Drug Repurposing: Considerations for Selection Criteria and Prioritization

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

Transcript – Afternoon

Session 3: Evidence and Submission Expectations

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Reactor Panel:

- **Amy Abernethy MD, PhD, CEO, Highlander Health**
- **Marie Bradley, PhD, MPharm, Senior Advisor, Office of Medical Policy, CDER, FDA**
- **Emily Freilich, MD, Division Director, Division of Neurology, Office of New Drugs, CDER, FDA**
- **Donald Lo, PhD, Director of Medicines Development and Scientific Lead, REMEDi4ALL**

Susan C. Winckler:

All right, everyone. Welcome back. We are going ahead and kick off our afternoon sessions. So I'll say welcome back. I hope that you had time to take a break and re-energize because we are ready to go. So I'm going to turn [00:00:30] the slide set right over to Dr. Sundeep Agrawal, who's Associate Director of Clinical Programs, not clinical problems, the programs of the Oncology Center of Excellence at FDA. And you heard a little bit this morning, Project Renewal was mentioned, and we are going to learn more about that. Dr. Agrawal.

Dr. Sundeep Agrawal:

All right. Thanks. Can you guys hear me okay? Good, good. Yeah, I'm Sundeep Agrawal. I'm a medical oncologist at the FDA in [00:01:00] the OCE, and I've worked on project renewal. So I'll talk a little bit about my experience there and hopefully some lessons learned that might help inform general drug repurposing efforts.

So Project Renewal is a public health initiative started by the OCE to update certain older oncology drug labels. These are off-patent drugs that have been used to treat cancers for decades, but don't have the actual indications in the label. So our goal is to have accurate labeling [00:01:30] information to inform

safe and effective use of these products. And over time, we've established repeatable, objective, and scientific processes for the labeling updates.

It's also created an opportunity to engage with the oncology community. We work very closely with subject matter experts, and there's an educational component for HemOnc fellows. These labeling updates can expand or add indications if there's substantial evidence, remove outdated information, and modernize formats as well.

[00:02:00] So the scope has primarily been cytotoxic chemotherapy, so that limits our potential pool of candidates. An external partner to FDA reviews drug Compendia sources and identifies the level of evidence cited to support off-label use. And then subject matter experts, which are typically practicing oncologists, are engaged to gain a better understanding of the clinical use of these products in the real world. So we review the existing data and then make a go/no-go decision on whether it's [00:02:30] worth looking at any further.

We have a formal evidence evaluation process. I won't get into all of this. We can talk about that a bit more. But we go over all the evidence and see what is justified, what might not be justified. And then FDA reviews everything and gets the process going.

We do have a unique ability in oncology because there's often decades of clinical experience, multiple trials with acceptable endpoints, [00:03:00] and we know the mechanism of action of these cytotoxic chemotherapies are pretty well-understood. Safety is pretty well-understood. So, in oncology, it may be a little bit unique compared to other disease settings.

So it's our way of updating longstanding labels for off-patent products. Also, creates a transparent review process with external experts. It's not a way to expand indications for drugs that are on patent or with exclusivity. It's not a way to review all possible indications that [00:03:30] may be in use, and there's no relation to cost, payment, or coverage decisions.

I do want to talk about guidelines and Compendia. These are, obviously, very helpful, and they're often a summary of the evidence, but they're not the evidence itself. So, Compendia for off-label oncology indications. They're not necessarily definitive, and I'm quoting Dr. Abernethy. I think one of her papers here. They can lack transparency in the evidence evaluation process that supports the recommendations. They may [00:04:00] cite little current or new evidence, and they can often lack systematic methods to review or update that evidence. And the cited evidence can be scant or inconsistent across Compendia, so the FDA has to do its own review of the evidence.

So we like to look at the references in the Compendia, look at the actual papers, and get an idea of what happened rather than just saying, "The Compendia says it, so we're going to go along with that." So it's still very helpful to use these Compendia guidelines to identify potential sources of what are standard of care treatments, looking up references to [00:04:30] key trials, and general education about a disease type, but they're not the evidence itself.

In terms of substantial evidence of effectiveness, the things that we consider to meet statutory requirements are the quantity of the evidence as well as the quality of the evidence, the magnitude and statistical persuasiveness of the results, the source of the evidence, and then the context. For example, the rarity of the disease and the unmet need.

We have used published literature to support labeling updates, and this [00:05:00] includes consideration of who conducted the study, how detailed is the published report, how objective are the outcomes, was the analysis pre-specified, are the results clinically meaningful, is there additional internal consistency within the trial's secondary outcomes or endpoints, and are there multiple studies that might help support certain gaps in the knowledge. So, overall, we consider whether the published report provides enough detail to be considered substantial evidence from adequate and well-controlled trials.

[00:05:30] In terms of some lessons learned, I'll note that the process is dependent on voluntary participation from companies, and we do aim to reduce the burden to companies because we know they may not be incentivized otherwise to do this. We acknowledge that the evidence is often generated with different historical standards, and we consider the context and the quantity of studies that may mitigate some quality issues.

It can be resource-intensive, and we're continuing to generate process efficiencies, [00:06:00] and we've had successful engagement efforts to date. There's bi-directional learning between the oncology community and the FDA. And this has been really a critical part of it is that it's not just FDA doing it. We're really talking to the subject matter experts, those that are treating the patients in the community as well to get an understanding of not just what the data shows, but how this is being used, and try to bridge any gaps that we identify.

The value of Project Renewal or PR is that we produce more accurate labeling information [00:06:30] to allow for safe and effective use of older drugs that are still used frequently. We modernize labeling into the most up-to-date formats. And as I mentioned just now, it increases our engagement with the broader community. And we've seen the potential for expansion to other therapeutic areas.

So candidate drugs for oncology here, most of these have established safety and efficacy. They've often been used for decades. The clinical practice patterns are supported by [00:07:00] pretty strong data. A lot of these drugs have overall survival benefit and things that are pretty objective endpoints.

Compendia and expert guidelines are important, but they're not enough. We review all the source references to ensure meeting statutory requirements. And there may be some challenges to think about with extrapolating to other diseases outside of oncology. It's important to consider whether there's adequate data to support the claim of effectiveness, of course. Can the safety be extrapolated from other diseases when populations are small in size? [00:07:30] And will repurposing approvals set precedent that might affect contemporary drug approvals?

So I just want to acknowledge some of my colleagues here who have contributed to these slides in this work and looking forward to discussing this more on the panel. Thank you.

Susan C. Winckler:

Thanks so much, Dr. Agrawal. I think what you just did... We were challenged by Dr. Woodcock to make sure that there was a path illuminated, and so you've [00:08:00] at least illuminated how OCE is thinking about that in what's required, what evidence, and how that works there. So we're going to have one more presentation, and then we'll go to a panel discussion. So we're going to turn the podium over now to Dr. David Fajgenbaum, who is the co-founder and president of Every Cure, which you heard

mentioned this morning, a leading organization in drug repurposing efforts. Dr. Fajgenbaum, take it away.

Dr. David Fajgenbaum:

Awesome. Thank you so much, Susan. It's so special with all of you today, and as a patient who is alive because of [00:08:30] a repurposed drug, I just have to thank all of you for the time and effort you're putting into drug repurposing and hopefully helping a lot more patients like me.

As I mentioned, I have a horrible disease called Castleman disease, and about 12 and a half years ago, discovered that a drug made for a completely different condition, a drug called Sirolimus, might be able to save my life, and I began testing it on myself. And as I mentioned, it's now been over 12 and a half years that I've been alive and well on this drug.

And pretty much every day for the last 12 and a half years, all I've been able [00:09:00] to think about is, "If this drug could save my life, how many more drugs are out there that are already at the pharmacy that could save a lot more lives?" And so that's really inspired the work that we've done over these last 12 years, first, through a center at the University of Pennsylvania called the Center for Cytokine Storm Treatment and Laboratory, where we've continued to search for potential new uses for medicines.

Over these years, we've now repurposed a total of 14 drugs across five different conditions, saved well over a thousand lives with these existing medicines for very rare conditions like Castleman disease [00:09:30] and DADA2 syndrome, Holmes syndrome, Angiosarcoma . Rare conditions where there were medicines that existed that could be repurposed for these patients.

And as we went one disease, one drug at a time, we've continued to ask the question... Every time we look within a specific opportunity, we're able to move it forward, reach patients, "How many more are there out there?" And so four years ago, launched a nonprofit called Every Cure that is on a mission to save and improve lives [00:10:00] by repurposing medicines across all drugs and all diseases.

Essentially, opening up the scope and not saying, "I'm going to find the best repurposing opportunity for Castleman disease or the best repurposing opportunity for DADA2 syndrome." But if you look across every drug against every disease, what's the best opportunity to help people? In doing so, you increase your likelihood that you're going to find great repurposing opportunities as opposed to starting within a specific disease area, and you're also able to really focus on those areas of high unmet need.

I'm [00:10:30] very excited about the partnership that we have right now in place, the RCA with FDA and the possibilities that Mitra shared earlier today. And Susan asked me if I would share some lessons from our experience over these last few years with drug repurposing. And maybe before I turn to those lessons, I'll just emphasize something that's come up a few times.

As we went one disease, one drug at a time in my lab at Penn, it became clear that there were a few barriers that were preventing this systematic matching all drugs and all [00:11:00] diseases. The first, which you've heard earlier, is that there aren't clear financial incentives to match old drugs against debilitating conditions. The second is that the technology didn't exist until recently to really be able to leverage the world's biomedical knowledge to predict which drug might work for which disease. And finally, there's never been an entity within our biomedical system that's had the responsibility for

making sure that every drug that's approved for one thing is used for every other disease that it possibly can.

And so at Every Cure, we've [00:11:30] tried to lean into all three of those areas. So we're a nonprofit organization, so we can go after nonprofit opportunities. We've built an AI platform that scans all drugs and all diseases to find the best repurposing ideas as a starting place to push forward, and we're taking responsibility that's end to end. So we find promising opportunities. We make sure they reach all the way to patients.

So we talk about drug repurposing a lot. What we do is somewhat like traditional drug repurposing, but it's a bit different. So, traditional drug repurposing, you start with a disease like Castleman disease, and you use a variety of different approaches. It might be high-throughput [00:12:00] drug screening. It might be some animal model work. It Might be computational work, but it's to try to identify among all the drugs out there, "Is there one drug that could be most effective for this particular disease?" And as I shared in Castleman's, that drug was Sirolimus for me and if we found others for other patients, but we found this drug for this disease and moved that forward. That's traditional drug repurposing.

What drug companies do is in the reverse directions. You start out with a drug that's approved for a condition, and then you say, "Okay. Among all the other conditions out there, are there other diseases that this drug might work in?" You do high-throughput screening, you do animal [00:12:30] model work, you might do computational work, but it's all in service of finding additional disease.

And drug companies are very good at indication expansion early on in the patent life. And so once a drug gets close to patent exclusivity, they cannot justify doing further work, laboratory work, and clinical trials to provide additional indications, and so this is something that's done early on. Over 80% of approved drugs are already generic, and so that means the vast majority of our drugs that are CVS, there's no incentive for companies to move forward.

What we do is a combination of the two. So rather than starting with specific disease or a specific drug, we start [00:13:00] with all drugs and all diseases, and then we utilize a variety of computational approaches. Mitra mentioned one of well over a dozen approaches that we utilize to quantify how likely every drug is to treat every disease, generate a single score between zero and one for the likelihood a drug may be useful in a new disease area, quantify all of them, and then say, "Among every drug versus every disease, what's the highest scoring match? What drug for what disease?"

And it might be a disease that oftentimes I've never heard of, it might be a drug that I've never worked with before, but it's utilizing the power of artificial intelligence to [00:13:30] score and rank things so that us humans can then review those top hits. And it's not that because AI scored something as a 0.999 that we need to give it to patients. It's that because it's a 0.99, it should be reviewed by patients, and then further work should be done in the lab and in clinical trials.

I also wanted to call out that in addition to our computational approach, we also love when people share with us great repurposing opportunities. So if you've treated a patient with a drug off-label and it's helped them, if you're a patient, you've benefited from a drug off label, tell us at everycure.org/ideas. We'll have our medical reviewers review [00:14:00] it right alongside all the AI-generated ideas. Over the last year and a half, we've reviewed almost 15,000 repurposing ideas. Nearly all of them come from our AI platform, and we'd love to include others that you guys might have.

So Lesson 1, of course, is that discovering repurposing ideas is challenging, but artificial intelligence provides a scale that was never possible before. The second one is that drug repurposing... and we heard this earlier. All opportunities are not the same. Everything is in its own space along this continuum [00:14:30] from we have no idea what the mechanism might be, AI just told us that this might look promising, where more lab work is needed through cases where the laboratory data has been done and the mechanism is clear, but we could benefit from some real-world evidence that might help us to understand an association, or maybe there's enough of a mechanism and maybe an association that we're ready for a clinical trial to actually prove this drug works, or maybe the trial's been done, and now it's about working with guidelines committees and educating doctors that this drug can be useful in new ways.

[00:15:00] Just two weeks ago, we began raising awareness about a drug, Lenalidomide, for a rare disease called Rosai-Dorfman disease. Based on work that we did identifying as a high-scoring match and working with a doctor named Luke Chen, we actually were able to get NCCN to update their treatment guidelines. So Lenalidomide and Dexamethasone is now a first-line preferred therapy for Rosai-Dorfman disease. And so now, our task at Every Cure is to get the word out about this to as many patients and as many doctors as possible. So the question is, "What's that path?" And every one of these, it may be different. What's the path from [00:15:30] where we are now with limited evidence to actually get it to where patients are actually on the medicine?

And then the third lesson is around something that Jana was emphasizing, and that's that in order to make impact, we really need... and actually Pam made the comment too. We need stewards who are going to steward these things from early stages all the way to patients, and we can't do it on our own. It really requires collaboration across the ecosystem.

So, at Every Cure, we think about our work in, really, three phases. So it's discovery, ranking all of the best repurposing [00:16:00] ideas in the world, every drug, every disease, and then looking at the top of the list. And then we have a really rigorous process from about 15,000 reviews we've done down to the several hundred that get what we call med reviews, which are a couple days of MDs or PhDs reviewing down to what we call deep-dives, which is several months of MDs and PhDs reviewing, down to laboratory work, down to clinical trials. We currently have 14 active programs.

So, once we discover something, then it becomes a program. It gets reviewed by our Scientific Advisory Council. Monday, [00:16:30] we just added... This past Monday, we just added two new programs. And then we can evaluate them in the lab and in clinical trials. And finally, once we've evaluated them and we feel the evidence is sufficient like we did for Rosai-Dorfman disease, then we're ready to make impact, to work with doctors, guidelines, committees, to get the word out so patients can benefit.

Our goalpost, our end goal is patients benefiting from existing medicines that may involve an FDA label change. It almost certainly will involve a guideline change, but the goal is patients benefiting from the existing medicine. And we have to [00:17:00] do everything we can possibly to make sure they get from early ideas all the way to patients who can benefit from them.

So I mentioned we've got 14 active programs. We review between 500 and a thousand repurposing ideas every month. Each one of these programs is... As I mentioned, at various stages, we've got three that are currently undergoing laboratory studies, a handful that are either about to be launched into clinical trial or there's clinical, excuse me, clinical research being done. And then a few that are in this,

what we call dissemination planning phase, where [00:17:30] the evidence is sufficient, but now we need to understand what's the right population that can benefit from this medicine.

So I'm going to close, oops, with my last slide by just putting up the pharmacy shelf. Every time I walk past the CVS, all I can think about is that the drug that saved my life was always on my pharmacy shelf for the years where I was dying and no one knew to try it. So we walk past the CVS, and we think about all those drugs that are there that could help patients and of course, all the patients who are suffering on the other side of it.

The biggest [00:18:00] takeaways I have from this now almost four year journey with Every Cure is that... and this is what Janet said earlier, and we're lucky to have Janet on our board at Every Cure. The discovery part is the fun and the easy part, finding a potential new use for medicine. I shouldn't say easy. It's the fun part. But once you've done that, there's so much more work to be done to translate that, to do the laboratory work, to do the clinical trials, and we're really honored to have the opportunity and responsibility to work with amazing partners. [00:18:30] ARPA-H is our primary funder, and they've been a tremendous partner as we've moved this work forward. So, I'll close with that. Thank you so much.

Susan C. Winckler:

So, thank you, Dr. Fajgenbaum and Dr. Agrawal, for giving us those examples of things that you're pursuing and how to generate this evidence. I want to invite our reactor panelists to come on up to the stage to help [00:19:00] us have a broader discussion. So, as they're getting settled, I'll note joining us from FDA Center for Drug Evaluation and Research are Dr. Emily Freilich and Dr. Marie Bradley, who serve as Director Division of Neurology Office of New Drugs and Senior Advisor on Real World Evidence in the Office of Medical Policy respectively. From REMEDi4ALL, we have Dr. Donald Lo, who is Director of Medicines Development and Scientific Lead. And finally, we have former FDA-er and current CEO and founder [00:19:30] at Highlander Health, Dr. Amy Abernethy. So, let me first say, do the four of you have any questions for our presenters? You don't have to. Yes, go ahead, Dr. Lo.

Dr. Donald Lo:

I have a "quick" question for David.

Susan C. Winckler:

Yep. Hold the microphone up a little closer.

Dr. Donald Lo:

Yeah, David. So, as you know, the Cures Within Reach Foundation, which has been, really, the pioneer in the drug repurposing space for 20 years, has this really exciting new program, right, for validating AI platforms [00:20:00] in partnership with Biohub. So this would be great, right, to be able to understand, really, what you can rely on. But now that the AI genie is totally out of the bottle and everyone is talking with ChatGPT or Claude, how are we going to be able to share the kind of rigor that you and others are placing on AI platforms so that the general public, in particular, patients and patient foundations, can really use this tool as opposed to getting led down the [00:20:30] wrong path?

Dr. David Fajgenbaum:

Yeah, it's a great question. I think that direct-to-patient personalized drug repurposing recommendations is something that it's happening every day on ChatGPT. And of course, there's no way that any of us are going to be able to regulate or validate those sorts of things. I think the best thing we can do is to take the same rigorous approach that we talked about where we're doing laboratory work, we're doing clinical trials, we're generating evidence to really be convinced these medicines work, and to move those forward. And then of course, ChatGPT will catch up, because then, [00:21:00] the drugs that we work on are recommended by ChatGPT. But right now, I don't think there's anything we can do, unfortunately, to validate the concepts that are coming from these direct-to-patient approaches.

Susan C. Winckler:

Great question. Amy, did you want to chime in on that? Okay. That's all right. And actually, it came up in an earlier conversation we're saying that that might be a place or a rationale for wanting the FDA drug label to be updated because then you know it's... Well, I think we assume it's a source that [00:21:30] these models are using along with a number of others. But I'm going to turn back to you, Dr. Lo. And some in the audience may know about REMEDi4ALL, but I think many don't. So would you talk a bit about REMEDi4ALL's role in Europe as it relates to drug repurposing and then provide your reaction to what you heard and how that might compare to the European approach?

Dr. Donald Lo:

Yeah. Absolutely. Thank you. Overall, [00:22:00] the regulatory landscape and the challenges and barriers are, really, so similar between Europe and here, of course. They're almost identical processes. I think one of the first big differences I noticed moving as an American moving to Europe, being able to move because the processes are so similar, is that now I'm the guy with the funny accent in the room. So that's been interesting.

Probably a more important difference is that [00:22:30] as we've talked about, the issue of reimbursement. And in Europe, it's much, much more the case that if the indication is not on the label, it's not reimbursed. So I think this has, in the European setting, driven much more motivation in terms of being able to incorporate drug repurposing more as a mainstream part of bringing new medicines to patients.

So, over the last decade, the European Union has made a number of investments in various areas, and one of them was the REMEDi4ALL platform. [00:23:00] And that's what I had the opportunity to go to move to Amsterdam a few years ago to help stand up and run. And the problem statement for REMEDi4ALL has already been extensively talked about in the last session. Pam and Janet basically said, after all the fun is over, as David just said, this is the really cool part, these amazing ideas. Now, who's going to create a feasible development plan? And who's going to partner with the people? Who's going to do it? Who's going to actually [00:23:30] take the ball and take it all the way through approvals, into market, into reimbursement, into payment? And that was the concept of REMEDi4ALL.

So it's a consortium of 26 different sites across Europe and UK. And the idea is to be able to partner with drug repurposing projects at any stage of development and take them not just to the next step, but again, all the way through to patient access. So we started a few years ago. [00:24:00] We've already

had engagements with over 300 active drug repurposing projects. About half of those are preclinical, half of those are in clinical stage, and the big lesson we've learned, the big theme is exactly what we've been talking about today, which is that for the most part, people that come up with drug repurposing ideas have never developed a drug before.

And so after the fun part, now it's drug development. And that's just not part of the current [00:24:30] ecosystem. So the idea is that we, as REMEDi4ALL platform, could partner with you on the drug repurposing project, envision this drug development plan that gets all the way into patients and reimbursement. And then among the 26 partners, be able to put together a team because translation really is a team sport to take that project forward and through and through.

So, right now, we have several projects in clinic. We're hoping to get our first label extension later this year. [00:25:00] So we're very excited that the promise of drug repurposing being faster and cheaper actually can be tapped into. So what we often do, our main role, really, is to be able to convert a scientific plan into a regulatory directed plan to clear IND. And then if you're in clinic, not to do another really cool academic study, but to do a registrational study because there's not a lot of money going around. You might as well spend the extra time to have a real path all the way to patient. So that's [00:25:30] about 90% of our work. The other 90% is then matching with industry to be able to get a sponsor.

Susan C. Winckler:

Okay.

Dr. Donald Lo:

And although we've worried about that in the last session, we have found that if you really can translate academic speak into business speak and make a value proposition, a company doesn't necessarily have to make money. You just have to make it so they won't lose a lot of money. And in a way, there's enough public funding to get the evidence data package for a label [00:26:00] extension. And if you can go with them with a professional plan, most of the time, they're willing to take a little bit of a hit on the bottom line as long as you can show that there's a reasonable risk benefit ratio to get that on label.

So about 20% of our projects come from the US, actually. So REMEDi4ALL is funded by the EU, but its perspective is global. So we're right in the middle now at the tail end of our grant from the European Commission to be [00:26:30] able to continue our work as a nonprofit foundation both in Europe, but also in the US to have a branch here as well. So we're hoping we'll be able to continue to contribute to what David and others have been saying, which is that after all the fun, we got to get to the expectations.

Susan C. Winckler:

How do you make it happen? Yeah. So it's great to hear, right, the articulation of where you have a drive, right, that there does need to be a regulatory decision because of the reimbursement side, but then also looking at the structure that's possible. Although I do have to note, I'm pretty [00:27:00] sure, if you were trying to convince the business side, you needed to convert your journal articles into charts and... Right?

Dr. Donald Lo:

Indeed.

Susan C. Winckler:

With the-

Dr. Donald Lo:

Business charts.

Susan C. Winckler:

With business charts, with the graphs and-

Dr. Donald Lo:

Yes.

Susan C. Winckler:

Yeah. Okay. As long as you did that. So let's talk a little bit on the US regulatory perspective. So, Dr. Freilich, Dr. Woodcock had observations about the challenges of a reviewer at FDA and how this is perhaps a different package of information that you might be accustomed to seeing. So [00:27:30] how do you think about the level of evidence for drug repurposing, particularly in the frame of what we heard from Sundeep and David?

Dr. Emily Freilich:

Thanks, Susan. I think that... and we've heard this from many people today, that the level of evidence that's needed is still going to be required to ensure the safe and effective use of the drug for the new indication. And so when we think of it, we think of, "Well, what is that level [00:28:00] of evidence needed? What's the standard? We know we need substantial evidence of effectiveness to show that the drug is having the effect it's reported to have, and where can that evidence come from?" The best way is still going to be a pivotal study in this new identified population. But as Dr. Lo just said, well, sometimes the other work has already been done, right?

Susan C. Winckler:

Mm-hmm.

Dr. Emily Freilich:

You know this drug is out there. It's safe. It presumably already had [00:28:30] all the nonclinical testing. It's had other information out there. So you can come in with an IND and go right into your pivotal phase

three study. So if there is anyone who wants to take on that task, then that is going to be the best path forward is to do a prospective study, collect data in the new indication, and get the label expanded.

Now, we've heard a lot about who's going to do that study, and who wants to do that study, and who's going [00:29:00] to fund that study. But from a FDA perspective, that's the easiest way. The other ways are to... We're going to hear from Dr. Bradley about real-world evidence, and we are open to considering that for substantial evidence of effectiveness, but it depends on the quality of the data. Again, how do you know that it's going to have that effect in all patients with that disease? Do you have more than anecdotal report? What is [00:29:30] the level of evidence in the literature from the academic studies?

In neurology, we recently approved Leucovorin for a very rare disease, cerebral folate transport deficiency, and that was a repurposing effort that took a lot of effort on the FDA side. And it was a drug that had been around for a very long time, decades, and used in oncology, [00:30:00] and there was basically standard of care for this rare disease where patients can't get folate into their brain, and therefore, you can give Leucovorin, which is a folate analog that is able to cross the blood-brain barrier and get into the brain.

So we had mechanistic evidence that the drug should work, and we had literature reports that demonstrated [00:30:30] patient level data that the patients were reacting to treatment with Leucovorin in a way that was totally unexpected from the natural history of this disease, which is inevitably a devastating neurodegenerative, progressive, fatal disease, and patients were living long lives on Leucovorin.

And so we were able to overcome that substantial evidence of effectiveness barrier by using a systemic review of the literature with patient level data. [00:31:00] It was a rare disease where placebo-controlled or any kind of controlled trial would not have been feasible in any way, and we were able to turn that systemic review of the literature into an adequate and well-controlled trial with confirmatory evidence coming from the mechanistic action of the drug. But that didn't mean there weren't other barriers that we had to overcome in updating the label.

[00:31:30] Dr. Agrawal, he referred to modernizing the label. We had to do that because the label hadn't been modernized. It had been withdrawn from the market in the '90s, and we had to reactivate the NDA to then update the label only to have it withdrawn again, but able to... to Janet's point, the generics were able to get the updated label.

It's a rollercoaster of regulatory hoops to jump through. [00:32:00] When you label a drug for a new indication, you have to worry about the dose, and potentially, the dose is different for this new indication. Do you have safety at that dose? Is it a more vulnerable population? Do you have safety that it's safe in... It might be safe in the original indication, but how do you know if it's safe and well-tolerated in the new indication?

We had to worry about bridging. We didn't know what formulation [00:32:30] of the drug was used in all these case reports in the literature, and so how can we be sure that the drug that we're approving is similar in pharmacokinetic effects as the ones that were used in the literature? And our teams had to do a lot of work to ensure all of this, let alone manufacturing issues and other things that could come up. So

there's a lot of work on the FDA side that has to [00:33:00] go into this effort as well. And I think if we did have a path that was clearly spelled out, that would make it easier.

Susan C. Winckler:

Yeah, yeah. So not only, as was observed earlier, for the outside groups thinking about, "What steps do I have to take?" but also, inside FDA, asking those questions. Well, you mentioned real-world data, and so let's turn to that emphasis. I'm going to turn to Dr. Abernethy. Would you apply your real-world data lens and expertise here?

Dr. Amy Abernethy:

Terrific. [00:33:30] So I think we're trying to illuminate the path and how to in this drug repurposing discussion, and a little bit of a historical context first. Sundeep mentioned the Compendia story in oncology, and what had happened was in the Social Security Act, I think, in 1993, we made a decision as a country to pay for cancer drugs provided that they were named as adequately safe and effective, and listed [00:34:00] in one of the authoritative sources, which were the Compendia.

Now, the problem was, and I was responsible for looking at this for CMS, that the Compendia were somewhat up-to-date, but not keeping as up-to-date as clinical practice. And so we had drugs being paid for in this country when they were in the Compendia, but also rapidly accelerating evidence and divergent clinical practice. And so that story led to the observation that we should use all accumulating [00:34:30] data around clinical practice to start to make sense of what drugs were working in the cancer space.

It led to ASCO, American Society of Clinical Oncology's CancerLinQ, Flatiron Health, Tempest, start naming all of the real-world data companies and efforts in the cancer space really all came from this one set of observations. And now we hear about Project Renewal, which is the current day version of now trying to understand, "Do we have adequate evidence based on a total accumulation of what [00:35:00] we know about this product to now update the label from a cancer perspective? And how do we make the mechanics work within the context of the FDA?"

So that is our current day story and serves as an inspiration as we think about where we are. And now the question is, how do we take that inspiration, what we've learned across that time, and bridge to all of the diseases that need us to consistently summarize what do we know and how can we make the best and most judicious decisions, including the reimbursement decisions when that's also [00:35:30] on the table?

Now, bridging over to real-world data and real-world evidence. So inherent into that story was, can we learn from all available data? If I define real-world data and real-world evidence as, really, first the data that is naturally occurring across the conduct of clinical practice, so we call that EHR and claims, but also now a multitude of new data types that start to get added in to now start to summarize where we are without collecting intentional [00:36:00] new data growing forward prospective data.

I think that really leveraging these data as a part of the story, but cannot always be the story is part of our task. And we have to be able to understand what are the opportunities and limitations, the real-world data and evidence. And I think this is where Marie is going to come in, so I'm not going to steal her

thunder. But practically speaking, recognizing that this isn't an opportunity of fancy blinking lights, pushing a button, and all the answers are in front of us.

There is the need to continuously [00:36:30] develop the right datasets, so having data that are fit for purpose, being able to design and conduct disciplined analyses, and then also thoughtful interpretation, and as we've heard over and over again, turning that into now also deliberate actions that translate to how actually medications then get to patients when we have the information.

The thing I wanted to say here is that we have an evolving story in drug repurposing. We also have an evolving story happening right now in the evolution [00:37:00] of modern real-world data and real-world evidence. And so we need to make sure that we don't essentially say, "Ah, it doesn't work," and/or, "It's never going to be good enough." But rather, recognize that there are some indications for which real-world data and real-world evidence will be useful in the drug repurposing space now, and there'll be a continuous evolution and movement towards better and better work in the real-world data space, and we might come back to what that might look like, and these two will start to converge.

The last thing is [00:37:30] that therefore, we have the opportunity, as we select some of the indications for this particular project, to look for some indications where is also the opportunity to build the real-world data, real-world evidence muscle for drug repurposing. It may not be the best indication that we want for all of the drug repurposing opportunities out there, but it might be the best opportunity to really build the muscle that we need for the real-world data side of the equation.

Susan C. Winckler:

So another factor consider in saying, "Where do we want to look at repurposing [00:38:00] candidates?"

Dr. Amy Abernethy:

Yes.

Susan C. Winckler:

Yes.

Dr. Amy Abernethy:

We'll talk about AI later.

Susan C. Winckler:

All right. So, Dr. Bradley, you think about real-world data from a slightly different perspective, right, in looking at it on the regulator side. So what dynamics about real-world data and real-world evidence would you add to what Dr. Abernethy has observed, would you add into that from the regulator side?

Dr. Marie Bradley:

Yeah, yeah. Sure. Thanks, Susan. I think the first thing I really want to emphasize is FDA is really committed [00:38:30] to evaluating the potential use of real-world evidence for new indications for drugs that are already approved since the 21st Century Cures Act of 2016. And since then, we have several examples, and these are actually, most of them, published on the FDA website.

So I would really encourage folks to take a look at these. It's in summary form, but we have examples where real-world evidence have been used to contribute to substantial evidence of effectiveness for a new indication [00:39:00] for Gamifant back in 2025 for macrophage activation syndrome. Examples maybe a little further back in history. One that's commonly known is the Prograf for lung transplantation, which was approved based on a non-interventional study. And with Gamifant, the real-world data contributed as an external control arm.

We also have examples of where real-world evidence contributed confirmatory evidence. So Isturisa was approved [00:39:30] last year for a new indication for a label expansion from Cushing's disease to Cushing's syndrome subtypes. And so we already have a history of doing this. Real-world evidence has been used for the approval of new molecular entities contributing substantial evidence of effectiveness in the rare disease space as well for changes in dosing regimens, new formulations.

And so obviously, these are always... or all, [00:40:00] to date, have had a high level of commercial interest, and so this is where they differ, right, from what we're discussing today. But I think it's really interesting to see, "Okay. Well, we've done this so far. We can keep going. There's no reason why the same standards don't apply to situations where there is much less commercial interest." And I think in this type of repurposing, I think one of the good things is, referring back to Dr. Fajgenbaum's picture of the dispensary in the pharmacy, many [00:40:30] of these drugs that we're considering may have been around for many years, right-

Susan C. Winckler:

Right.

Dr. Marie Bradley:

... and may actually be used off-label for the new indication. And so there can be considerable amount of real-world data from the various sources, EHR, registries, claims, whatever, document, and use, and can provide really helpful information in that sense. But I think I do want to highlight, really, that the evidentiary standard has to remain the same, right-

Susan C. Winckler:

Yes.

Dr. Marie Bradley:

... whether there's commercial [00:41:00] interest or whether there's little commercial interest. And so at FDA, we have a broad suite of real-world evidence, related guidances that, really, are designed to help folks reach that evidentiary standard. They cover key considerations. We have a framework. I would encourage anyone interested in using real-world evidence for repurposing to check these out.

I think there are three key considerations, and I won't go into depth on them right [00:41:30] now, but the problem of having data is not... It needs to be able to generate meaningful clinical evidence. And to start with that, you need to identify a fit-for-use data source, you need to identify a study design that's going to be adequately able to answer your regulatory question, and you also have to conduct your study, very importantly, to align with regulatory requirements, which many people who maybe have less of a commercial interest, maybe don't have as much experience with.

[00:42:00] And so along with our suite of guidances, which I think can be very useful to interest the parties in this space, I think we really encourage folks to come in and really engage with the FDA early if you are considering real-world evidence for repurposing. And there are various ways to do this, but I want to pitch one.

We have a real-world evidence subcommittee, which is staffed by real-world evidence experts, subject matter experts at the agency. And we actually offer listening sessions for interested parties [00:42:30] to come in and speak with the agency. And it's potentially less formal than maybe a traditional pathway meeting where you could get feedback on some of the ideas. And so we also, in our CDER Center for Clinical Trial Innovation, have the STEP program, which is designed to help interested parties with developing trials with more pragmatic elements, which, again, point-of-care trials can be a really good way to generate real-world evidence and maybe of interest to the repurposing space.

So [00:43:00] I guess what I want to say is we're really keen to explore this with folks. Please come in and talk to us. Please read our guidances. Please look at our examples that set the precedent for what has been done before.

Susan C. Winckler:

And I heard you emphasized that you have relevant data sources, that you're asking the right questions, and generating the answers to those questions that are of regulatory relevance.

Dr. Marie Bradley:

Yes.

Susan C. Winckler:

Okay. I just want to give... Sundeep and David, do you want to add anything to this [00:43:30] discussion as we're thinking about the broader application and reflecting on what it is that you do?

Dr. David Fajgenbaum:

Sure, happy to. Yeah, a couple of things coming to mind as we think about real-world evidence. I think about a condition called DADA2 syndrome that I've been involved with for, I guess, over 10 years now. DADA2, rare condition where kids were having dozens of strokes and dying in their teenage years as a result of these strokes. And then a doctor decided to try a TNF inhibitor because he thought these kids... [00:44:00] Their syndrome looked similar to another condition that's due to the TNF inhibitor.

First couple kids benefited, and then about 10 years went by between this first early observation, and then actually, a number of doctors using it in other patients. And then a paper being published in the Journal of Medicine and eventually, treatment guidelines. When you think about cases like that where the drugs being used in some patients somewhere, there's really clear evidence. These kids stopped having strokes. It's incredible. But years went by where kids were dying from having so many [00:44:30] strokes because we hadn't picked up the signal in the real-world evidence that if you use a TNF inhibitor, you save these kids' lives.

And to me, I think that's even more of a tragedy than it just sitting at the pharmacy shelf is that someone in the world already knows that it could be useful for kids and they're still dying. And so how do we think about creating the right systems to use RWE so that we capture these signals as soon as they emerge?

And then the other quick comment I'll make is that when we think about prioritizing repurposing ideas at Every Cure, we're considering [00:45:00] three things mainly. One is biological plausibility, "Is it likely this drug will work for this disease based on mechanism?" The second is the impact that you could have, the unmet medical need. We have a score that's publicly available for every disease. And the third is the feasibility, "What's our cost going to be related to moving forward?"

The reason I bring it up is because real-world evidence can provide some real confidence that that mechanism that we think looks promising for biological possibility, if it's actually been used in some patients, even if it's just a few patients, right, that can give us the confidence [00:45:30] that will actually help us to leapfrog even many laboratory studies with animal models.

Susan C. Winckler:

Yeah, yeah. You can jump in.

Dr. Amy Abernethy:

I want to respond to what David is saying because I think that this is where the space of real-world data and real-world evidence continuing to evolve alongside drug repurposing actually provides us hope.

Susan C. Winckler:

Yes.

Dr. Amy Abernethy:

So with respect to generating better datasets, the data-sets of old... often maybe had electronic health records, maybe not. We were just mostly working on administrative claims. Then, we moved into the landscape [00:46:00] of real-world data and real-world evidence, and the datasets having electronic health record and claims data, but missing out on medical case notes and the data that exists in unstructured documents being available for analysis.

Now, in a more modern context, the unstructured documents themselves get curated into meaningful data that can be analyzed, combined together with administrative claims, but then combined together

with patient-reported outcomes, and biologic details, and environmental details. So now what you're seeing is linked [00:46:30] datasets with much richer information that reflects a longitudinal health across time in very rich ways. So that's one thing that's changing, and AI is making a big difference here. It's helping with data curation. It's helping with data linkage and solving for lots of data cleanup challenges.

The second thing is we're seeing evolution in the analysis and the signal findings. So now being able to build platforms that actually much more quickly identify those signals and persist them so that we can see this. So this is another area where that [00:47:00] change can be added to your drug repurposing efforts.

But probably the other thing that people don't talk enough about is the dissemination of knowledge side of this equation and how do we now also match that to much more efficient ways of making sure that when there's meaningful signal, it routes to the regulators, but also it routes to those who need to make the decision afterwards.

Susan C. Winckler:

Clinicians. Right. Mm-hmm, mm-hmm. Which I think is a piece, right, Sundeep, people were thinking about in Project Renewal. It was to make sure that the label is capturing some [00:47:30] of those to broaden clinical impact, I would think, right?

Dr. Sundeep Agrawal:

Yeah. We had a very close collaboration with the community, and that was critical to actually making the process work. Yeah, that was really important.

Susan C. Winckler:

Yeah, yeah. Super important. All right. So I want to open this up a bit. So this is what is most important. So, from each of your perspectives, what is the most important element to keep in mind when you're thinking about candidates for repurposing? Amy, I imagine yours is a bit more in the, "Well, [00:48:00] do we have good data? Can we build that longitudinal piece?" But any of you, what is that that you would be thinking about as the most important element to keep in mind?

Dr. Donald Lo:

I'll answer that.

Susan C. Winckler:

You're just on the raising your hand today, Don.

Dr. Donald Lo:

Sorry.

Susan C. Winckler:

It's great.

Dr. Donald Lo:

I'm raising my hand. It's a very broad statement. I think we've talked about, as Marie just said, the evidence standards have to be the same. This is not a lower bar, you know?

Susan C. Winckler:

Mm. Mm-hmm.

Dr. Donald Lo:

From the patient point of view, physician point of view, you have to have the [00:48:30] same confidence in risk benefit. So there is an importance, as we talked about earlier, to have a clearer path for drug repurposing. But frankly, most of the path is already there, and you just have to... It's more of an understanding of how do you take advantage of the data you already have.

So Barbara Goodman of Cures Within Reach has a nice way of saying it. She says, "We're drug repurposing, but what are we really doing? We're repurposing human data." And so what parts of that path then [00:49:00] can you really leverage existing human data to be able to achieve a more efficient path towards some kind of approval? Label extension, patient access. And as part of that, I think we have to remember that drug development has always intrinsically been a gigantic team sport. And no matter how clear the path is, no one person or no one group is ever going to be able to achieve everything.

So I think as we think about this, the ability to put together... [00:49:30] not necessarily fixed infrastructures that are huge and burdensome, but networks where you can access the type of expertise and experience you need on demand in order to progress your project forward towards patient access, if we can keep this kind of... It's a dissemination of knowledge question. Can we work together as a community to leverage existing human data to be able to bring these new treatments to patients?

Susan C. Winckler:

Mm-hmm, mm-hmm.

Dr. Sundeep Agrawal:

Can I just make a quick comment?

Susan C. Winckler:

Yes. I was going to turn to you, so excellent.

Dr. Sundeep Agrawal:

[00:50:00] Yeah. One example from Project Renewal that may be helpful here is when we were looking at Capecitabine and updating some of the indications there, we had heard from the breast cancer community that the real dose used in practice is not even the one in the label. Most people start at a thousand. People don't really use the 1,250. There's a lot of toxicity.

So we were able to get that dose into the label, but we didn't have a large formal non-inferiority trial making sure there's no loss [00:50:30] of efficacy and hundreds of patients on one dose versus the other dose. Based on existing data, we were able to build out that picture without it having to be too onerous or expecting there to be some large burdensome expensive trial just to show that the 1,250 and the thousand are both reasonable starting doses.

So there are ways to do it, but we couldn't do it only based on anecdote. We were able to find some small studies that showed similar response rates to the different doses, and comparative safety [00:51:00] evaluations, and so on and so forth. So you do have to get a little bit creative, but it can be done.

Susan C. Winckler:

Mm-hmm. And that was striking me as it might be a good example of where if you could interrogate that human data better, that you have that opportunity to repurpose it. We're going to use the "repurpose human data" phrase again, I think. David.

Dr. David Fajgenbaum:

Yeah, I was just going to add one comment where I think that we get really excited. We've had repurposing opportunities where there's really good mechanistic rationale for why it might work, where there's a [00:51:30] biomarker once you give the drug to the patient, you see immediate improvement in the patient, at least within that biomarker where there's some real-world evidence. So I think it's almost less about like, "Is there this one thing?" But I think it's when there's multiple.

I'll just quickly share about an example of a condition called Bachmann-Bupp syndrome where kids are born with a mutation, a gene called ODC1, and it causes increased levels of ODC1 accumulation of poly. It means a drug was made called DFMO for African sleeping sickness 50 years ago that's a really great inhibitor of ODC1. [00:52:00] So if you treat these young children who have a horrible degenerative condition or neurodegenerative condition where they're bedbound, they're unable to engage with their loved ones, you give them this drug, DFMO, you can see really tremendous improvements in these kids.

And I mention it because not only do you see clinical benefit, but because we're clearly hitting the mechanism, you're going to see biomarker changes in the blood at the same time, see clinical benefit, biomarker changes. We know how the drug works. We know exactly [00:52:30] where it is working. So, in this case, even just treating a handful of patients and seeing a really tremendous benefit from it like that is convincing to physicians and also to us at Every Cure that this is clearly effective. And so I guess just the comment that we love it when there's multiple lines of evidence that are all pointing towards the same thing.

Susan C. Winckler:

Yes. And I got the head nod over here from Emily, so I'm going to turn to... Right?

Dr. Emily Freilich:

I would just say the-

Susan C. Winckler:

Biomarker and clinical evidence?

Dr. Emily Freilich:

Definitely. That's what we're looking for.

Susan C. Winckler:

Yeah.

Dr. Emily Freilich:

So we talk about confirmatory evidence when we have... [00:53:00] We want to confirm what we're seeing in the clinical trial or in the real-world evidence is due to the drug. And so when you have a biomarker and you have a mechanistic rationale, that adds a lot to our ability to say that it's the drug that's having this effect and not something else.

And the other thing that what David just said reminded me of is that when we're talking about substantial evidence of effectiveness and the standards, which is the most important thing, [00:53:30] I think, is keeping our standards high, is that if you're talking real-world data, or you're talking external control trials, or you're talking comparisons to natural history, there is inherent bias in that. But if you have a treatment effect that's large enough to overcome those biases, then that is all you need sometimes.

Now, of course, we don't see that often. But in the cases that we've been talking about today, some of them have had that large and convincing [00:54:00] treatment effect that shows that this is not expected in the natural course of the disease, and then that alone can be substantial evidence of effectiveness.

Susan C. Winckler:

So the combination of things and looking at the magnitude and multiple signals?

Dr. Emily Freilich:

Exactly.

Susan C. Winckler:

Yeah.

Dr. Sundeep Agrawal:

Just a-

Susan C. Winckler:

Yeah.

Dr. Sundeep Agrawal:

Oh, I'm sorry.

Susan C. Winckler:

That's okay.

Dr. Sundeep Agrawal:

Oh, just a question for Emily and maybe a comment. One of my recommendations, little notes I had here was I though it would be helpful when you look at diseases that are similar [00:54:30] biologically where the plausible causative pathways are similar. And I think from a regulatory perspective, there is precedent to extrapolate to help fill some of those gaps in the clinical data. Can you speak to that a little bit? Because I know that, at least in oncology, there are times where we understand we may not be able to get randomized trial data or everything we would want, but extrapolation ends up playing a role where we understand there may be limitations in actually generating that data in an ethical manner with equipoise.

Dr. Emily Freilich:

Mm-hmm. [00:55:00] Yeah. No, that's a great thought. And I think that there is a role for extrapolation of data to new populations, especially when we're talking about rare diseases or safety. You can sometimes say, "Okay. We have this disease, and this has been done before..." Not in the repurposing world.

Susan C. Winckler:

Right, right.

Dr. Emily Freilich:

But if you have a drug that has been used in one indication [00:55:30] all the way down to age two, and then you have another study that came in, and they only studied down to age six, but the disease might occur down to age two, and you're saying, "Okay. Well, if they have similar pharmacokinetics and similar patient populations, can you say, 'Okay. The safety in the first indication is similar enough... expected to be similar to the safety in this new indication?'" And so you don't always need data in every age

[00:56:00] group or in every stage of disease. Sometimes you can extrapolate data or efficacy if it was only studied in a late stage of a neurodegenerative disease, but you could say, "Okay. Can we extrapolate that that should have the same benefit if it's a little earlier?"

Susan C. Winckler:

So, some opportunity. Amy.

Dr. Amy Abernethy:

So I've been listening to this conversation and continuing to think about the figure David had of all of the different spheres of work that needs to be done [00:56:30] to get from the disease to now getting to treatments for patients in the drug repurposing space, and two historical concepts. One is in the oncology space, there's a meeting called AAADV, Accelerating Anti-Cancer Drug Development. You guys will remember what this is. Importantly, these meetings where industry researchers, academia, and FDA all came together for one week every year and went through the mechanics of how-to, "How did this [00:57:00] go from a scientific target and concept all the way through to the regulatory decision and all the steps on the way?" and teaching each other the how-to.

Fast forward, in COVID, we had the Evidence Accelerator together with Susan and Reagan-Udall Foundation where we looked at how could we leverage rural data and real-world evidence within the context of COVID and all of the players coming together in a crucible to actually, in very rapid succession, [00:57:30] teach each other the mechanics of how-to, what is possible, what gives regulatory pause, and concern, and consternation, and where could we push forward in new ways.

And one of the things that I think about here, and Marie, you said it quietly, but was really important underneath what you said, which was there are mechanics to doing this in addition to all the pieces that we talked about. For example, how the data has to be submitted, what are the features of the data. If you were going to use real-world data, that's just one of the mechanic issues.

There's mechanics [00:58:00] as it relates to access of the drug, a dissemination of the information, and do we need a crucible that actually provides, in rapid cycle, the how-to mechanics and teaches each other in a way that now makes this much more efficient? And Every Cure is probably doing this in a lot of ways.

Susan C. Winckler:

Yeah.

Dr. David Fajgenbaum:

I love the idea, and I think that we're learning from others. We're applying it in our own case, but I love the idea of us coming together with REMEDi4ALL and Cures Within Reach, and really pushing this forward.

Susan C. Winckler:

Yeah, have the broader shared learning. All right. [00:58:30] Marie, you get the last word in-

Dr. Marie Bradley:

Yeah.

Susan C. Winckler:

... reflecting on all that's been shared in this panel.

Dr. Marie Bradley:

Yeah. And I wanted to take this opportunity to talk a little bit more technical, right, about what does fit-for-use data look like. And I realize we don't have a lot of time, but basically, in order to get a new indication, you need to identify a data source where it captures the population, it captures the candidate use, it has the availability of confounders that might be needed in your analysis. [00:59:00] I think in repurpose and sometimes off-label drug use can be highly selective, right?

Susan C. Winckler:

Mm.

Dr. Marie Bradley:

And this could be... The people who get the drug can be systematically different from the people who do not, and so that can reflect severity or access to specialized centers and things, which can all affect your outcomes. And so being able to identify this data that captures everything you need, applying a robust study design that accounts for all the types of biases that very often are inherent in studies using real-world data.

But also, and [00:59:30] I think maybe this is a little bit less underappreciated, is conducting your study to regulatory requirements. And so one of the big pieces of that is the ability to submit patient-level data to the FDA. And so you can have this wonderful fit-for-use data source and this beautiful study design with your target trial framework. And then the vendor that you got the data from or the registry have all these privacy restrictions, and then FDA can't [01:00:00] sign this agreement, and so it becomes a major barrier. And so my advice, which is really important, is upfront, you need to consider this very upfront, discuss with the FDA how you're going to get your data into the FDA so we can verify your results as part of the review process.

Susan C. Winckler:

Yeah. Because you take a real close look at it. All right.

Dr. Marie Bradley:

Yeah.

Susan C. Winckler:

So we know we need to have all of this tied up and really illuminating from thinking about what we need to the ecosystem to help for shared learning to examples of making this happen. Thank you so much for joining us.

Session 4: Federal Partner Discussion

Andrew Brack, PhD, Program Manager, Proactive Health Office, ARPA-H

Christine Colvis, PhD, Director, Office of Drug Development Partnership Programs, National Center for Advancing Translational Sciences

Shari Ling, MD, CMS Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services

Marta Sokolowska, PhD, Deputy Center Director for Substance Use and Behavioral Health, CDER, FDA

Danielle Turley, PhD, Acting Director, Division of Regulatory & Quality Affairs, BARDA

Susan C. Winckler:

[01:00:30] So it's now time for our panel discussion among federal partners. So if I could have our colleagues from various federal agencies, come join me on stage for this conversation. And I'll note here, we have four folks who are in person and one joining us virtually.

[01:01:00] So we'll get our adjustments made. There we go.

We're almost balanced on the stage. There we go. All right. Yeah. You can just sit right on it. [01:01:30] So, Dr. Colvis, I'm going to turn to you first. All right? So you are one of our folks who is thinking about drug repurposing a lot. Given it's nearly in your title as Director of Drug Development Partnership Programs at NCAT, but add your perspective about what we've been talking about today.

Dr. Christine Colvis:

Ah, sure. Thank you. Well, so, first of all, let me say, this has been a fantastic meeting, and [01:02:00] I'm just so excited at the diverse perspectives that you've actually pulled together. I think that that has been really, really important. And so I do think about drug repurposing a fair amount. In 2016, we had started developing the Biomedical Data Translator System, and we were really trying to initially just assess feasibility. Back then, this idea of actually connecting all the data [01:02:30] was... It was a pipe dream.

Susan C. Winckler:

Right. Well, because it was in little silos everywhere.

Dr. Christine Colvis:

Exactly, exactly.

Susan C. Winckler:

Yes.

Dr. Christine Colvis:

And so we just wanted to, first, understand, is it even going to be possible? And after about three years of doing that, we convinced ourselves not only does it look like it's possible, but we are already seeing signals of that potential, the effect that you could actually get from that. And Dr. Hall, this morning, shared a couple of examples from that. I think Every Cure is using some of that infrastructure [01:03:00] for developing their hypotheses and exploring their hypotheses, and so it's really great to see that expand further.

But before I was even doing that, I had initially started by leading a program that Francis Collins had established with pharmaceutical companies. In that case, we were looking at drugs that hadn't made it to market yet. But because I was [01:03:30] in that role, I would receive phone calls and emails from the community about marketed drugs that they wanted to repurpose.

Susan C. Winckler:

Sure.

Dr. Christine Colvis:

But then, you run into the problem of the incentive issue. There's no business model. So I started to think, "Well, who would benefit from a business standpoint?" And payers come to mind right away.

Susan C. Winckler:

Right.

Dr. Christine Colvis:

And so I was really thrilled that you had Susan here today. I stole her away for lunch to-

Susan C. Winckler:

Good.

Dr. Christine Colvis:

... [01:04:00] to talk with her because it was a rare opportunity for me to talk to somebody from that perspective. And so I think that for me, having us start to think about payers, because if we can actually treat a high-cost condition... This really works best for high-cost conditions. If we can treat a high-cost condition with an inexpensive generic drug just to actually keep patients out of the hospital as much, to

[01:04:30] manage symptoms, and everything, this will be resulting in cost savings for payers, which means that savings can then be used and distributed to other patients.

Susan C. Winckler:

Right.

Dr. Christine Colvis:

Right? And so it isn't just that you're affecting that disease that you repurposed for, but it really should affect many other patients. And so to that end, our most recent effort is now we are on, I hope, the precipice of [01:05:00] issuing a prize competition. So I can't say that it's official. It's not a done deal yet, but we're very close. Hopefully, in the next month, if you keep an eye on nih.gov/challenges. I've been talking with Marta, and Amy Rick, and Shari, and others at CMS to try to develop this competition to support people to submit evidence packages that help to shine a light [01:05:30] for FDA, for NIH, for CMS to say, "These are the generic drug repurposing areas you should be looking at."

Susan C. Winckler:

Really helpful. And you remind me, we actually had a question submitted as we've been talking about this where someone said, "What do you mean there are no commercial incentives?" And so I think just for those who are not familiar with the environment, when the product is off patent and then manufactured by a number of different generic manufacturers, the financial incentives for market exclusivity and then the [01:06:00] financial benefits that you could bear are just different in the generic market. But excellent to be thinking about who it is that does benefit besides the patients, so in addition to the patients, I should say, but with the advantage.

So very helpful, and we'll come back to the payer piece later when we turn to Dr. Ling and think about the CMS side, but I want to turn to my left. So Dr. Turley, you probably deal with drug repurposing a little less daily, but [01:06:30] you still do it, and so help us understand how BARDA or... I'm always reminded. For everyone outside the Beltway, that is HHS's Biomedical Advanced Research and Development Authority. So how are you thinking... And tell us more about the drug relevant repurposing work at BARDA.

Dr. Danielle Turley:

Yeah. Great. Thank you. I also want to echo that this has been a great discussion throughout the day, so really appreciate being able to be here. So I'm going to speak on [01:07:00] behalf of BARDA's repurposing efforts. And again, BARDA sits under the Administration for Strategic Preparedness and Response under HHS. And we work on medical countermeasures or the MCM space. So our focus is on national health security threats, pandemic influenza, emerging infectious disease, chemical, biological, radiological, or nuclear threats, or CBRN threats, and severe illness that follows these threats.

So BARDA's starting question is [01:07:30] often, "here's the threat that we're facing. Do we already have an approved tool or one that we can adapt quickly?" So repurposing is an important strategy for BARDA. It's core to fulfilling our preparedness gaps without building a new product from scratch for

every emerging threat, and we do try to focus on the advanced development. So we want to do... when [01:08:00] preclinical data is over and we're moving into the phase two, three space.

But in additional to repurposing drugs, there is also a great interest at BARDA in platforms to rapidly identify new repurposed drugs. I think there's a new program that's about to be launched, which if you go to BARDA's website, you could learn more about the PICID program, platform to identify candidate repurposed drugs. So it's leveraging [01:08:30] multi-bottle data networks.

So one of the, I think, core issues out there is this no commercial interest that you mentioned, and it's really a big consideration for the BARDA threat space. MCM markets often only materialize upon a declared emergency.

Susan C. Winckler:

Right.

Dr. Danielle Turley:

Development and stockpiling depends on government funding, not market demand, and we're also... USG is often the only [01:09:00] customer for these products.

Susan C. Winckler:

Right.

Dr. Danielle Turley:

I think they really would be helpful for additional incentive programs. So similar to rare disease, which has the orphan drug pathway and has associated inducements such as tax credits, waived user fees, access to funding, market exclusivity. More incentives would help this area. Also, repurposing, we think about [01:09:30] it also as a bridge of... a valley of death for MCM development, so finding a new purpose. Also, if there's a [inaudible 01:09:40] indication, there's a lot more opportunity for drugs to stay on the market and be used during a pandemic.

Also, just want to raise the issue of... I think the RFI talked a lot about chronic disease, and BARDA also thinks about high-consequence acute illness that is associated [01:10:00] with outcomes of a threat. So, example, sepsis and ARDS are common outcomes of threats to pandemic influenza that are also outcomes of other chronic diseases.

Susan C. Winckler:

Right, right.

Dr. Danielle Turley:

We also, additionally, think about additional high-potential areas. So broad acting antimicrobials, and I'm including antibiotics, antifungals, antivirals in this space [01:10:30] that may act on shared

mechanisms across multiple pathogens. Host-directed therapeutics is also of great interest to BARDA. So target the body's dysregulated response, not just the pathogen itself. I think just... Only five minutes.

Susan C. Winckler:

That's all right. Well, you know what I'm struck by? Is I said you aren't thinking about repurposing a lot, and I'm wrong, right?

Dr. Danielle Turley:

Yeah.

Susan C. Winckler:

Because [01:11:00] it's fascinating, particularly as you said with... I think one of the things in saying developing medical countermeasures. Then, if there were some repurposing to use those in other ways, it also broadens the availability or stability perhaps of the countermeasure availability. So you can have a little bit more time.

Dr. Danielle Turley:

Okay. So I guess just to close. We're often thinking about the mechanism and preparedness for relevance and looking at platform-based models. And FDA has put out tools out there like the Platform Technology Guidance in 2024 and [01:11:30] the promise and ability to use real-world data and real-world evidence. But at the end of the day, we still have a gap, and there's a lot of challenges for manufacturers to either get labeling and changes, especially for these high-consequence pathogens that have no commercial value.

Susan C. Winckler:

Mm-hmm, mm-hmm. So it's an interesting... gives us another example of an area where repurposing [01:12:00] could have great value and is difficult to pursue, right?

Dr. Danielle Turley:

Yeah.

Susan C. Winckler:

It's simply developing a new product is a longer timeframe and a broader financial endeavor versus the opportunity in repurposing.

Dr. Danielle Turley:

Yes.

Susan C. Winckler:

Okay. All right. So let me turn to the other end of the stage. And so joining us from the Advanced Research Projects Agency for Health, otherwise known as ARPA-H, Dr. Andrew Brack. You were on this stage [01:12:30] a couple of months ago on a different topic, and yet, drug repurposing came up. So tell us... We've heard a bit. We know Every Cure and ARPA-H interest there, but what else should we know about ARPA-H and a role in drug repurposing?

Dr. Andrew Brack:

Yeah. Well, it's great to be here. Thank you very much for having me on the stage again. Yeah. So, just as a brief intro, ARPA-H was started in 2023, and it's really there to take on those complicated health challenges that seem like too risky, complex, or coordination-heavy [01:13:00] for traditional grants or industry alone. And so if you think of something's awkward, put-together, needs a biomarker, needs a therapy, and there's no way-

Susan C. Winckler:

Mic up.

Dr. Andrew Brack:

... and there's no way-

Susan C. Winckler:

There we go.

Dr. Andrew Brack:

So if there's no biomarker, there's no drug, there's no regulatory path, that's an ARPA-H program right there. And we're really trying to execute on new pathways that don't exist currently. And so the program that I built is called PROSPR. Every program has an acronym. Proactive Solutions for Prolonging Resilience. So this is ARPA's first [01:13:30] sort of program focused on extending health span, right?

And so we know what health span is. We know at some point, we die. Some point, we get diseases a little bit earlier. But before all of that, we start losing our health, our function, our independence, loss of muscle. We fall. We lose cognitive function. But actually, there is no way to measure that as a holistic level, and there's no way to treat it. We're given exercise and protein shakes, right? And so the question is, can we build something that is regulatory-approvable so that when someone [01:14:00] is experiencing that loss of independence, they can be treated?

We know aging is the single biggest risk factor for chronic diseases of aging, far outweighing any other single disease, and it's an amplifier of those diseases as well. And yet, there's no single treatment. So that's what the PROSPR program is intending to do. So it's not just about living longer, but maintaining independence for longer. Imagine being able to function as a 70-year-old like you could when you were a 40-year-old.

And so why does repurposing [01:14:30] become a part of that? Right? Well, there are many different things, but therapeutic repurposing is a part of PROSPR because we want to start building that evidentiary database, datasets that can say, "Here's a therapeutic that is safe, but actually could improve health, not just treat a single disease."

Historically, the TAME trial attempted that under Janet Wilcox's leadership actually to repurpose Metformin, not just for treatment to diabetes, but for health declines associated with aging [01:15:00] by asking the question, "Can it prevent or delay multiple chronic diseases?"

So, in part of PROSPR, we've got a panel selected, which we're going to test. We're going to ask whether health span can be extended with SGLT2I inhibitors, metabolic drug. Rapamycin or Sirolimus, as David was referring to, GLP-1 agonists, and Censavudine, which is a HIV medicine. Can they extend health span? PROSPR will ask that question, determine if it's a yes or no.

The other part. So if we talk about specifics... We've touched [01:15:30] on this with the rare disease cases and the orphan diseases, and there's a really good rationale for treating with rare disease, which is this few people. Aging has the opposite. Everybody ages. Everybody will go through a sort of age-dependent loss of function and health. The problem is there's no regulatory path, right?

Susan C. Winckler:

Mm.

Dr. Andrew Brack:

So we need to build that first. So repurposing is a great example why they're safe. The second point was talking about real-world evidence. We age in our homes. We don't age in a clinic or a medical center. That's [01:16:00] actually when we've lost the bet. So, actually, real-world evidence for aging and health span is going to be instrumental.

The other part is we know the dosages, we know the safety profiles, and we know some of the mechanisms that overlap with, let's say, diabetes or inflammation do overlap with health declines during aging. So there's some biological plausibility there as well.

Actually, repurposing can actually help define the standards of what a health span industry would look like, [01:16:30] right? First of all, we need those accepted measures. We need regulatory clarity. So it's going to be easier by generating new biomarker or clinical endpoints than also trying a new drug at the same time. So we're accelerating a pipeline to get to this evidence.

We can also... Obviously, we know repurposing can be affordable and accessible. Any drug or therapeutic for aging, we're probably going to be taking for multiple decades as a first pass, and so we need to know it's safe, we need to know it's affordable, [01:17:00] and that'll be a different question for CMS versus FDA. It could be affordable, but does it impact what matters to CMS, i.e. hospitalizations, falls? Not just, "Is it just cheap?" And so that's an important point where I think health span and that longevity angle is going to be important.

And so we talked about commercialization. So the unique thing about ARPA is we don't have to worry about it. We can pay for those trials, get the evidence in spite of those, but we do think that that [01:17:30] can create the evidence that will then build the train tracks for a commercial market. The first repurposing drug might not be the most efficacious. We've seen that in every other disease today. The first isn't always the most effective. So we can build out the data. Then, the second or maybe the more commercially viable new modalities, which will take longer, cost more money, can be built on top of that framework.

But I think overall, what I'd like to say is this new nascent science of health span therapeutics. Repurposing is going to be that [01:18:00] early test case. It's going to actually get buyer... sorry, buyer and the public involved to say, "This could be therapeutically tractable."

Susan C. Winckler:

And I think it's a great example, the phrase we heard from the last panel about repurposing human data. Your broader effort is really doing a lot of that, but then we'll learn things that might be applicable in the drug repurposing application that every one of the players on this stage can use.

All right. I want to go to our virtual panelist, [01:18:30] Dr. Shari Ling, who is Deputy Chief Medical Officer at the Centers for Medicare and Medicaid Services. Thank you for joining us virtually. And if you had had the chance to listen, if I were keeping track of something that's been mentioned most of the day, it's the payer perspective. And we got a little window of that this morning, but tell us how CMS is thinking about or engaging in drug repurposing initiatives.

Dr. Shari Ling:

Sure, and it's a pleasure to [01:19:00] be with you. I'm sorry I'm not there in person, and I'm even sorrier that my image is projected behind all of you, so I'm much larger than life. But suffice it to say, really, it's delightful, and it's an honor to be part of the panel and to really have the honor to represent the agency on such an important topic that really represents efficiency, system efficiency, right, from-

Susan C. Winckler:

Mm.

Dr. Shari Ling:

... discovery to application [01:19:30] in a clinical setting, but really, that can be enabled through programs and policies. So just by way of background. So CMS is a agency, part of the department, which has a very specific role as a payer. And as a payer, the largest payer for healthcare and services globally, the agency is able to touch [01:20:00] upon the lives in roughly one in three, if not one in two, Americans in some way.

So in the role as a payer, I think it's important to say that the emphasis has moved away from paying for volume to paying for value. And just to take a moment to focus on what value really means, [01:20:30] it is not necessarily just the calculus of cost that may have been mentioned a few minutes ago, but really, the cost of a product, it is really meant to be thought of as value as defined by outcomes, outcomes that

are not only measurable, but meaningful to the people who we serve, our beneficiaries, you may call them patients, [01:21:00] but also that clinicians and those who deliver care and services can see value of the services that they have delivered.

So it's a from-volume-to-value construct where CMS enters in by way of not only the role as a payer, but in paying for value, we have an opportunity to think about how [01:21:30] do we do this through the statutorily approved and granted authorities CMS has, including by way of measuring quality, quality of the care provided and across the care continuum.

I think from the conditions that have taken place during the course of the day, there is [01:22:00] focus on ambulatory care settings, but the whole notion of a community of healthcare providers in the system to be prepared. We learned some lessons the hard way through the public health emergencies. I'm really glad to see our BARDA colleagues and our ASPR colleagues also being involved in this conversation.

But in the spirit of care and services delivering [01:22:30] to health outcomes, this also implicates and creates opportunities for healthcare providers that is facilities that CMS regulates. CMS does not regulate the practice of medicine. So the agency is prohibited from doing so by statute. I will say I'm very encouraged by the conversations [01:23:00] on real-world evidence, real-world data sources. And there, just to be able to call out not only what the opportunities are, but also what has been missing in our real-world data sources, and that is the areas of outcomes that are really meaningful to the people who we serve.

I will be very specific here because there are often and necessary [01:23:30] disease-specific outcomes that may be thought of in the approval processes for FDA, but keep that for Medicare specifically coverage really goes... It has a different authority that's synergistic to that of FDA in that it's a reasonable and necessary authority. So reasonable [01:24:00] and necessary also implies clinically useful. That is clinical utility. And therein, what is the evidence that a treatment or service is not only safe and effective, but useful in the care and keeping of the person who it's being prescribed to?

So, broad strokes, how the agency works specifically for drug repurposing though, CMS actually aligns [01:24:30] with the FDA's definition of drug and also, for any repurposed product, would also... The fastest pathway to access and approval for CMS purposes will be by way of inclusion, acknowledgement in the FDA label as specific medical indications, and that is what's [01:25:00] referenced in the statutory basis for drug coverage.

Drugs are covered by Medicare under Part D as in dog. There are four parts. A for hospital and post-acute care pay- B for physician services, C is the health plans, and D is the drug plans, which have authority to [01:25:30] make decisions about what is on their formulary, but the process, really, is uniform across drug plans.

Specifically though, the efficient pathway is going to be by way of inclusion and acknowledgement in not only FDA drug labels, but also evidence guidelines that will support the meaningful and clinical usefulness [01:26:00] of a repurposed drug product. So I will stop there and turn it back over to you all in the room. Thank you.

Susan C. Winckler:

Yes. And I think what you helped us with, Shari, is underscoring that for CMS as a payer, the label matters. And so when we were thinking earlier about there are times when that may not matter. But then, also, penetration into clinical guidelines and other components matter and that FDA... Not FDA, but rather CMS is [01:26:30] a source of some of the real-world data that we might also use to generate some of that evidence.

All right. There's someone else on stage who I haven't yet turned to, but that's because we already heard from you this morning, but thank you, Dr. Sokolowska, for... You're one of the primary reasons that were gathered today, and you framed the FDA role in this space earlier today. So take us to the next part of the conversation. In what you've heard today, what piqued [01:27:00] your interest or inspired more questions?

Dr. Marta Sokolowska:

First of all, thank you very much. It was very, very informative day. I learned a lot. So when I started my presentation earlier today, I started with a 2019 meeting that you led and many people in this room, including some on this panel, have participated in. And I think that one aspect that I really like to emphasize is progress. So we had the meeting in 2019. We learned a lot. Now we are six years later, seven years later, and we moved some needle, but have we really made progress? And that's really the question, right? How do we make sure that when we have this meeting next time, we don't repeat the same talking points? We don't complain still that there is no incentives. Dr. Woodcock doesn't have to emphasize the fact that there is no pathway.

Susan C. Winckler:

Well, she gave us a pathway. She said we have to build some of the steps, but yes.

Dr. Marta Sokolowska:

Well, yes. So how do we build those steps to make sure that the next meeting we actually can talk about these steps? And also what I'm thinking about and listening to a lot of these presentations and also being part of a lot of federal discussions, which are really informative, two things. How do we make sure that we are not thinking about repurposing in silos? My organization is doing X, your organization's doing Y, and we might be working kind of on the same thing, sometimes in opposite direction, but we all have a paper at the end. So we reached our goal. How do we make sure that actually we have definition of what is the deliverable that we all want to have at the end of a day? And I think that this discussion actually helped me to really think about it and being very mindful of, I'm from FDA, labeling matters to me a lot. And definitely I'm the one who, well, with the teams and with our leadership and with our great organizations who are trying to figure out the steps, as Dr. [inaudible 01:31:11] have mentioned, to get to the label.

But also being mindful and being able to take a step back to think, "Well, what is the label important for? What are other components?" Maybe summarizing all that evidence that we've been hearing about and having FDA even as part of obviously this discussion when we are having collection of all that evidence, is then opportunity to think at which point the package that whatever is the format of a packet that we would have would be sufficient for engagement with professional organization who are

drafting guidances. And maybe if our goal is education, maybe we should make sure that when we are creating the pathway, we have education component integrated as we are collecting more information. And I couldn't be more thrilled [01:32:00] to hear about the real world evidence, because these are drugs that are on a market. We have real experiments ongoing all the time with these drugs. As we are collating that information, when the data is created enough, good enough, that we have a pathway for FDA labels, but FDA labels shouldn't be the roadblock to whatever is the definition of repurposing success. And that's what I really hope that we can get at the end. Have a common definition of what's the definition of repurposing success.

Susan C. Winckler:

[inaudible 01:32:34], as you noted, it's not five different papers from five different federal partners, but rather where are the parts that are helpful and you have some crossover. And I think, too, we've heard about the merit in drug repurposing efforts may help us improve in other areas, whether that's generation of higher quality real world data and evidence or better understanding in endpoints and learning from all of those systems.

So Marta started us off in reflecting on the discussion, and I'd love to hear from each of you, too, about what's of greatest interest, what says ... You can also, if you want to disagree with Marta, that's okay too. Or the thought on how do we make sure that from the federal perspective, we're starting to pull some of these things [01:33:30] together? Andrew, I'm going to turn to you first for that.

Dr. Andrew Brack:

So I guess there's a couple of threads I'd like to pull on. And I think we're in a technology explosion, whether it's access to data, AI, in silica digital twins. And I think the challenge I would forecast to everyone is Marta's point about silos. ARPA-H's cousin, DARPA, they built the internet. There's only one. One internet. And so I think to David, it was like, is [01:34:00] Every Cure the one that we can plug into and expand to everyone who has an ... And can we add biomarkers into that data set? And all of those things, so there is one resource, one sort of repurposing network that everyone can plug into. And so I think that's something I would put out there is to say, so we're not working in silos, but there's one data set that we can all use, whether it's repurposing, whether it's in vitro experiments that can be added to it, biomarkers.

I think the other thing is, again, reiterate real world evidence. Many people are suffering and then they're in their homes. So I think there's a real opportunity there. And I think we need probably some standards to say what is good enough. A statement paper that someone says from the FDA, "This is what real world evidence looks like." Less ambiguity and less, "We've done these experiments, is this sufficient?" And sort of more clearer upfront statements.

And the second thing I'd put onto that is sort of a provocative idea. It's all about the quality of the [01:35:00] data. And at least in the longevity space and the gray market of sort of GLP-1s and things like that, the wellness community, they are these early adopters to technology. They're monitoring everything in their own body and taking multiple types of drugs. These could be your first adopter to build the thing that is an infrastructure where people will help to build the data sets and the software and the hardware to enable this to go into, let's say, a rare disease indication.

Susan C. Winckler:

Thanks, Andrew. Shari, could we turn to you?

Dr. Shari Ling:

Certainly. So I've been thinking about this and really just want to highlight the opportunities and build a real world data set or data source that actually crosses multiple care settings from outpatient setting all the way to long-term care. [01:36:00] And just to also say one of the areas of work that we started well before, but initiated across post-acute care settings, really introduces domains of outcomes that really matter to the patients. And regardless of what condition or what disease they have, people pretty much want something similar. They want to be able to get about. That is mobility. They want to be able to take care of themselves. That is be able to provide their own self-care. They would like to be able to be clear in thought and to be able to represent themselves cognitively as well. So really we're talking about areas of function that have domains that have been included in CMS legacy data sources that are often not thought about [01:37:00] when you are thinking about study designs and outcomes and things.

I mentioned this because separately we've seen over time that drugs that are developed and tested for indications that pass a safe and effective bar, then as they're utilized and prescribed in more complex older adult populations, things may not go as well because of the complexity of the populations. And some of these new products may end up on the Beers list, which is, it's not as in alcohol beer, it is in named after an individual, Beers Criteria. But this list of potentially inappropriate medications really represents an inefficiency of the system where the very population [01:38:00] that it's intended for use in is not the one that drugs were tested in. So the opportunity here is, as we're thinking about real world data sources and drug repurposing to be able to utilize some of the existing data that comes by way of the CMS legacy instruments and also claims-based data to see X drug, what did it behave like when used in a population? That may be more complex.

This is something that goes well beyond existing clinical trials, if you will, but utilizes existing data. So that may also include outcomes that matter, that could be measurable, but perhaps differently. So I think these are some opportunities for the test and the opportunities that drug repurposing brings to us.

Susan C. Winckler:

[01:39:00] Yeah. So clearly Shari's thinking about how do we move this evidence generation opportunity forward with the resources at CMS? Very helpful. Christine, I'm going to turn back to you. What are you hearing and kind of threads that you want to pull forward?

Dr. Christine Colvis:

So I think the thing that I've been most impressed with in recent months and weeks really is the big difference I think between 2019 and when we had that meeting in 2019 was at that point I feel like we were all just trying to figure it out. A little bit dazed, a little confused, not sure what we were supposed to be doing.

Susan C. Winckler:

I think there's a song about that. Dazed and Confused.

Dr. Christine Colvis:

Something like that. Yeah. And whereas now my sense is, first of all, there's not just an increased level of interest, but I think an actual momentum. And it's happening at the highest levels of [01:40:00] government. And it feels more to me like the agencies are actually working more like an orchestra. I'm a musician. More like an orchestra where we each understand our part. And I'm not supposed to be the loudest instrument the whole time, just supposed to come in when I'm cued to come in and I do my part. An FDA comes in for their part and CMS comes in for their part.

But the other part I think that makes me really happy is that I feel like for the first time, everybody is talking about getting past this thing of the very academic accomplishments that we've been satisfied with historically. And so I think everybody is talking about, "But how do we actually get this into practice?" And that is first and foremost above all else without worrying [01:41:00] even about our own individual roles and the importance of that role or anything, but what do we actually need to do to get it actually into providers' heads and then into patients' hands? And I think that that really now is giving me a lot of ... It's energizing me. It's making me feel really excited about where we're at right now.

Susan C. Winckler:

Yeah. Excellent. Excellent. And I appreciate that thinking about the orchestra and everyone has different roles. So I'm going to turn, I don't know which section of orchestra do you want to be?

Dr. Danielle Turley:

I'm tone-deaf, so-

Susan C. Winckler:

Oh. We're putting you in percussion. You're in the percussion section. But Danielle, as you reflect on what we've heard today, what did you find of greatest interest, particularly in your narrow, somewhat narrow, but thinking about medical countermeasures?

Dr. Danielle Turley:

Yeah. So I'm going to hop around because there were I think several topics to touch on. So from a regulatory perspective, [01:42:00] BARDA is able to have conversations under the ASPR/BARDA MOU. So these are usually high level discussions on a variety of topics, but related to our different threat spaces and different programs. But there's still a gap there. So formal labeling changes, regardless of the data and evidence, still require an industry partner to file for that label change. So there's lack of infrastructure if there's not commercial motivation for someone to partner with the federal government for further development. So riding on that, the no commercial interest. This is definitely a challenge for BARDA, especially for indications like sulfur mustard. We hope we never have to use such products, but-

Susan C. Winckler:

But we want to have them available.

Dr. Danielle Turley:

We want to have them available.

Susan C. Winckler:

Yes.

Dr. Danielle Turley:

We also want to make sure the American public has confidence that these are safe and [01:43:00] efficacious, they're products if they ever have to be used. So we don't want the regulatory rigor of the evidence, there's no lowering the bar. But I think having a pathway that could rely on some of these real world evidence databases, clinical guidelines. We do a lot of engagements also with DOD where we have shared overlap and interests. But getting the conversation and getting the data at that patient level data I think is a real challenge for some of these areas. And I think when there's a broad lens of safety data and historical safety data, can there be other pathways, especially in this MCM threat space, which has a very narrow indication.

And just echoing [01:44:00] the opportunity to have these kind of shared databases and not only to kind of pharmacovigilance safety signals, but ways we can ... it was mentioned earlier when there is something that shows a positive outcome, that collective knowledge is put out there. And FDA has, I think, the Sentinel database. So if something like that could be expanded upon, that is publicly available and forward-facing, I think would be great.

Susan C. Winckler:

Right. Right. So thinking about ... I think your wheels are also turning and thinking, "All right, where are these things that we can pull additional information?" As well as the levers that BARDA may be able to pull to talk with companies and think about the repurposing, particularly in the MCM space.

Dr. Danielle Turley:

Yeah. I mean, especially we want to be prepared for the next emergency. We don't want to generate the data during an emergency. So I think that's [inaudible 01:44:59]-

Susan C. Winckler:

Yeah, we don't place fire hydrants [01:45:00] when there's a fire going on.

Dr. Danielle Turley:

Right.

Susan C. Winckler:

Yeah. Yeah. Yeah. Have everything in place. Well, I want to take the last 15 minutes that we have with this panel to think about what do next steps look like. Each of you, as you said, there's the government operating as an orchestra. And so what do you see? Are there opportunities for collaboration? Other players in the ecosystem? Who wants to talk about what we do next and where we go from here? Christine, would you go first? You gave me the fabulous orchestra metaphor, so you have to lead now.

Dr. Christine Colvis:

[inaudible 01:45:43].

Susan C. Winckler:

Yes.

Dr. Christine Colvis:

Okay, I'll get ready. So actually for myself personally, and I'm on the funder side of the NIH, and I really [01:46:00] am going to look at the sort of clinical studies that we do in this space with a much more directed lens toward FDA, towards CMS, to understand what is that level of evidence that you need. For this specific instance, what is it? What is that bar? So that we are filling the gap that is needed to the extent that we are able to do that. So that it's much more deliberate toward, at the end, like I said, actually impacting patients, actually being used by patients, and not allowing it to simply be an academic project. And I think that, as I said, I mean, Shari and I think we had the first conversation about this 10 years ago. We started talking about this. And Heather [01:47:00] was in some of those meetings. And so now though, it definitely feels very different to me in that the fact that we really are, I think, all trying to follow the same lead and work toward this same goal.

Susan C. Winckler:

So enthusiasm and this sense of coordination and then thinking about directing the NCATS efforts where it has collective impact. Is that fair?

Dr. Christine Colvis:

And even, as I mentioned, so we're exploring the possibility of a prize competition. Stay tuned. Maybe in a month or so. And that is hopefully going to take the kind of information that came from that RFI to the next level. It's not going to be at the level that FDA or CMS [01:48:00] can act on the evidence package. But what it will hopefully do is it will hopefully say to NIH, "These are things where we think it looks pretty promising, but we know it's not enough for FDA or CMS to act on." But hopefully there might be some examples where FDA and CMS look and say, "You know what? Before you invest in more studies, we're going to go look and see what we've already got because there might be something there already." And that would be fantastic because that, I mean, talk about a short timeline, it'd be much, much shorter than if we actually have to do studies.

Susan C. Winckler:

Right. So you're gathering earlier signals, sharing the information, say, "What else? What might we have?" Yeah. Excellent. Shari, may I turn to you? What do you see next steps looking like? Is it further collaboration, digging into some of that CMS data? What do next steps look like?

Dr. Shari Ling:

I think all of the above. [01:49:00] Yes, I am a bit mortified. Christine, I was not a Medicare beneficiary at the time we first started these conversations, and now I am. So time matters. So I think it's a matter of us bringing to bear with true focus on what the opportunities are and also really being able to enable a focus on what the health outcomes that would be measurable and includable and documentable in real world data sources such as the EMR. And to be able to connect the dots there with products that could be used in the context of routine care and services, service delivery. I think there's also an important opportunity or need for us to really understand [01:50:00] where can we move in the journey that we actually would not have visibility into from consideration of a product to actually thinking about, and Marta mentioned the FDA label, and to think about how else, what are the other impediments that there might be to bring a product to market, not bypassing the FDA label, but really where are the hangups in the system? The administrative potholes, if you will.

Sometimes we don't know what they are until someone tries to take the journey and to let us know what those impediments might be. So where we have authority, we can address those impediments, [00:22:00] but also understand what are needed authorities that may not be currently available that could help us in the process. And again, this is about improving outcomes through efforts like this that this team has been focusing on with how to bring repurposing to life for very, very good reasons to meet the unmet needs. So thank you. Over.

Susan C. Winckler:

Yeah. Great. And Shari, you helped us earlier today, Janet Woodcock, who had been at FDA for a long time, pointed out that we have to illuminate the path or build the steps. And I think you phrased it a different way in that you're also, we need to know what are those regulatory potholes that we might fall into. I can imagine, for example, if you have an existing drug that's for an indication where CMS is statutorily prohibited [01:52:00] from covering it, but it's repurposed for something that would help beneficiaries, that's a place where the label would matter a lot. That's a regulatory pothole that we wouldn't want to fall into. We'd want to make sure that it was available. So Danielle, let me turn to you. What do you see as next steps? I already saw your wheels turning and thinking about how we might be improving in the medical countermeasure space, but what do appreciable next steps and where you think BARDA can be helpful in those next steps?

Dr. Danielle Turley:

Yeah. So the existing pathways for labeling changes, 505(b)(2), again, requires a sponsor. If there's off-patent drugs, there's little commercial incentive for initiating those changes. Similarly, I think it was mentioned earlier, Citizens-

Susan C. Winckler:

Citizen Petition. Yes.

Dr. Danielle Turley:

... petition, yes, that lets FDA evaluate data, but doesn't also result in a labeling change. The Project Renewal-style FDA literature reviews I think are also promising, but where they go from there. And like I mentioned already, our FDA/ASPR MOU, it's great to have initial conversations and share evidence early and let FDA know the current thinking on how we're going to attempt to find products for some of these challenging threats. But it still takes a long time to enact these labeling changes. And it's great up until the point of we're asked to undergo procurement or there's an emergency.

So I think in the MCM space, a more structured specific step, maybe [01:54:00] something bridging above the MOU, but more formal conversations with a defined meeting structure where we could pull in some of this real world evidence and tackle, I think, deliberative questions without necessarily having a sponsor yet. So we could maybe further evaluate a path forward. I think there's other challenges, the pharmacovigilance responsibility, liability, that are also not fully resolved. And I think mechanisms to further work through some of these considerations. And with CMS on the panel, I think earlier alignment with FDA, BARDA, and CMS on some of the products that do have commercial indications, ways to get them funded and adopted. Again, just would help break down, I think, some barriers. But for us, it's all about timing.

Susan C. Winckler:

Yes. [01:55:00] Because you might be one of the ultimate hurry up and wait agencies that you've got to have things ready and ready to deploy and we hope that we don't ever deploy them. Yeah. Yeah. Andrew, I know you've been thinking about this and you've said that, but what do you see as helpful next steps? Obviously, ARPA-H has discrete initiatives in the space and then it overlaps in others, but what do next steps looks like from your perspective?

Dr. Andrew Brack:

Yeah, thank you for the question. So I think ARPA programs, one of the core objectives, to move fast. Another thing is we think about treating patients. It needs to be now. And so I think about how can we build something that is streamlined? So I think the collaboration between the agencies so that everyone's sort of in align so sponsors don't produce the wrong data types and say it wasn't sufficient. So clarity of what could get you there, that can be internal, it could be external. So that's one.

And then the second thing is I've heard about [01:56:00] silos and everyone needs to be an expert in their domain and they cannot do everything. And so this is my plug, which is if you want to become program manager and solve the problem, build the team that is needed to break down those silos, come and talk to me.

Susan C. Winckler:

Well, there you go. Thanks, Andrew. Marta, we let you have actually a fair amount of time, more than I usually give you, to think about what do next steps look like. I'm actually excited for the public comment period next because I know we have some great thoughts about, outside of federal agencies, what it is that you all should be thinking about. But how do you see next steps in the opportunity to collaborate with all of the partners here?

Dr. Marta Sokolowska:

So as Andrew mentioned, we do need the team and we need to figure out how to amplify each other's work [01:57:00] and ensure that we are driving together to the same goals and really having the well-defined deliverables to make sure that we can define the value proposition at the end of this initiative, because I think that's really the value. The value proposition can be defined in different ways, but improving patients' health, it's definitely a very important one. And I'm sure that Shari has different versions of a value proposition. I'm sure that we all can figure out how to fit that in.

From FDA perspective, again, we issued the RFI. We are very interested to hear both the comments, it's a summary of the comments, as Caroline so adequately summarized, the additional analysis that is ongoing, as well as hearing the comments regarding the selection criteria that we'll be hearing very shortly, and essentially built on that.

We have statutory authority such as Modern Labeling Act. We have great examples of projects that have already led to positive results such as Project Renewal, for instance, that have led to label updates. [01:58:00] So the question is how do we amplify that work? Understanding that there are also limitations within our divisions. They have plenty of work already as it is. So how do we build the system to help to support it? So I've heard a lot of really great input, some of the potholes and some of the steps from Janet as well. So I'm really looking forward to hearing also regarding the comments on the selection and other public comments because it is not just FDA initiative. It's not only government initiative. It's really public health initiative. And their voices are really important.

Susan C. Winckler:

Excellent. Well, it's been so helpful to be thinking from all of these different federal agency perspectives about how to solve a problem that I think we acknowledged earlier today requires federal government intervention and coordination. So we appreciate, Shari, you dialing in virtually, and for each of you joining us on stage. [01:59:00] I'm going to look forward to announcements. I think I'm supposed to look at NCATS and maybe I'm supposed to look at BARDA to keep an eye out for things. And obviously FDA will continue to work in this area and Andrew's going to organize a working group. Well, okay. I leaned a little too far there. But there's opportunity for the continued collaboration and obviously we talked about that there is significant government interest. So let's thank our federal government panel.