these mechanistic profiles as well where there may not be as deep data as there is in common diseases. And again, generate potential repurposing approaches. We're really here to play in Christine's orchestra. [00:46:00] We're here to find partners to get from our mechanistic understanding through now all the regulatory pipelines we've been talking about today so collectively we can make some music that makes a difference in people's lives. Thank you.

Susan C. Winckler:

Thank you. Our next public comment will be from Susan Lin. Then in the queue we have Mariia Markitanova, Simon Vukelj, and then we will move to topic number three. Commenter Lin, please proceed.

Susan Lin:

Thank you. I'm representing the Road [00:46:30] Back Foundation today. I'm pleased to be here. And I did play the flute in orchestra, so I love that analogy. The Road Back Foundation is a nonprofit dedicated to promoting antibiotic therapy to treat rheumatic diseases. And we urge the FDA to consider these factors. First, rare diseases without a cure. Scleroderma, as it happens, is a rare autoimmune disease [00:47:00] without a known cure.

Second factor is the effects of the disease and its impact. To what extent does this rare disease affect one's body and quality of life? Women are more affected by scleroderma. Up to 80% are women. And it often strikes adults in their prime years between 30 to 50 years of age. And it profoundly affects their ability to work and care for others. If you don't know about scleroderma, [00:47:30] just picture a

woman you might know between ages 30 to 50 years of age, and their body slowly turns to stone inside and out. And you can just imagine the effect of what busy women, middle-aged women are doing. They can't work, they can't care for their children. It just affects every facet of life.

Third factor is strength of evidence. In rare diseases, [00:48:00] as we have learned today, you don't find RCTs very often. And so we urge the FDA to consider all levels of evidence. The founder of evidence-based medicine, Dr. Sackett, said "You should consider your clinical expertise and the best available level of evidence." And so case studies and observational studies, they might count as [00:48:30] the best available level of evidence for some rare diseases. So we have two asks. Name scleroderma as one of the diseases on the priority list. And secondly, evaluate tetracycline antibiotics as a treatment for scleroderma. The Road Back Foundation is willing to collaborate and share information about treatment protocols. Thank you very much.

Susan C. Winckler:

Thank you. Our next comment will be from Mariia Markitanova. Then [00:49:00] we'll turn to Simon Vukelj. We'll then turn to topic number three for our virtual commenters in the queue. That begins with Megan Golden and Nicolas Grundmann.

Mariia Markitanova:

Hello everybody. My name is Mariia Markitanova. I'm a founder of Curada, a public benefit corporation. We built a differential layer for approved drugs, and we are also submitting a candidate to this docket targeted naltrexone for pharmacological extinction. [00:49:30] So let me start with the obvious objection. Why bother repurposing it all? The drug exists. The physician may already prescribe it off-label lawfully today. The Duke-Margolis work lists seven barriers. Uneven uptake, reimbursement gaps, law awareness, patient hesitancy, supply risk, liability. And at least three of those seven share a single precursor, the promotion [00:50:00] ban. You cannot educate, you cannot detail, you cannot reach the prescriber. So labeling is what lifts that ban. And Dr. Woolcock put it precisely earlier today. "Identifying candidates is the fun part. Getting them into patient hands is the [inaudible 00:50:22] part." So once the ban lifts, who pays for the promotion, it is durable exercise and [00:50:30] it is capital intensive.

Public health impact evidence and regulatory pathway all rank higher in the screening segments as they should. But deployability determines whether anything at all happens after the label. And deployability requires an owner, an owner with an asset someone will underwrite. This is where I would ask the agency to shift the frame. The standing assumption is that pharma has no incentive to [00:51:00] repurpose generics. The more useful question is how is underwritability engineered onto a molecule that nobody owns? And the question has already answers. Epinephrine is more than a century old and unpatentable. The [inaudible 00:51:17] injection held roughly 90% share for years. Same [inaudible 00:51:22] molecules public, the delivery layer is owned and enforceable. [inaudible 00:51:27] is a layer for this generation and it arrives as a category [00:51:30] the agency itself creates. So my recommendation is narrow. Keep the segments, then add a four screen. Can this candidate be underwritable? And that is the model several speakers [inaudible 00:51:44] today closer to biotech with big pharma in the equation.

Susan C. Winckler:

Thank you. Our next comment will be from Simon Vukelj. Then we will turn to the third topic in the virtual queue. We have Megan Golden, Nicolas Grundmann, and Lisa Kane. [00:52:00] Commenter Vukelj, please proceed.

Simon Vukelj:

Terrific. I'm Simon Vukelj. I'm the Chief Marketing Officer for the Children's Tumor Foundation. We are focused on a group of genetic conditions called NF or neurofibromatosis or schwannomatosis. These are tumors that develop throughout the body. We're very focused on finding treatments for the disease, but also importantly, these are chronic lifelong conditions. So finding treatments that have low toxicity so people can take them for their entire [00:52:30] lives. We've had some great metaphors today about the orchestra. On slide, I'm not going to read everything on slide, but the three layers on the right side. I almost see them as three doors that are wide open. There's a drug behind each door. Each door is open at different widths.

In the first one, which is wide open, but not quite there. And the important question is what is the blocker? [00:53:00] And the example there is brigatinib. Brigatinib is a repurposed drug. Sorry, a drug that was ... Yes, it's repurposed. Apologize. I don't know what happened to me today. It's a drug that was approved for lung cancer. And we at the Children's Tumor Foundation, in partnership with NCATS, were able to figure out that it works for NF2. That drug is now in the NCCN Guidelines, but it could use a label expansion. I'll [00:53:30] take a breath.

The second door that is open, but it could swing shut, is that there is clinical evidence available, but the sponsor has stopped providing interest and we could use an FDA lever to keep that sponsor committed.

The third door is barely open at all. This is a case where in this particular instance, one of the drugs, mirdametinib, is approved. It's something that we've done together with Pfizer and SpringWorks, but the other drug we cannot get from the company [00:54:00] that we could use an FDA lever to help us unlock access. So the work here is to identify those blockers. Is the problem a path to label expansion? Is it continued sponsor engagement or is it access to the drug itself? And brigatinib showed us that the door can be wide open for all three instances. Thank you very much.

Public Comment

Topic 3: What evidence gaps or policy/regulatory barriers most commonly hinder the advancement of promising repurposing opportunities?

Susan C. Winckler:

Thank you. We'll now turn to topic three, which is about evidence gaps [00:54:30] and policy and regulatory barriers that hinder advancement of repurposing opportunities. So we'll turn first to our virtual commenters in the queue. Megan Golden, Nicolas Grundmann, and Lisa Kane, and then Nichelle Santos. Commenter Golden, if you are with us, please proceed.

Megan Golden:

Okay.

Susan C. Winckler:

Please proceed.

Megan Golden:

Imagine your child is screaming in pain again, and she's curled up, unable to sleep or eat, [00:55:00] and nothing you try can stop it. The doctors tell you it's pancreatitis. Her pancreas is inflamed caused by a rare mix of genetic mutations. There's no cure, no treatment, just fasting, IV fluids and pain meds, specifically opioids. When my brother Eric experienced that type of pain, it was so unbearable that we founded Mission: Cure to stop the suffering. Like many others, [00:55:30] Eric has CFTR mutations that affect his pancreas. Experts believe a CFTR modulator approved for cystic fibrosis could help him, but his sweat chloride falls just below the cystic fibrosis cutoff. The drug's not approved for pancreatitis, insurance will not cover it, and it costs more than $300,000 a year. The medicine exists, but for Eric and others, it might as well not.

Now, Mission: Cure worked with the pharma company on adding CFTR pancreatitis [00:56:00] as an indication, but eventually it decided not to pursue it and has declined to provide drug for investigator-initiated studies. So we know that there's an incentive problem for repurposed generic drugs. It also applies to highly profitable on-patent drugs where pursuing a new indication seems too risky, and also drugs near the end of their patents. We need a public interest repurposing pathway that does not depend on a profit-driven sponsor. [00:56:30] With clear evidence standards, feedback from FDA reviewers, and a low-cost efficient process, patient organizations can carry this work forward. We're highly motivated, we act with urgency, and we have patients and leading scientists on our teams.

Finally, we need to turn individual treatment experiences into credible evidence. We're building a platform using rigorous N-of-1 methods, allowing patients to serve as their own controls when [00:57:00] appropriate. By combining results across patients, we can learn who benefits and whether a treatment works more broadly. We hope the FDA will help define how this evidence can support regulatory decisions. Thank you.

Susan C. Winckler:

Thank you. Our next comment will be from Nicolas Grundmann. In the queue, we have Lisa Kane, Nichelle Santos, and Marian Saxon. Commenter Grundmann, if you are present, please proceed.

Nicolas Grundmann:

Good afternoon, everybody. I'm Dr. Nicolas [00:57:30] Grundmann. I'm a physician and the Medical Director of Ember Health, which is a multi-site practice that provides intravenous ketamine, medically supervised for clinical depression. I'm also a board member of the American Society of Ketamine Providers. Thank you for this opportunity to speak. On behalf of ASKP3 and of the Think Tank Brain Futures, we submitted public comments nominating generic IV racemic ketamine for FDA drug repurposing for the treatment of major depressive disorder, bipolar disorder, and suicidal ideation. [00:58:00] I noted in that comment the studies and data supporting the repurposing, which would affect the lives of literally millions of Americans. This verbal comment is specific to the repurposing challenge when a medication has no single fiscal sponsor.

Since becoming generic in 1996, ketamine has become the most studied medication for depression with more clinical trials than Prozac and Zoloft combined during that timeframe. This is not an evidence gap for getting this drug approved. These trials [00:58:30] includes dozens of RCTs, hundreds of clinical trials, and thousands of peer-reviewed publications, as well as hundreds of thousands of patients who've already been accessing this treatment in the off-label process. Our clinical practice alone has treated 2,500 individuals, and there have been 42,000 infusions that we've medically monitored, data that we have made available to the FDA through a broad agency announcement agreement.

Despite all of this evidence, and despite the existence of [00:59:00] seven separate ANDAs for the generic product, there is no single fiscal sponsor for the medication. Consequently, there has been no clear path for FDA approval of these new indications for the generic. Inversely, a dozen ketamine derivatives and analogs are working their way through the FDA approval process, all using that same generic data to short circuit the trials that are required for approval.

The enantiomer S-ketamine was approved under a REM system for public safety on label for clinical depression. [00:59:30] All of that is possible because those are done with fiscal sponsors through an IND. FDA repurposing of IV racemic ketamine with a clear label standard, clear pharmacovigilance pathways would help guide patients to evidence-based care, improve safety across the country, and expand access to an effective treatment for one of our nation's most significant unmet medical needs. The countries of France, the UK, and Norway have already taken this path, and I'd urge the FDA to take action as well. Thank you for the time.

Susan C. Winckler:

Thank you. [01:00:00] Our next comment will be from Lisa Kane. In the queue, we have Nichelle Santos, Marian Saxon, and Sarah Tompkins. Commenter Kane, if you are present, please proceed.

Lisa Kane:

I am present. Can you hear me? Yes.

Susan C. Winckler:

Yes.

Lisa Kane:

My name is Lisa Kane. I'm founder of Health Designs, LLC. I'm a registered nurse and a clinical research assistant. Thanks for this highly valuable session and opportunity to comment. [01:00:30] As you can see in the slide, my current work is inspired by an itsy bitsy spider, also known as chronic refractory systemic demodicosis. Many people experience Demodex-associated disease. It's frequently diagnosed as rosacea, blepharitis, acne, seborrhea dermatitis, and frequently dismissed as psychogenic. For many patients, it's also [01:01:00] a highly stigmatized condition. Recognition of demodicosis by the NIH as a genetic and rare disease motivated us to develop an AI-enabled precision medicine platform to advance personalized prevention, diagnosis, and treatment for chronic ectoparasite-associated and immune-mediated disorders, which actually crosses other platforms into Lyme [01:01:30] disease, other, again, vector-related conditions that stimulate the immune system.

While the long-term work continues, patients still need effective topical management today. One policy barrier involves how payers interpret current FDA-approved labeling and quantity limits. For example, quantity limits for topical ivermectin [01:02:00] are based on labeled dosing that may not reflect treatment needs for patients. For instance, 4.5 milliliters, one teaspoon to cover the whole body. For patients with extensive body surface involvement or circumstances requiring individualized clinical judgment, this can create practical barriers to treatment and limit clinician's ability to tailor therapy to the patient's presentation, as well as lead to resistance, proliferation, [01:02:30] and harm. I respectfully encourage continued evaluation of the evidence supporting dosing strategies, formulation optimization, treatment sequencing, and adaptive drug repurposing research and delivery as ...

Susan C. Winckler:

Thank you. Our next comment will be from Nichelle Santos. Then we have Marian Saxon, Sarah Tompkins, and Arnab Chatterjee. Commenter [01:03:00] Santos, if you are present, please come on camera and proceed.

We'll move to the next commenter. We'll hear from Marian Saxon. Then in the queue, we have Sarah Tompkins, Arnab Chatterjee, and then we will turn to our in-person comment beginning with Sarrin Chethik. So Commenter Saxon, if you are present, please proceed.

Marian Saxon:

[01:03:30] I am Marian Saxon with UCB Regulatory Affairs. UCB supports FDA's efforts to establish a practical science-based framework for drug repurposing that can help address unmet medical needs across diverse patient populations. Cimzia, a TNF-alpha inhibitor approved for Crohn's disease and other rheumatic diseases illustrates why FDA flexibility matters [01:04:00] for rare or special conditions like pregnancy where randomized controlled trials are not feasible or ethical in a highly vulnerable patient population with no approved treatment options. In this example, a prospective trial supported by relevant historical control data, the IMPACT study reported clinically meaningful reductions in adverse pregnancy outcomes following treatment with Cimzia during pregnancy and high-risk patients with rare antiphospholipid [01:04:30] syndrome. The use of Cimzia and APS is not approved. However, promising opportunities like this frequently struggle, largely because no clear regulatory pathway guides their development, even when supported by strong scientific evidence. Most common barriers to advancement include fragmented ownership of evidence, limiting access to data, unclear expectations from FDA, and limited incentives for sponsors.

[01:05:00] Advancement may also depend on early FDA engagement, acceptance of innovative study design, and defined pathways for regulatory. A fit for purpose evidence framework for repurposing, especially in cases of high unmet need should incorporate six factors. One, reliance on established safety and pharmacology from approved uses, particularly during pregnancy. Second, externally controlled trials, including investigator- [01:05:30] initiated. Third, natural history studies and RWE, particularly for rare and pregnancy. Fourth, a defined pathway to confirm data traceability. Five, consider published data as credible sources of evidence when data accessibility is an issue. And finally, supportive mechanistic and translational evidence. Thank you.

Susan C. Winckler:

Thank you. Our next comment will come from Sarah Tompkins. Then Arnab Chatterjee. We'll [01:06:00] then pivot to the room where we have in the queue, Sarrin Chethik, then Laura Ford. So Commenter Tompkins, if you're present, please proceed.

Sarah Tompkins:

Thank you. I'm Sarah Tompkins from Bellevue, Washington. I'm a rare disease Ehlers-Danlos syndrome connective tissue patient and disability advocate and activist. I'm a member of Northwest Rare Disease Coalition and Connective Strength, the patient organization here in Washington. Drug repurposing gives rare disease communities something we don't often [01:06:30] have: hope. Using drugs that are already approved, tested, we can reduce the time, cost, and risk, but too many barriers still stand in the way. The greatest regulatory barriers are uncertainty about evidence requirements, the need for costly clinical trials despite existing safety data, limited acceptance of real-world evidence, and insufficient incentives to pursue approval of repurposed therapies. These barriers keep promising treatments from patients even when there is strong scientific rationale and significant unmet [01:07:00] medical need.

Rare diseases affect small populations, so there's small financial incentive to invest in clinical trials, especially for drugs that are already generic and funding is limited. Patient recruitment is difficult and regulatory pathways remain complex. There's an urgent need for further creative incentive and protection for these vital incentives like Orphan Drug Act, balancing incentives with CMS eligibility by passing legislation and policies like Orphan Cures Act. I know this personally [01:07:30] through my experience with vascular EDS. Celiprolol was developed in part through these incentives through the Orphan Drug Tax Credit, and the drug can reduce the risk of the life-threatening aortic rupture or arterial dissection. It's a powerful example of drug repurposing, but it's not enough. Too many connective tissue disease patients face a complex diagnostic odyssey. And in vascular EDS, clinical diagnosis depends on having a first-degree relative. And yet half of [01:08:00] the patients have a de novo mutation and they are the first in their family to have this mutation.

If we rely too heavily on family history, we miss the patients who benefit most. We need to now incentivize and fund studying how this drug could benefit other connective tissue disorders in at-risk vascular patients, a true representation of how we need real-world data at adaptive trial designs, earlier clinical recognition, and true patient partnership and research legislation and policy. Thank you.

Susan C. Winckler:

Thank you. [01:08:30] Our final virtual comment in this section comes from Arnab Chatterjee. Commenter Chatterjee, if you are present, please proceed.

Arnab Chatterjee:

Can you hear me okay? Thanks.

Susan C. Winckler:

Yes.

Arnab Chatterjee:

Wonderful. Thanks a lot for the opportunity to speak today. I appreciate it. I'm Arnab Chatterjee. I'm a medicinal chemist by training and currently the Executive Vice President of Calibr-Skaggs. We are a nonprofit drug discovery institute within Scripps Research Institute here in San Diego, California. [01:09:00] We have built a drug repurposing library we called ReFRAME that has been funded partially by the Gates Foundation to enable access to drug discovery models, both AI-based models as well as physical drug screening through building a library of nearly 14,000 molecules. We think that's important. Certainly in the context of today's conversations, we include not only all approved drugs from the FDA and other major global authorities, but we also have [01:09:30] included all drugs that have been put into human clinical trials to date to be able to find real opportunities for repurposing beyond FDA screening medications. That is important because nearly 7,000 of the molecules in the ReFRAME library are actually not commercially available and required nearly a $20 million U.S. investment by the Gates Foundation to be able to build this collection and provide it to the community free of charge.

So similar to what Evan and others, of David and others have [01:10:00] presented today and amazing opportunities in repurposing medications, we provide this chemical library for free to screen with anyone in the world. They conduct drug screens. They can take all of the drug data that's already present on our open access portal, reframedb.org, and they own any intellectual property that comes out of the drug screens. All that we ask is that that data be made available to the community within a period of 12 months. We have screened this collection ourselves over 300 [01:10:30] times and have now put in the last 10 years since we started ReFRAME 4 drug repurposing phase 2 trials as well as 7 new chemical entities where we improve on existing drugs in terms of safety and tolerability and moving them into clinical studies ourselves. We welcome the community to access not only the drug data, including pharmacokinetic data, drug safety and mechanism of action data, but also the screening collection itself to be able to further the opportunities providing therapies [01:11:00] to patients who are in desperate need. Thank you.

Susan C. Winckler:

Thank you. We will turn now to in-person comment, the first being from Sarrin Chethik. Then in the queue we have Laura Ford, Laura Kleiman, and Shayanne Martin. Commenter Chethik, please proceed.

Sarrin Chethik:

Thank you for the opportunity to speak and thanks for running such a great event. I'm Sarrin Chethik and I work for some economists at the University of Chicago. Today I'll focus on what I view as the primary gaps, which is an evidence gap and the commercial [01:11:30] incentive gap, which causes that evidence gap. So first, the evidence gap. As people discussed today, there's often lots of biological modeling and observational research and even small clinical trials that are suggestive of another use, but they lack the large randomized control trials necessary to prove that new use and get approval. Why are these trials not conducted? This is because of the commercial incentive gap. So once relevant patents [01:12:00] and exclusivities no longer prevent generic entry, generic competition drives prices down, which means that there isn't the financial incentive to go run large clinical trials.

This commercial gap has been studied by economists. So one recent analysis, which a graph from that analysis is up on the slide, studies the relationship between years of exclusivity and the probability of attaining a new approval. [01:12:30] And as you can see, as the years of market exclusivity wane, you see a drop in the probability of getting a new approval. So the paper estimates that with appropriate incentives, we would've seen an additional 200 to 800 additional approvals these past few decades. So

importantly, if you provide the financial incentive, I'd argue that in many cases you wouldn't have a gap in regulatory pathway. The commercial incentive gap would [01:13:00] just serve as the primary gap. So to deal with this bottleneck, we basically propose that funders like CMS or NIH could use prize-like funding to incentivize developers to run large clinical trials, get regulatory approval, and drive adoption. Thank you.

Susan C. Winckler:

Thank you. Our next comment will be from Laura Ford. In the queue, we have Laura Kleiman, Shayanne Martin, and Jeffrey Martini. Please proceed.

Laura Ford:

[01:13:30] Good afternoon. I'm Laura Ford. Thank you for the opportunity to speak today and for engaging community voices like mine in this conversation. My husband, John, has Huntington's disease. It's a progressive fatal neurological disorder with no approved therapies to slow or stop it. He is 64 years old and he's been sick for 15 years. John got Huntington's from his mother who got it from her mother, and every generation has the same 50-50 risk of inheriting the disease. [01:14:00] So that's what sets HD apart. One genetic mutation, moving through a family generation after generation and taking mobility, speech, cognition, and independence. New research adds urgency as measurable brain changes may begin up to two decades before diagnosis. So while researchers pursue novel gene therapies for earlier stages of HD, repurposed drugs offer a faster path to help people like my husband who are already sick.

[01:14:30] And we've done this repurposing before. Tetrabenazine moved from a 1950s antipsychotic to an approved Huntington's treatment in 2008. But most drugs with repurposing potential never start that journey. Instead, they drift into long-term off-label use like so many of the medications that we rely on today to manage chorea, psychiatric and cognitive symptoms in HD. So we have tools to do better now. We have computational systems that can screen thousands of compounds for hidden potential. [01:15:00] And we have Enroll-HD, which is a research infrastructure built by dedicated HD families over decades for tracking natural history, recruiting participants, and lowering cost and risk for sponsors. What we don't have and what we need is clear, durable guidance and an expedited pathway to move these drugs from off-label use to approval. When policy slows access, this disease does not slow down. I ask you to look at Huntington's as [01:15:30] a priority, a single genetic mutation, tremendous unmet medical need and burden, a committed community and potential for generations of impact. Sponsors and the community need certainty about how to move forward. Families like mine cannot afford to wait. Thank you so much.

Susan C. Winckler:

Thank you. Our next comment will be from Laura Kleiman. Then our queue includes Shayanne Martin, Jeffrey Martini, and Thomas Seoh. [01:16:00] Please proceed.

Laura Kleiman:

Thanks for the opportunity to provide input on this important topic. I'm the founder and CEO of Reboot Rx, which is a nonprofit focused on repurposing in oncology. We are actually launched in 2019 around the time of that last convening. Today, I'd like to focus on what we see as two of the biggest barriers to

advancing repurposing opportunities. The first is the need for definitive randomized controlled trials. We encourage NIH to create [01:16:30] dedicated funding for repurposing clinical trials. We also recommend modernizing IND requirements to allow nonprofit-sponsored trials of repurposed generic drugs to use any therapeutically equivalent product, and this would help reduce regulatory hurdles.

The second barrier is the lack of a practical FDA approval pathway when manufacturers aren't involved. Here we propose a labeling only [01:17:00] 505(b)(2) pathway to allow nonprofits to seek approval of new indications by relying on FDA's previous determinations of product quality and manufacturing. And this would allow nonprofits to focus their applications on the clinical evidence supporting those new uses. We also recommend expanding the MODERN Labeling Act and leveraging existing FDA mechanisms such as citizen petitions and the Federal Register [01:17:30] to evaluate evidence and communicate FDA's conclusions for repurposed uses. Some of our recommendations could likely be implemented under FDA's existing authorities while others would require legislation. Our full RFI response is available on the FDA docket, and it includes many other topics such as information on three repurposed generic drugs for cancer with published clinical evidence [01:18:00] supporting new indications that may warrant FDA evaluation. We'd be happy to discuss these ideas with anyone afterwards. Thank you.

Susan C. Winckler:

Thank you. Our next comment will be from Shayanne Martin, and then our queue includes Jeffrey Martini and Thomas Seoh. Go ahead.

Shayanne Martin:

Thank you. My name is Shayanne and up on the screen will be my daughter, Cora, who has a spontaneous mutation in the NALC and ION channel that causes a severe [01:18:30] ultra-rare neurodevelopmental disease called CLIFAHDD. Her disease is neurodegenerative and with no treatment, she has so far maxed her potential at about 12 months developmentally. But that isn't necessary because her gene is a promising target for small molecule therapeutics. Since she was diagnosed at six weeks old, her father and I have done everything we can to find a treatment. We started the Channeling Hope Foundation and put together an international team of scientists to pursue high throughput screening and preclinical [01:19:00] validation. And after securing grant funding and donated medical product, just last week, an IND was submitted for a phase one trial with a drug that is available generically.

This may sound exciting, but by the time we dose our first patient, two years will have passed since we discovered our first drug hit. During that time, my daughter took her first steps at two and a half, gained speed and coordination by age four, then lost the ability to walk independently and safely within weeks this summer. [01:19:30] During this time, I began a PhD to advance patient-oriented regulatory science, and my husband as a neurologist has facilitated the translational and clinical research. It is our organization's biorepository, natural history study and patient priority survey that are enabling investigators to identify clinical trial endpoints. Yet in our position as patient advocacy organization leaders, we must work through academic collaborators to navigate the regulatory space and we are too rare for [01:20:00] commercial interest.

So today I have two asks. My first is that FDA create an engagement framework for patient advocacy organizations to interact directly with regulators and play a leading role in drug trials. And second, that new incentives for generic drug repurposing address the challenges faced by the smallest disease populations. This includes incentivizing drug manufacturers to support clinical trials for ultra-rare diseases. We are testing a drug priced at $250 per dose name brand [01:20:30] and $100 per dose as a generic. However, the actual manufacturing cost is less than $1 per dose. With a more affordable drug, we could have started the clinical trial more than a year ago. In that time, our daughter has rapidly declined. There is a remarkable convergence of interest in rare disease AI and drug repurposing, but ultra-rare disease communities are at risk of being left behind ... So that patient advocacy ... Thank you.

Susan C. Winckler:

Our next comment is [01:21:00] from Jeffrey Martini and the last will be from Thomas Seoh.

Jeffrey Martini:

Afternoon. My name is Jeff Martini. I'm Chief Scientific Officer at Palvella Therapeutics. Palvella means to serve and finish. Our mission is to serve patients with serious rare diseases for which there are no FDA-approved therapies. We want to be first for these patients. Our strategy is to transform FDA-approved molecules into targeted therapies for the skin. [01:21:30] Many rare skin diseases are chronically debilitating, lifelong, and profoundly underserved. Developing an effective topical therapy remains difficult, time-consuming, and expensive. A drug must penetrate the skin, reach affected cells at therapeutic concentrations, and limit systemic exposure. This still requires substantial formulation, manufacturing, toxicology, clinical, and endpoint development work.

As a result, reformulating an established molecule for [01:22:00] the skin can approach the time and cost for developing a new chemical entity while providing fewer efficiencies than traditional repurposing with the same formulation as studied in a new indication. Venous malformations illustrates this challenge. These are lifelong, chronically debilitating lesions that can cause pain, bleeding, functional impairment, and recurrent complications. Oral sirolimus is an established medical therapy for internal venous malformations supported by a well-understood mechanism and substantial [01:22:30] clinical experience, including more than 26 publications and a 76-patient phase 3 study. Yet oral sirolimus does not adequately treat disease in the skin because of limited cutaneous biodistribution. A targeted topical formulation can deliver the same molecule directly to affected skin while minimizing systemic exposure.

We believe FDA should establish a dedicated rare disease repurposing tract that builds upon established [01:23:00] scientific [inaudible 01:23:01], published clinical evidence, and real-world experience. These data do not replace a prospective registrational study, but they should meaningfully inform its size, design, endpoints, and choice of control. Development requirements should be proportionate to the evidence already established, particularly when the standard of care is the same molecule delivered by another route of administration. A clear rare disease repurposing pathway would accelerate development, reduce [01:23:30] unnecessary duplication, and create the incentives needed to bring therapies to patients who may otherwise remain untreated for life. Thank you. Thank you.

Susan C. Winckler:

And we'll turn now to our final contribution of public comment, Commenter Seoh.

Thomas Seoh:

Thank you, Susan. My name is Thomas Seoh. I'm the CEO of Kinexum, a regulatory consulting firm and EVP of the not-for-profit Kitalys Institute, dedicated to healthy longevity for all. Thank you for this opportunity [01:24:00] to comment. The largest barrier to developing promising repurposed drugs is the lack of private sector incentives. Few sponsors will fund evidence for new uses of generic drugs if competitors can free ride by selling their generics for the new indication. Kitalys has proposed a draft THRIVE Act, an optional pathway, evidentiary tiers, and incentives for health span products, including repurposed drugs that includes market exclusivity, priority review vouchers, and prizes as incentives. [01:24:30] But beyond incentives, streamlined predictable regulatory practices help too, especially for repurposed generics with extensive safety experience. We're involved in two repurposing projects among others. Verapamil, a generic antihypertensive being developed for type one diabetes based on academic trials suggesting delayed disease progression in new onset disease. We're also developing a fixed dose combination of low-dose metformin, sildenafil, and leucine with phase two cardiometabolic benefit signals [01:25:00] in obesity and MASH now being studied for hypertension.

For such products, reforms such as the following could help. First, scale safety exposure requirements to residual risk. Hundreds of exposures, not thousands by default where safety is well characterized.

Second, sensibly prune factorial design expectations under the combination drug rule, especially for low dose mechanistically supported FDCs.

Third, allow dose or formulation optimization for new indications without automatically [01:25:30] restarting phase two.

Fourth, adopt fit-for-purpose endpoints and biomarkers faster with transparent standards. Bone mineral density took about a dozen years. C-peptide for type one diabetes still lacks full acceptance on and off. After more than two decades, such cycles need to be compressed.

Fifth, consider a dedicated accelerated pathway, perhaps a dedicated office for repurposed generics with substantial safety experience. Duke-Margolis has recommended this. Incentives, regulatory clarity, [01:26:00] and evidentiary standards proportionate to known risk are the keys to unlocking more repurposed generics. Thank you.

Susan C. Winckler:

Thank you. So that concludes the public comment portion of our meeting. Please join me in thanking everyone who invested their time in providing public comment today. The investment was an important use of your time and we appreciate it. So reminder, in addition to the comments we heard today, [01:26:30] the foundation is accepting two pages of written comments via electronic submission through Friday, August 21st. You can see the foundation website for more information on how to submit written comments. Final reminder, or rather a recap. Thank you so much to all of our speakers and panelists who joined us. Thank you for the public commenters. And thanks to all of you here today in the room and online for joining in our shared learning experience. The recording, slides and transcript will [01:27:00] be available and posted next week on our website, reaganudall.org. Have a great rest of your day.