REGULATION FOR THE MODERN ERA OF MEDICAL INNOVATION

Announcer 00:00

Thank you for joining us. Please welcome the panel to the stage.

Steve Usdin 00:24

Hello. The clock's ticking down there, so I'm just going to get started. And I'm not really going to do proper introductions for my panel because if I gave everybody the introduction that they deserved, we wouldn't have any time to talk. So, very briefly, Michael Davis, director of the Center for Drug Evaluation and Research at FDA. Adora Ndu, chief regulatory officer and executive vice president at BridgeBio. James Frith, minister for health innovation in the United Kingdom. Isn't that cool, having a minister for health innovation?

James Frith 01:02

My work here is done.

Steve Usdin 01:06

And Karim Mikhail, director of the Center for Biologics Evaluation and Research at FDA. So, we're here to talk about regulation, and I want to start by saying that I think that regulation is a very unfortunate word because it conjures up this image that there's some kind of giant valve somewhere, and that regulators crank it open to speed things up, and they can turn it the other way when medicines start flying around the room too much. But to me, what regulation is—or what regulators do—is it's a search for truth, and they're answering critical questions. Are the data telling us what we think they're telling us? How do you balance uncertainties about benefits and risks against unmet needs? How do you make the path from scientific discovery to medicine as efficient as possible? And regulatory innovation, to me, means inventing better instruments to provide the answers to those questions, which are almost never easy and almost never as obvious as people who are on the outside think that they are. So, I'm going to start with one example, to me, of how you make regulation real, how regulatory innovation improves the lives of patients. And then I'm going to ask all of you to start with—to give an example. So, my example is from the early 1990s. At that time, FDA generally required evidence that a drug helped patients live longer or feel better in order to get approved. For people dying from AIDS, that meant waiting for deaths to pile up. It was

unacceptable. FDA developed a new instrument. It made approvals based on a surrogate that was reasonably likely to predict clinical benefit. Later, that got called accelerated approval—another kind of misleading name, but anyway. And there were similar policies that were adopted around the world. And they turned AIDS into a manageable condition and saved millions of lives. In the absence of accelerated approval or something like it, this wouldn't have happened. And that same way of thinking has transformed oncology and some other areas. But it's also a reminder that these tools can be imperfect. Some surrogates don't pan out. That's why confirmatory trials are needed. They close the loop on the search for truth. And so that's a lot more complicated and interesting than just turning a valve, right? So, I want to go down the line to start with, and ask each one of you to give an example of something—a regulatory innovation that is or could make lives better for patients. And if you can, what you learned from it, and maybe what was it that had to change? What kind of thinking had to change in order to make it happen?

Michael Davis 04:17

Okay. Well, I guess I'm first in line. This is an excellent question, and I've thought a lot about this question. Accelerated approval was obviously the first thing that popped into my mind, and it's almost like trying to codify—because if the goal of regulation is to protect patients in the end from treatments that are unsafe or don't work, then that's valuable for society. But then, on the other hand, these cases of uncertainty—I think accelerated approval is a great example of a risk-proportionate approach to regulation, and it's been a very successful program. So, to date, CDER's approved over 350 drugs and biologics based on a surrogate endpoint. And so, I think that's a good example. Thinking of another one, I would say in the realm of expedited programs, I think breakthrough therapy designation has had a really big impact. In CDER, we receive so many INDs and applications and meetings at an early phase. And I think breakthrough therapy designation, the process of applying for it and reviewing it and considering it, brings attention to really promising programs at an early stage to senior leadership within the center. And with that additional attention—and there are also various sort of features or benefits of receiving breakthrough therapy designation, but I think there's—rolling review and other ways. But it puts the staff and really the whole center in the mindset of, all right, this treatment has—there's preliminary evidence that it could be game-changing for patients, and it forces people into thinking about what's the most efficient way we can support the development of this treatment and make it so it's available for patients. And there have been too many cases to list where, for serious and life-threatening conditions, the existence of breakthrough therapy designation, the additional attention, a priority review, rolling review, these sorts of features that are often associated with breakthrough therapy designation, have dramatically sped up the time for getting new treatments to patients. And that's just another example of an expedited program beyond accelerated approval. I see that as accelerated approval accepting that people may be more willing to take a risk. And if you interview patients, there is a greater likelihood of taking a risk for a treatment that we think will work, but we're not quite there in terms of having the complete evidence of efficacy. And breakthrough therapy designation is a little bit different, but I think it does support a very efficient program.

Steve Usdin 07:22

And I think two other things really interesting about that. One is that when it was first announced, there was a lot of skepticism that it would have—how much impact, and it has had a lot of impact. And the other is that it's a signal for investors that this is something important, and so it helps propel things. Adora.

Adora Ndu 07:38

Yeah, you both touched on points that I agree with. And you started this by talking about how regulation plays a role in this search for truth, being able to inform benefit-risk decision-making. And so, I would highlight the role that patient-focused drug development has played in drug development as part of advancing regulation and enabling us to innovate in a way that really allows us to serve, informing the benefit-risk decision-making. And so that was introduced—the PFDD really was introduced under PDUFA, and that has led to a number of things from the agency, from guidances, patient-focused drug development meetings, and, from a development standpoint, engaging with patients from the beginning to understand the disease, to define endpoints, to understand our patient population targets, enrollments, et cetera. And then also pulling that through in the regulatory process, the regulatory decision-making. So, PFDD and the role that it plays—not just from a development perspective, but also from a regulatory perspective and of course from an access perspective—is one advancement that I think has really transformed how we develop treatments and I believe will continue to transform it. One example that I can think of was with an earlier product in PKU that we were developing in my prior life, where we met with the agency, with a group of patients, with PIs to really talk through the disease, to talk through management of adverse events. And in that moment, the agency realized what was going to be palatable and manageable from a risk perspective by a patient, and that informed label, that informed post-approval requirements from the agency. And so, the more we can identify ways to ensure that we are listening—we are not just listening, but we're actually incorporating what we're hearing in our development. We are considering that in the regulatory requirements. I think we play a much bigger role, and we're able to better serve the patients. I mean, we're ultimately all patients at some point in our lives, and so it's really critical that we are able to incorporate that in an intentional way throughout development.

Steve Usdin 10:00

So, we didn't coordinate this in advance, and I know it gets harder as we go down the line because the easy examples have all been taken. But James.

James Frith 10:06

Well, thank you, and thank you for calling me cool. That'll be the bit that reaches my family and the children's take-home. Well, I'm going to go for the challenge that you outline as coming third of four. I'm going to take a more personal approach to this and confess, or admit, to having had childhood epilepsy. I had meningitis as a very young boy. I was then put on a series of trial drugs that concluded eventually with me, for the best part of 15 years, taking four to six tablets a day. My seizures were only ever between 4:00 a.m. and 6:00 a.m. I had seven in total, including during a sleepover, bunking down in my younger sister's room, and I had managed to somehow get a grip, a control in some form, to steer my act of convulsion, my seizure, to wake my sister up, who went and fetched one of—my mum or my dad—to come and tend to me. And the transformative—if I take that point now as a dad of four, with an eldest daughter having tests now for epilepsy—that there is an entire sector and an entire ordination of getting safety and drugs possible to transform a life condition that I have never, ever been held back from post-adulthood, really, in terms of once I'd reached about 20, 21. There were very few side effects. But it did have a huge impact on my own development at the time, my behavior at school, my cognitive attention. Now, some may say I may be oblivious to the impact of that still and have impact or consequences still to that. But the fact that there were regulated substances that I could take that ensured that I was not held back, that I have gone on, and I hope achieved, despite that experience, and that then that allows me now, in turn, to speak with,

I hope, understanding, with empathy, but also the impatience that we should have in this place for how we make the dream the do, how we turn what we believe to be possible into reality. And I think regulation and regulating in this space is about that art of the possible—of course it is—but it is regulation as an enabler. And on an individual level, taking somebody whose human experience can be transformed, can be turned around, can be put on a different track as a result of that. And so, I feel very honored to be in the position I now am in, where my job is to expect more of you all because of the experiences that we all benefit from—and to the point that was made, we have all been patients, or we all will be patients—but to expect regulation as the enabler for things to take less time, for more people to be accessing the benefits of that regulated innovation, so that our human-evolved state gets stronger, better as a result of it. And I hope I can speak to that authoritatively on a personal level in such esteemed company.

Steve Usdin 14:03

Karim.

Karim Mikhail 14:04

Yeah. It becomes very difficult now.

Steve Usdin 14:09

That's why we put you last, because we knew you'd come up with something.

Karim Mikhail 14:11

So, first of all, I'm one of the few people who have been two to three decades on the other side of the review desk. So, I've been not on the regulator side, but on the regulated side. And I used to imagine that it's way easier to be on the regulator side, right? It's very difficult when you're the subject of the regulation rather than—but I actually realize it's times more challenging. But okay, it's the challenge we have. But I want to pick on a very recent example of a regulation that I believe was very close to making it happen and seeing it see the light, which dates from this year, which is really the individualized gene therapy draft guidance that came out. And the story for this is when the Baby KJ case was announced—and you've seen the national excitement about the promise of gene therapy: What can this really deliver? Then everybody said, "But now there is an incredible silence." There is no second Baby KJ, third, fourth. Why are we where we are? There was a concept around a plausible mechanism that you can actually do that, right? So, the concept, yes, we accept, but there is no path. And this is where, to me, almost regulation started to have a new meaning. It's almost like a bridge—a bridge that takes you from a place where it's not possible, or it's a vision, right? You can see it, but you don't know how to get there. The regulation is getting you there. So, the team took the concept and said, "How can we make sure that there is a true pathway for individualized gene therapy?" We know that the disease is monogenic, but there are so many variants, and we cannot expect that every sponsor for every patient will come with a completely new BLA, have to run all the clinical trials. What is the concept that can be developed? Well, the concept is how can we use AI and bioinformatics to set thresholds on what you can demonstrate in terms of clinical efficacy, not in the clinic, but outside of the clinic. And if that threshold is defined, if you can meet that threshold, all of a sudden, instead of submitting a full BLA, you can actually have a manufacturing supplement to say, "I'm able to deliver on that promise," and then we can help so many patients. So, to me, that was just a great example of saying regulation can make things happen. It can provide true solutions for patient-by-patient cases, not just a population. So, I've had the honor of being close to that. Zero credit for me, just to be completely

transparent. It's the Office of Gene Therapy, who have been incredibly creative and worked very hard to ensure they deliver on this promise. In rare diseases, they take every patient case very seriously because each life counts. So, that's the CBER example.

Steve Usdin 17:30

I'm sorry. I neglected at the beginning to say also, but some of you must have been here before because some of you are already doing it, that if you have questions, there's a QR code in your program, and somehow or other, you click on that and you ask questions. People are doing it, so it works. So, I think that what Karim said is really a good segue to what I was thinking of going to next, which is rare diseases. That's really the frontier case for regulatory innovation. And I think it's also a place where there's a clear need. So, regulatory agencies around the world have struggled with this. In some cases, there have been very creative approaches that have helped to get drugs developed and to patients. And in some cases, there have been failures. And I think broadly speaking, the consensus of the rare disease community is that there's a lot more that needs to be done. So, I want to start with Adora and kind of ask you for an example. What's an example of a stumbling block or something where the regulatory system isn't making it possible to turn science into medicine, or not making it possible to do it as efficiently or as inexpensively as it should?

Adora Ndu 18:52

It's a good question, and probably building a little bit on what Karim has talked through—we need a regulatory framework that is right-sized for rare diseases, ultra-rare diseases, nano-rare diseases. We don't have that. And so, in the absence of that, we often try to make the regulatory framework fit within the constraints of development challenges for rare diseases, and it's very, very difficult. And companies like BridgeBio, that are focused 100 percent on rare diseases, are constantly navigating these very challenging paths where, as we all know, there's usually no regulatory precedent. There's usually a lack of natural history. And so, there's a challenge across the board. It starts from day one, understanding what are we even evaluating? What are the endpoints that we need to measure? Are they objective? Are they subjective? Are they accepted by the regulators? Because it's not a GLP-1, so we don't know. And so, we need to engage in the dialogue with the regulators, not just FDA, but globally. And the FDA may have one view; EMA may have a different view. And so, that complicates an already very complicated program, where you're—for starters—trying to find patients. And so, for one example, we're developing a gene therapy for Canavan disease. There are about 1,000 patients across the US and the EU. And within our two sites, we are literally flying patients across the world to enroll in the study, and there's a very narrow window for when they are eligible to be enrolled and to receive treatment. And so, you're sort of running against many, many barriers. We're trying to serve the patients that we know may miss an opportunity to receive treatment, and missing that treatment could mean that the disease continues to progress. It could mean an increase in mortality. It could mean many different things. And so, working very closely with these communities to identify the fastest way to get into first-in-human, which I know we're going to talk about here. In some cases, can we go directly into patients? And being able to work with the regulators to align on why it makes sense to go directly into patients versus into healthy volunteers. And then identifying the tools that could be used to expedite the development program—biomarkers, for example. Most rare diseases are genetic, and so, to the extent that we understand the biology of the disease and we understand the targets and the mechanism of action of the treatment, if a treatment is targeting the root cause of disease, we should be able to align on a streamlined development path. And that's often where

things get caught up, is that alignment. How do we know that this biomarker is a reasonably likely-to-predict biomarker such that you could advance the development program faster?

Adora Ndu 22:00

It used to be that what we would hear from regulators was that, "Well, since you're the first, you actually have to go and generate clinical data, and you create a path for everybody else." And that's challenging because quite often in rare diseases—for some rare diseases, especially slowly progressive diseases—you're not going to see those clinical outcomes for years. And so, it's not feasible to run a 10-year study and to expect patients to wait that long. And so, we've made progress. The Rare Disease Framework that was just announced a few years ago has a lot of promise. I think there are a lot of proposals included there that will allow us to get to the right-sizing of regulation for rare or ultra-rare diseases, and some of the initiatives coming from CBER for nano-rare diseases, because it is absolutely necessary. And I do believe that regulation and innovation can and should coexist. And the agency has made significant progress just in this year alone in—and it's partly, I think, because we have folks like Karim and Mike who have a breadth of exposure and are able to balance regulation with innovation and thinking through how to actually implement. And of course, once you implement, we want these changes to be sustainable and to have an actual, tangible impact. We want to be able to look back and say, "Because of these changes, we were able to get these treatments that are safe and effective for these patients." And the role of FDA is not—you started by talking about regulation being a bad word, not a bad word, but a word that sort of evokes a certain kind of emotion. And we need to be able to transform that so that regulators are also partners and enablers. And we're working hand-in-hand to actually get treatments to patients. That is why we are all collectively here.

Steve Usdin 24:02

So, I don't think there's anything that you said that anybody on the panel or in the audience is going to disagree with. But the question is—and I think that most of the things that you've said could have been said five years ago or years ago. There's been some progress, but it's frustratingly slow, I think, for people that care about this. So, maybe starting with Karim, James, Mike, what are you going to do to make good on the promise that you're making and that Adora is calling for, and the patients need?

Karim Mikhail 24:39

It's a tough challenge because there have been many incremental steps to try to improve the Rare Disease Framework. We are at a point where I believe, with the pace of the science, we need to make a true quantum leap, 10 steps in one, which means we need to take all that we learned already from the 18 programs that are being implemented in the FDA—because they were successful—but to actually build on this everything else that is necessary. And when I say everything else, it means, one, the scope of the clinical development program from pre-IND up to actual access to patients, and understanding where the key barriers are today. And again, for me, the key barriers are just clearly defined. We have a clear issue with clinical trial design. We have a clear issue with endpoint definition. If you look at most of the complicated 11th-hour outcomes and what we're sitting and debating, we're debating whether the clinical endpoint is the right one or not. Is it clinically meaningful, yes or no? And I want to say it's not the mistake of anyone. It's just that, unfortunately, most of these therapy areas, you have had, during four or five years, significant evolution in the science. So, your trial started with some sort of an understanding of what you need to be measuring, and by now you know that this may not be perfect. That's why we need to step

back and say, “This is not now about tweaking right and left. This is almost rethinking how to approach it,” which I believe needs to start with what the disease is about. What are the prognostic milestones? Because we end up with a clinical trial design and an endpoint that does not always correlate with the life of the patient. Like, what are we trying to impact today? So, that’s why this approach will have to be encompassing all those different levels. I want to make sure also to give a balanced view of what needs to happen, because the pendulum—what I’m worried about—is that there is this perception that today it’s very restrictive, but it actually needs to go all the way to the opposite side, which is honestly not rigorous, not scientifically sound, and potentially not useful—I don’t want to say unsafe, but not useful for the patient. So, we have to make sure that while we’re doing this, there will be a standard. It will be a fit-for-purpose standard. This does not mean that for rare diseases, we’re not going to have a standard. We will not be able to accept study conduct that’s not acceptable. We will not be able to accept an endpoint that’s missed if it was truly agreed upon. So, the key elements of a clinical—a successful development program will have to be delivered. We just have to agree on what is attainable evidence—truly attainable evidence that is connected to the life of the patient, not to some theoretical benefit that is in a textbook.

Steve Usdin 28:00

So, James, I want to hear what you’re thinking about this. And also, just to kind of point out that you’re in a—besides the fact that minister for innovation is really cool, that the UK is in a different position from the United States because you have a centralized health-care system, you have a biobank, you have these kind of resources that allow you to do things that either can’t be done elsewhere or can be done much easier.

James Frith 28:24

Yeah. I think that’s right. And part of the job this week has been to make very clear the unique proposition that Britain presents to the US, to affirm and strengthen that relationship, that brilliant relationship that we understand, and the work that we are doing in this space together, in collaboration, not competition. But as minister for health innovation, it is not just simply about pointing to or empowering of innovative device or medicine. It’s also, I think—part of the job is innovative thought and giving innovative thinking a chance to shine, to your point about some of the creative answers that have come about with some rare diseases and drug discovery, and it’s really, really important. My three priorities in this work is about the digitization of health—and I’ll come onto detail on each—around health inequality, second, and then of sovereign capability, which is what we do uniquely in Britain, but also crucially what we do then with other sovereign territories and close allies and partners, obviously, US being the first and best ally for Britain. The digitization of health: One of my responsibilities is the NHS app. A population of 67 million, with some 30 million downloads. Device of choice, access to NHS app, the introduction soon of a single patient record, the empowerment of data through an individual patient’s records, and a national conversation about what data can bring as a national asset, as an unending mineral wealth for the UK because of the point Steve makes about the singular focus or the singular arch that is the NHS. And so, through that work, I’ve commissioned the innovative thinking of how we would begin to recruit for clinical trials through the NHS app, which reaches into 50 percent of the population with downloads. Also, how we then support that in the speeding up of clinical trials, the safe, faster, better clinical trial program. We’ve enjoyed success recently, down to 100 days for commercial clinical trials. We don’t stop there, but it’s a leap forward from the 150 or so that it was at.

James Frith 31:01

Health inequalities—and this is the rare diseases point that Steve spoke to: In that moment of diagnosis or the worst news of your life, if in fact you're told it's a common drug that's required for your common disease, and you join a large boat with everybody having received all that bad news before, but they are on their way to solid treatment, accessing drugs that are known. If in fact it is a rare disease, then that health inequality compounds that moment, and you are in the worst news of your life, but it is singularly worse than any prospect of drug discovery or treatment. And I think that health inequality is something that drives me, it drives the government that I represent, because we haven't done enough for rare diseases historically. There does need to be creative thought given to how we incentivize the private sector, as well as working with the NHS and public sector, whether that's some form of pairing, whether that's incentive through R&D or tax credits, and the market needing to be stimulated to come on board with that. It's really, really important. And then the final point is really about sovereign capability, and I think when we have as good a relationship with the US, it's building on that and testing each other's ambition, testing each other's speed and capability, understanding the strengths and uniqueness that we each bring, whether that's through the significant scale and investment in the US system or the singular data points that the NHS has, and a whole host besides. That's really important, and that's the sovereign capability working with others point. But it's a really exciting brief. And this week, I'm very encouraged by the direction of travel that we're going.

Steve Usdin 33:17

Mike.

Michael Davis 33:18

Yeah. So, you want to learn a little bit about how we're implementing—

Steve Usdin 33:22

Yeah, basically. How are you making good on the kind of expectations that Adora mentioned? Everybody who's in this community, in the rare disease community, has been talking about these needs for a long time, and they're not mysterious. But the question is how do you put the solutions into action?

Michael Davis 33:42

Yeah. Well, first, I want to say that we are laser-focused and more than 100 percent committed to this. Just even right before this meeting, I had a meeting with Karim and Amy Rick. Well, I guess before I get to talking about specific procedures that we're doing, I'd encourage people to watch the video from the Reagan-Udall Foundation meeting about the Rare Disease Framework from a couple of weeks ago. It was truly powerful, just hearing the thoughtfulness that went into the proposals people were bringing in. A lot of the people who went up there were parents. One that even chokes me up thinking about it was a father whose daughter has one of these, I guess you could call it nano-rare, extremely rare conditions, where he's just basically begging for some movement towards a treatment for his daughter so she still can have the movement in her hands to be able to propel her wheelchair, that things have gotten that bad, and just before she completely loses movement. And it's just so touching seeing the commitment, and just as a parent, putting myself in their shoes. So, we're moving very quickly towards implementing, and where things in government sometimes—well, they basically always take longer than people would really like them to, and there's reasons. But this, we're moving very quickly on, and we formed four specific workstreams. And I have to say, we had the volunteers and nominations for people to be in these

workstreams. It was very tough just even deciding who could be on there because there were so many people who were really committed to supporting this effort. But like most workgroups, they can't get too large, or else it can sort of bog things down. But we're trying to be agile. And so, these workstreams will be starting imminently. And a charge, Karim and I, and Amy Rick, and with full support from the commissioner's office—we're going to be really laying out the vision that we want people to not start by thinking, what are the regulations, how can we fit in it, but thinking almost like a blue-sky approach of what if there weren't—what would make sense for FDA regulation of products for these conditions? And I think a lot of it is going to be kind of like accelerated approval, where there's increased tolerance for uncertainty, where perfect can't be the enemy of a meaningful benefit for patients. And I think a big challenge of rare diseases is, like Adora mentioned, a lot of times, I think around half of our approvals now are for rare diseases, but there's tens of thousands of rare diseases with zero treatments available, and more rare diseases keep—I went to medical school back in 2000, and I learned about a lot of rare diseases, but I'm always learning about new ones that weren't even described when I was in training.

Michael Davis 37:06

And so, there's a lot of work to do, and challenges are related to—as Adora mentioned, one is the lack of precedent, that a lot of more common indications have long decades of history in drug development and in developing outcome measures and fine-tuning trial design, and just when we're thinking a lot of these rare disease applications will be the very first time it's being developed for often very serious, life-threatening conditions that often affect children, and it may affect their lives. And just really thinking about what makes sense, what's attainable, because I don't think anybody wants to approve things where we just know it doesn't work, because that doesn't do anybody any good, or where the benefits don't outweigh the risks. I really like the benefit-risk framework for thinking about drug approval, where you consider the seriousness of the condition and available treatment options in the regulatory decision-making. So, we'll be launching imminently four workstreams within the FDA, and also having a series of roundtables with external stakeholders, such as patient advocacy groups and industry, because we really want to hear feedback, such as we did at the Reagan-Udall meeting, and we're also receiving a lot of comments in the Federal Register notice. And we're working full speed towards, at the end of—sometime in the first quarter of next year—being able to have actual product to be able to share as a result of the effort, and really sort of move into implementing it. And I think part of it is going to be looking at, as Karim mentioned, there's 18 programs related to rare diseases across the centers, and there's a lot of really great work and really great thinking that has gone into that, and a lot of successes. But in many cases, there's, say, a pilot that may be open for a small number of programs per year. And really, a lot of it is taking the innovative thinking and approaches and making it the norm across—because rare diseases, inborn errors of metabolism, that's definitely an area with a lot of rare diseases, but rare diseases are part of almost every therapeutic area within the center I run. And so, training's obviously going to be a big component of it, but really tapping into the internal and external expertise on rare diseases so we can do the right thing for patients.

Steve Usdin 40:02

So, I want to say just very quickly that it's really refreshing and kind of old school the way that we're seeing FDA approach this compared to what we saw a couple of years ago, where there was a less deliberative, a less interactive approach to decision-making. So, apparently, a lot of you did figure out how to use the app and you gave me a lot of questions here. I apologize in advance. I can't get to all of them. But several of them had to do with AI. And the question I have, obviously—okay, everything we're going to

do is going to be transformed by AI. The question I think for you guys is how do you ensure transparency and accountability with the use of AI? For example, when AI is used to make regulatory decisions, do sponsors, do the public deserve to know how and why AI is being used in particular ways? So, that's kind of shifting gears from what we were talking about before, but I wonder what your thoughts are. Start with Mike.

Michael Davis 41:12

Yeah. So, just in terms of the framing of the question, I would say that AI is not making the decision without the expert clinicians. I think regulatory decisions of health and life and death in many cases, we feel it's imperative to always have physicians and other scientists and experts in the loop. And really, the way I see it, AI can be an extremely powerful tool for the way we do our work, for making sense out of complex datasets, for organizing information, for being sort of a second set of eyes to look at things, to make us be able to work more quickly in what we do. But we make it very clear that reviewers need to stand by—if content is being drafted with the assistance of AI tools, that they need to be able to stand behind the accuracy and verify it. We have quite elaborate AI infrastructure within the FDA. Within CDER, my center, we have—across all the super offices, we have representatives in a CDER AI council, and we liaise with the commissioner's office on AI governance and infrastructure and think through these issues. And we're moving very quickly, and already the vast majority—I see metrics on reviewer utilization and token usage and so forth—and the vast majority of reviewers are using it in their work now. And we have a lot of very smart people within the centers and within the commissioner's office who have technical expertise and are developing innovative tools and agents and approaches to not only help assist with the review work, but also help with verifying the content, because we don't want to make mistakes when we're talking about decisions so consequential. So, I would say that integration—just as probably all the industries at this conference, like everybody, we're moving very quickly towards adoption of AI in our work and trying to do it the right way.

Steve Usdin 43:40

Any other comments really quickly, because we're moving to the end.

James Frith 43:45

I mean, trust is vital. And I think your question of transparency needs to be met with a straightforward—absolutely, transparency is key, and we need to have the argument with, or make the argument, rather, on the need for AI, but the adoption of AI safely. Innovation can only move at the speed of trust, and unless we take people with us on that journey, then adoption will be harder. We already have a challenge with adoption at scale and some change behavior issues and challenges with people readier than others to adopt AI. But I do think the regulator has an extremely important role to play in that. The same is true for our legislature as well. As AI moves so quickly, as tech moves so quickly, it presents challenges to the lawmakers of the land, and it especially presents challenges for the regulators, and they need to be evolving with innovation. So, that's new models of sign-off and approval. It is being readier to, if trusted and tested once, not to expect, in the case of the NHS, to have to go trust by trust, NHS trust by NHS trust, to prove again and again the same thing that we know to be valid and approved elsewhere. I can see you want to move on, but it's hugely important that we keep up and not let the analog system deter us.

Karim Mikhail 45:32

Just very quickly. From a CBER perspective, 90 percent of what we deal with is NMEs, new molecular entities. So, obviously, we use AI, but the reality is most of the time there is no precedent. The machine goes back to read. There's not much in the machine, right? So, there is always a requirement for a human being to basically—and as Mike said, we have a rule that whatever is generated by AI has to be reviewed, has to be accepted, has to be signed off by an expert in the field. Having said that, I want to also present different parts of the work. We have so many, for example, single-patient INDs. We have so many cases where you need human attention because that's just a unique case that needs to be studied. You cannot just feed that into the machine and the machine will come back and say, "Here is what you need to do." You actually have to study it yourself. So, nothing to slow AI, but we need to continuously generate data to feed the machine. We heard about rolling IND within the expedited IND. One of our ideas: How can you feed the 50,000 INDs that we have historically to support early decision-making on some of that stuff? So, all of that is at hand, and then it needs a lot of wisdom to decide when you need to fully depend on AI or when you need to truly do something different.

James Frith 47:01

But I don't think it's about fully depending on either/or. I think it has to be a blended approach. And actually, deployment of AI as a means of triage and tech as a triage is a hugely powerful way of addressing certainly where there are perhaps early identification, where there is a much higher detection rate success. I'm thinking of some of the systems being put into the NHS digital offer around skin cancers and scanning of skin markings with a really high, very confident percentage, higher than the accuracy of the human eye even. That's not to say you forfeit or discount the involvement of human clinician or clinical oversight. Of course you don't. But it is a way of really triaging and then refining the information that you're putting to the clinician for assessment.

Adora Ndu 48:05

One thing I would add to that is, from the FDA perspective, from the outside looking in, we see meaningful opportunities for AI. One example is the issue of inconsistencies and the role that AI could potentially play in decreasing the challenge with what I've heard referred to as the "reviewer lottery." And so, while you still need the human element, absolutely—because ultimately somebody has to make a benefit-risk determination—I think that there is a role for AI in helping sort of inform, educate in the moment.

Steve Usdin 48:55

And to create an institutional memory, because one of the things that—I've been watching FDA for three decades, and one of the things that I've seen is that the institutional memory for many years was, well, ask Janet Woodcock or ask Bob Temple or something, how they did it. Well, neither one of them is there anymore, right? And whoever's making those decisions now isn't going to be there at some time in the future. We've got 10 minutes left, and I've got a lot of questions here. Interestingly, most of them are around rare diseases and pediatric rare diseases. Here's one that I think encapsulates some of the thinking, and I would like maybe for you all to give a brief kind of one- or two-sentence answer, if you can. I know you can't, but if you can. So, I'm the mom of a child with a terminal rare disease. He's losing his memory, vision, and mobility. His life could be almost half over. We've been working for seven years to get access to promising science. What advice do you have for me and families like mine? What should we be doing? Founding our own biotechs, raising money, seeking off-label use of existing drugs? I know you can't give a comprehensive answer, but thinking about that in real terms, what are some of the things that you—kind

of the advice or the things that you think somebody who's in that situation, because there are an awful lot of people who are, can do now?

Michael Davis 50:13

I guess I can take a first stab at that. So, first of all, I'm really sorry. This sounds like the kinds of cases that were being talked about at this forum. It's just heartbreaking. And I would say one approach is, without knowing the condition, if it's a named condition, sort of connecting with other families who are also—there's sort of power in the group, to connect with other people. Because even with very small conditions, with technology, people can connect, and they do form alliances. And the rare disease—I don't know if infrastructure is the right word—but it's very elaborate and robust, the number of groups and advocacy groups and umbrella groups and so forth in this space. And so, I think really being part of and connecting with other people who are dealing with analogous situations is good. And then, I don't know, without knowing any more details, if there's a product under development, you can contact the company and ask if they have an expanded access program or if there's a trial to be enrolled in. If there's absolutely nothing for it, then I would say look at researchers at universities who are studying the condition and connect with experts in the field. The Baby KJ case was remarkable, but I also thought that a lot of people may be in similar situations and not know how to make that happen for their own children, and just that it would take a lot of sort of knowing people and resources and just knowing how to navigate that space to be able to make that happen. So, those are just a few thoughts.

Adora Ndu 52:02

Yeah, Mike, I think you did a really nice job covering it. It's hard—as a mom of four myself, all of the above, right? Because this is your child, these are your children. And then, just from a developer's perspective, we ventured out a couple of years ago to look for treatments that were on shelves. And there are many. There are many treatments that have been shelved that have promising science, but perhaps are not commercially viable. And so, in academic institutions, pharmaceutical and biotech companies—and there needs to be an effort to identify these treatments and to bring them forward. And so, my hope is that at some point there will be some sort of public-private fund that enables these treatments to advance. In the absence of that, I agree with what you've suggested, which is connecting with the advocacy organizations, reaching out to researchers that have ongoing research in this space, contacting companies that may have these treatments in their pipelines. Organizations like CZI also work very closely with families that are—it's fascinating meeting parent after parent who have gone from perhaps being in the arts to now being a drug developer because nobody is developing treatments for their child. And there are so many of these because there are thousands of rare diseases without a single treatment. And so, really, I see this as a public health issue in the US and globally. But there are resources. The resources may not be perfect. Working with FDA, EMA, other health authorities, MHRA, expanded access, and just really excited to hear, Karim, about the guidance that was just issued because this is exactly the type of case that hopefully it will make a difference for these families.

Karim Mikhail 54:13

I just want to offer one suggestion. Just start with the right academic institution that has expertise in the area you're going. Because you can get distracted in a million things, and there are so many things you can do, but remember, without a hospital center that can administer something to your child, you can go nowhere, right? The beauty about this approach is once you have a contact there, they are exposed to all

the research in the space. So, if there is a sponsor that's working on something, they will know. If there is nobody, they can actually help you think of how that can start. And I want to communicate that as a vote of confidence in some of the amazing centers we have for gene therapy, who are exceptionally at the real forefront of the science. Let's make sure we have this collaboration, and we work with them very closely. And some of the ideas that we implement come directly from the needs of the clinicians of how can we best facilitate bringing to them the solution they need to deliver to their patients.

James Frith 55:24

I don't think there's much more I could add to a comprehensive answer from my fellow panelists. It is sadly all too familiar as a constituency MP as well, that as a member of Parliament doing my surgeries, we have examples of this happening very often. And whilst we talk rare diseases affecting individually very small numbers, collectively that's six million with rare diseases in the UK. And so, to my first point, the challenge is on us to expect more from each other and do more for each other. If the person is still in the room, I'd be very happy to speak to them about some of the ways in which I've made arguments as a constituency MP, and I'm now making arguments as a health minister to pull those levers. But I'm all too aware that false hope is damaging as well. But without knowing too much more about it, I don't think there's much more I could add. But, yeah, my deepest sympathies as well.

Steve Usdin 56:30

So, we're running out of time, but I want to ask very quickly, and just really if you can make a very brief answer. If we come back a year from now, what will or could have changed at FDA, in the UK regulators, in industry, in the regulatory space that will have made life better for patients?

Michael Davis 56:53

I'll say the Rare Disease Framework . I think a year from now, we should have a new approach that we're actively implementing, and my hope is that—I know FDA doesn't think about the financial side, but it is a real factor that investment is required to develop drugs. And my hope is that there'd be a renaissance in development from large and small companies for conditions working with us as we try to deliver more treatments to patients.

Steve Usdin 57:23

Adora?

Adora Ndu 57:24

Same. Real, tangible, impactful change coming out of the Rare Disease Framework. They're great ideas. We're looking forward to it.

James Frith 57:38

Clinical trials recruited via the NHS app in a year's time would be quite a moment. At the very least, beginning that process, proven and piloted. And then from a UK/US point of view is building on what I've been calling this week as a backbone to what we go on and do next, which is the UK/US pharma deal, and UK's commitment to paying its fair share and contribution to innovation. Walking the walk as well.

Karim Mikhail 58:14

Ensuring that we deliver on our evolved vision for the FDA, which is continue to be the gatekeeper, the guardian of public health, but at the same time, play a very critical role to lead clinical development and innovation for the sake of the patients. Because if we do that, and if we commit to it right, we will have an evolved rare disease, we will have an evolved maybe vaccine framework. All that needs to advance will come from that evolved vision, that it's not just only about saying no, but it's about saying, how can we contribute to advancing the field?

Steve Usdin 58:57

Well, I really want to thank all of you for very, really profound, very thoughtful answers to—it's a lot easier to ask questions than to answer them, so I appreciate that you did. And again, I apologize to the audience. There were a lot of questions, really interesting questions that I didn't get a chance to get to. But if everybody doesn't run away, maybe you'll be able to ask them later when we're at the meeting here. Thanks again.

Disclaimer: This transcript was reviewed by individuals for accuracy and serves as a reference. However, it may still contain errors or omissions. Please verify any critical information independently.