THE FUTURE OF US BIOMEDICAL INNOVATION

Announcer 00:00:01

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

Alice Park 00:00:27

Good afternoon everyone. I'm Alice Park, senior health correspondent at *TIME*. It's really my pleasure to be moderating this discussion about US biomedical innovation. And I want to just start out by reminding you we will have Q&A at the end of the session. So, keep your questions in mind. You've got the—I think there's a QR code that will appear—so you can use that, and I will see them up here. All right. So, I think most people in the biomedical industry would agree that the US has long been a leader in this space and has long been innovating in this space. But we're going to talk about some of the areas where the US appears to be—where that US leadership appears to be at risk. So, Jake, I want to start with you. You founded a company to turn mRNA technology into treatments for cancer and autoimmune disease. Relatively novel platform. We saw great success with the COVID vaccine. And you talked about some of the challenges with the current clinical trial system in the US. And in one of our conversations, you described the US biotech system as "getting sicker and sicker" and as "atrophied." What do you mean by that?

Jacob Becraft 00:01:44

So, thank you for having me here, and thanks, everyone. I think for the past—arguably 20 years, but certainly the last 15 years—we have seen an atrophy, an incredibly weakening ability of our scientific community to get breakthroughs from the lab into patients, and then to get through an amount of patients that give us conviction about whether or not medicines work, and then get them out into a broader swath of patients. There's this concept, sort of joke, in the drug industry called Eroom's Law. It's Moore spelled backwards. And essentially, if Moore's Law, in that transistors and silicon get incredibly cheaper every year, we get more transistors per chip. In drug development, every year it gets more and more expensive to bring drugs forward. What that's done is it's had a chilling effect on innovation because if you think about, in drug development, an approved drug has a sort of fixed reward, what you can charge for a medicine. Your risk then has to be adjusted. And the risk is both, you know, the probability of success times the cost of testing that success. If that cost has increased exponentially, as it has over the last few years since COVID—in fact, the cost of a phase 1 clinical trial on a per-patient basis since COVID has gone

from $50,000 a patient to an average of over $500,000 a patient—that's in less than a decade. If that cost continues to balloon and become incredibly long, you have to adjust your risk. And you do that by making less innovative medicines. You go after de-risked targets. And so, unfortunately, it's become almost prohibitively expensive to run early-stage clinical trials here in the United States. It's become even harder to run later-stage clinical trials, in the way that most large phase 3 trials are done by large pharmas or in partnership with them. And so, we see a real hollowing out of our ability to do early-stage radical innovation to really push for cures.

Alice Park 00:03:39

To what do you attribute that ballooning cost?

Jacob Becraft 00:03:43

I think it's multifactorial. Part of it is regulatory, but I don't think the FDA is even the majority of the problem within this case. We have a medical infrastructure that both does not prioritize clinical trials at a lot of sites and isn't set up to move quickly. We have a distributed IRB system at these hospitals that is—can be incredibly inefficient and bespoke from each site. We have no real metric of success of moving things efficiently forward. We have confused moving slowly with moving safely, and that is not necessarily the case. And, you know, at this time, of course, China has become a much more efficient clinical trial runner. But before them—and now even Australia does a radically better job than us and actually runs, with one-tenth of the population, four times as many first-in-human clinical trials in Australia than we do here in the United States. So, if we want to be serious about this, I attribute the problem to sort of our entire system. We need to get our doctors and medical schools and education system prioritizing clinical trials nationally. We have to view clinical trials as a national resource. These are lifelines for patients that are in need. If you find yourself in a clinical trial, often it's not because you have a lot of options left on the table for your disease. We need to get our health-care systems and our hospitals, both major medical centers but also the sort of small community health centers, we need to fund them to build the infrastructure to run clinical trials. And then we need—and luckily, this current FDA that we have had, of course, Grace is sitting next to me, but has really taken to messaging that they view this as a priority. And so, we do need to have that sort of regulatory reform that allows us to move faster. Because in drug development, especially for early-stage companies that don't sell medicines, time is the same as money. You're burning money every day. And time is also the most important thing to patients that are staring down the end of their life.

Alice Park 00:05:41

David, you've just heard Jake, who's obviously very frustrated with the system, and especially at the early-phase trials. Do you agree with that from the pharma perspective?

Dave Fredrickson 00:05:54

Well, I agree. What I think is the start of Jake's thesis, which is that the global competition for fast-moving, innovative science is growing remarkably. If we take a look at statistics from 2013 to 2023, we've seen an increase in 40 percent in clinical trials. And an enormous portion of that has come through China-based clinical studies. And so, the pace of innovation—

Alice Park 00:06:26

All three phases?

Dave Fredrickson 00:06:26

Yeah, in all three phases. And I think also Australia is another good example of it. So, it's not just something that's limited to China; there's other parts of the globe. I do want to pick up, though, on a really important thing that Jake spoke about. You talked about kind of if the value is fixed. I would actually make a strong argument that the value is not necessarily fixed, and the value needs to be cherished. I would also say within this context that we need to remember one of the strengths of the US biomedical system is that innovation that meaningfully improves outcomes and lives for patients is able to get rewarded. And that reward results then in increased capital—capital that goes into trials, into manufacturing, into academia, into jobs. The reverse is also true, that if the reward isn't there, then investment doesn't follow, and you see that migrate somewhere else. And so, I think it's very, very important to recognize that an ingredient of the US system is reward for innovation. And it's relevant in the context of the MFN conversations that are happening right now. It is shining a light on the fact that, right now, there has been an imbalance that has existed in terms of the burden of global innovation sitting on more of the shoulders of the United States than other parts of the globe. And the answer is not a convergence on low prices. The answer is a rebalance. Because what that would allow to happen is an increased level of investment within Europe, prices coming down in the US, but the US needs to do that while continuing to maintain reward for innovation. Because that's what creates the incentive for people like Jacob to keep taking the scientific risk, people like AstraZeneca to invest at scale, and for us to be able to have the chance to really do what it takes for discoveries to be turned into true medicines.

Alice Park 00:08:38

So, Alex, I want to pick up on what Jacob and David just talked about, which was the reward, right, for innovation. Of course, you were head of HHS during the COVID pandemic. We had a very unprecedented example of when incentives really aligned, right? Of course, there was an urgent need, and it's not a normal situation. It's not the standard everyday way that medicine is practiced. But I feel like it's a good lesson, right? So, Operation Warp Speed focused on vaccines, which traditionally the US biomedical industry doesn't focus on because of the low reward. And Operation Warp Speed showed what could be done when the need was there. So, tell us about some of the lessons that could be taken from there. Obviously, that was a pandemic, you know, different circumstances, but what lessons can we draw from how that was done, how the government helped to de-risk the development and manufacturing for a lot of manufacturers? What lessons can we take from that to address some of the issues that Jacob and David raised?

Alex Azar 00:09:50

Well, I think there are—there are lessons that one can take from Warp Speed that are relevant to a future pandemic or a future crisis. And there are lessons one can take that are relevant to the ongoing crisis we have right now in drug development and regulatory systems, in our competition with China and the rest of the world. I'd say, with regard to pandemics, it's a lesson of understanding the incentive structures within

pharma and taking them as they are: today's point. You could assume the drug industry is not for profit. Well, you'll be mistaken.

Alice Park 00:10:25

They're businesses. Right?

Alex Azar 00:10:26

So, if you're in a public-private partnership, if you don't respect the incentive structures and the needs of your partner in that public-private partnership, you're not going to get what you want. I teach down at the University of Miami in the business school. Every class I begin, I say, "Health care goods are economic goods. Economic goods follow economic laws. And if you fail to respect that fact, you're going to be sadly mistaken in the outcomes of what you do." Same with vaccine manufacturing and the drug industry. And so, we created the incentive structures to make it work. A guaranteed purchase, for instance. "Keep it simple, stupid" distribution. Basically everything in a box, everything using Six Sigma-type execution risk minimization of—

Alice Park 00:11:03

Standardizing.

Alex Azar 00:11:05

—use what already works. Advance funding by us taking on the risk of phase 1, phase 2, phase 3 at the outset, as well as commercial-scale manufacturing, scale-up beginning in June of 2020. All things that uniquely positioned for a pandemic where the government is the unique purchaser for value of the product. But then there were other things that were done that are completely replicable for the private sector that we just—you know, everyone thinks that because of the name of Operation Warp Speed—I'll be honest, I didn't like the name Operation Warp Speed. Peter Marks, you can blame Peter. He's a Trekkie and liked it, and the team liked it. And as a leader, you just—you have to defer to the team, what they find motivational. So, I did. I was afraid that it conveyed that we were—that we were cutting corners, moving too fast. We didn't cut corners. We didn't cut corners. We went fast; we didn't cut corners. What we did was, FDA, for instance, was in a complete partnership of communication with drug sponsors. NIH was working to ensure that we had a single unified protocol of enrollment and IRB work across all clinical trial sites to ensure that we could compare results and move clinical trial participants based on which products were having the greatest levels of success. All of these things are things we could do, we can do as part of our routine day-to-day operations in the government. Now, Grace is trying heroically through Operation TrialBlazer to fix this issue of phase 1 initiation. China, Australia are eating our lunch on this right now. And if you own phase 1, you're going to own phase 2, and you're going to own phase 3. And the tragedy of this is we are at a golden moment in human health history right now, on the order of clean sewer and water, vaccines, and antibiotics. This is a moment. It's the fruits of the Human Genome Project, and it's our molecular and genetic understanding of the nature of disease. We can now custom-design drugs that have a vastly higher probability of technical success at the outset, and especially at phase 3, to completely cure elements of the human condition. So, if there's any time when you want the United States dominating this industry, it's now, even more than 10 or 20 years ago. It's right now. And China went from being basically a copycat to a fast follower to now rivaling us on innovation. I don't know what Dave would say, but I've talked to CEOs of pharma companies where over 50 percent of their new innovation they're buying out of China. And, you know, listen, take the innovation where it is. But we should be—we should be out-

innovating and out-developing and out-producing here in the United States because this is a critical part of human health for the future, and the US has been dominant and we should remain dominant. And we need, basically—and this is where Milken has been great—we need a US biopharmaceutical ownership strategy, leadership strategy. Milken's got a plan on this. BIO's got a game plan. We need—but we need the government to, you know—Grace has been trying her best—but we need the leadership at the highest level to say the US will win biopharmaceutical innovation in the world and will dominate it as it has done for the last many decades.

Alice Park 00:14:22

All right. We're going to get into some of the details of that.

Alex Azar 00:14:26

My soapbox. But I care. I think this is—the time is now.

Alice Park 00:14:28

I agree with you on that. We've got innovations, really. But we have to remember that those innovations are the fruits of decades of investment, right? In research, in trials. So, it doesn't happen overnight. John, I want to turn to you. Alex, of course, talked about the wonderful example of Operation Warp Speed and the vaccines during COVID. You also have a great example of how that trial process and testing process was really streamlined during COVID because of the urgency of the pandemic, but could be used and made more standard and normal in non-pandemic times as well.

John Halamka 00:15:05

Well, thanks so much, and wonderful to see you all. So, for the last 40 years, I've been working on curating the world's data, trying to clean it up and normalize it and make it accessible in a privacy-protected, ethical way. The technology we have today is good enough. The policies are serviceable; some are complicated and could be simplified. It's the psychology that's the issue. And, of course, what did we have in COVID? A sense of urgency. So, I was asked, as I think some of you were asked, "Hey, I wonder, does hydroxychloroquine help recovery?" Well, okay, let's define what recovery is, and, oh, maybe we'll look at ventilator days, hospital days, morbidity, mortality. In two weeks, we were able to put together 2,400 hospitals, get them the scripts to run against their electronic health record real-world data, and get an answer—in two weeks. Now, this wasn't an RCT, but at least it told us signal. Probably hydroxychloroquine was not something we should pursue. And hence, the question you should ask is, as these folks are trying to do the right thing, decide what targets to look at, try to simplify the process, should not real-world evidence be more accessible? And should not we as a country decide, not say no, but say, "Here's how"?

Alice Park 00:16:29

Okay, so Grace, everyone has referred to what the FDA is doing. So, now the ball goes to you. And Alex mentioned the Operation TrialBlazer, and we also heard about it from Doctor Bhattacharya yesterday, as well. So, there's a lot of things I want to get into. Let's start there, with the intention there and how that's going to transform the way we think about clinical trials. You know, to the point that John just made.

Grace Graham 00:16:58

Well, and to the points made earlier, it's a top priority and not just at FDA, through HHS and from day one, that everyone got in the door. We saw the stats about early phase 1 research moving out of the United States and started to act. Now, in government fashion, I'd say getting a big launch with five or six HHS principals at an event within 15 months of the administration coming into power is not as fast as we need to go, but it's pretty quick. And so, I think what you saw in June at the launch of Operation TrialBlazer was a first phase, a first step, of what we've been working on. In some of the expert careers I work with, even before we got in the door, have started, been trying to tackle this and think through this. How do we keep that early-stage research here that's so important? So, there's a number of fronts to cover from the FDA perspective. First is how do we make sure our regulatory requirements are precise and specific to the moment? What do you need for your first-in-human that you may not need for your phase 3? What do you need for a healthy population in your phase 1 versus someone who has late-stage cancer? And how do we make sure that we are not getting more than we need? Or where we are? We are sharing that with sponsors. We often get a lot more than we need, because at some point we told AZ or another company, we asked for a study once. And from then on, that is what you're giving the FDA, even if that person may have asked, and we no longer need it because the science has moved to a different place. So, that—you saw a lot of that come out kind of on that day for early stage. Second is working across the department. So, NIH has different levers with academic centers. When FDA says you may proceed, or after those 30 days, you can proceed, even if you don't have a letter from us. It can still take two, six, eight months before that first patient is dosed. And that is after the FDA has signed off. And so, what do we do about those six, eight months? That is where NIH, Office of the National Coordinator in terms of the health IT tools we have available, CMS in terms of how we get more sites and physicians off the sidelines doing clinical research, are all participating, and all meeting routinely, and all working ARPA-H, funding new clinical trial networks.

Grace Graham 00:18:57

So, work is ongoing. I appreciate Alex's passion for a national strategy and something written down, but I will say it is a top priority for this administration to make meaningful headway and meaningful progress. We recently have had a lot of interest from external stakeholders. We have a pilot program we are working on now where—to model it a little bit after Australia—maybe FDA can work with a third party to have more iterative feedback in that early-stage development. One meeting where you try to cover your preclinical work, what your protocol looks like, and what manufacturing data you need is not enough for many sponsors, especially early ones who haven't been through it before. So, who can we task on the outside that we think, "Oh, they give good data"? How can we give more rolling feedback? So, we got over 100 applications and are looking through those now to roll that out, to build confidence and build trust that we can have a good system, a more iterative process, to streamline some of those bumps early on. And again, get to that first-in-human more quickly.

Alice Park 00:19:55

What is that interaction like now with—I know that there's also some legislation, right, that very strictly defines what interactions the FDA can have with companies that are planning to submit and all of that. Are

those too antiquated now? Do we need to revisit those? And what is that interaction like now with companies? And how can that be modified and revised to really become more streamlined in a way?

Grace Graham 00:20:20

I think it's a balance. You're always going to have more people who would like FDA feedback than we can give, or we can meet. And we, end of the day, while IND meetings are important, we also have new drug applications and BLAs on the desk. I mean, any one reviewer may have 40 to 50 INDs and a handful of NDAs or BLAs at one time. And you want that feedback to be meaningful and to stand the test of time, and to not just be, "Oh, this"—not that anyone would sort of blithely give feedback that these companies are relying on to make long-term, large investments. So, you'd rather us get information early, specific questions, and then take a little bit to make sure we are giving you the best advice, following up the right questions, so that doesn't change later. And we try to make sure the goalposts are certain. So, it is a balance. Right now, the user fee process has goals for when we have to get back to sponsors, different types of meetings for different questions. And this is a good opportunity to think through that. We just negotiated another recommendations for how to update that process over the last year. Those recommendations are due to Congress by early January of next year. And then Congress has to authorize those by September 30 to continue a lot of really important FDA funding for us to make our mission. So, sort of foundational to all of what we're talking about today is getting confirmed leadership at the FDA and having a streamlined process for the user fee reauthorization, so we can continue focusing and working with the career experts on how we can, again, go fast but not reduce any of the safety and give American patients confidence they should, and continue to participate in clinical research even more so than they have in the past.

Alice Park 00:21:52

Jake, you have recently talked about an example of an interaction with the agency that took you eight weeks?

Jacob Becraft 00:22:05

I'll rewind it. We had an IND cleared earlier this year on time. Right on time, thank you very much to the FDA. We run our clinical trials, our first-in-human clinical trials, here in the United States for a whole host of reasons. But we had an IND cleared, and then we were able to successfully move from that IND clearance to a needle in an arm of a patient in less than eight weeks, which, I think, to every person I know in the industry, at this day and age, especially for a small company, that is vastly ahead of schedule. And one of the frustrating conversations that I had with a different medical center, where I don't run clinical trials, but the head of that medical center, I said, you know, "I did this. So, it's clearly possible here in the United States to move quicker through the IRB process. And I did it with multiple sites. Why is this not the way that things always happen?" And their response to me was kind of disappointing. The response was, "Well, you know, in my experience, the way to do it is you get an internal champion. They'll help shepherd it. They'll move it through." And I said, "I think you're misunderstanding my question. I know how to do it. We just did it." I know that that's the—I'm frustrated that that is necessary, right? Like, if it's possible, then, you know, to Alex's point about the things that we did with Operation Warp Speed that are not unique to COVID, other than we had buy-in that we needed to move fast. We always need to move fast. You know, I tell our company, if our drugs work, we run oncology trials right now, and we run them in late-stage patients that often have a very short window left to live on their life, and they're out of treatment options. And so, taking for granted that our drug will help those patients, if we're six months late to getting started

in a trial, there is a very real possibility that the patient that would have gotten onto our trial six months earlier could have died in that amount of time. So, your urgency is getting to people faster. Safety is important, but inaction is also toxic to a lot of these patients. And so, that was the frustrating piece, where we sort of said, we have been able to do this. We do this in the United States, and I was proud of that, to say it can be done. But now why are more of you not doing it?

Alice Park 00:24:21

Why is it the exception?

Jacob Becraft 00:24:22

Why? Why is it the exception to the rule instead of the way it goes? There's a ton of bureaucratic reasons. And of course, we worked with institutions that we knew. But these are top level institutions that probably move much slower most of the time that we were able to move much faster. And so, I think it's possible. I think it's a matter of will. It's a matter of a recognition that speed is an element of getting to patients, and speed without sacrificing safety is possible. And so, that's what I hope we can, we can do. And of course, there's work ongoing with the NIH and a number of places across HHS to try to reform these processes and work with our medical centers to move this much quicker.

Alice Park 00:24:59

So, Dave, both Jake and Grace mentioned Australia as a model. And, if I'm not mistaken, I believe one of the things they do is they have different review processes from the regulatory agency, depending on what they consider to be riskier versus non-riskier products. Your thoughts on that? Does that make sense?

Dave Fredrickson 00:25:23

It does make sense. I mean, I think that this gets back to what Grace was talking about, which is, that I think what you're seeing Australia do, and others do, is modernizing towards where science is evolving. So, again, John talks about it. We've got a lot more confidence in real-world evidence. We've got a lot more confidence in the quality of data coming out of community-based trials. We should have a lot more confidence to eliminate a lot of the eligibility criteria that have historically been part of the work that we've done. And so, yes, in Australia, I think that there's a confidence of a lower burden of proof as it relates to, not lowering safety standards, but in meeting the standards. But you can meet them with a different level of proof than, or a different burden of proof than what you've maybe held to need to have before that. I think that, you know, and Alex mentions this, I mean, Milken has an opportunity, I think, and you're doing this to play a role of convener, to say, and this is why you have a panel from the different parts of the ecosystem that are here, right, between industry and providers and sites and together with the agency. And then Alex, who's done a little bit of all of it, you know, like we all kind of come together within this. But in all seriousness, how can we start have a common sense of urgency like we did in the pandemic? I think the common sense of urgency is patients are waiting. It's very clear, right? So, from my standpoint on all of this, it's that there's—we are in the golden age. We need to move at pace. And so, I think that having a common sense of mission, which is that let's modernize, there's an enormous opportunity to identify what each of us can do to get through the things that are just no-joy work that we don't need to be doing anymore, but are part of how we've always done it.

Alice Park 00:27:20

It's the inertia of—

Dave Fredrickson 00:27:22

Yeah, and it is inertia. And it's just needing to take a fresh look and be willing to cut it out. You know, you take a look at, again, I think, I mean, some again, there's, you know, John will know better examples of this than I. But why was telehealth during the pandemic, something that we were able to cut through? Well, because it just made sense that we needed to provide telehealth. Were there were a bunch of regulations that got in the way of that? Absolutely. Did some of them make sense? Probably. Did 80 percent of them not? I would think so. And so, you move through it. Did it make more sense to give infused therapies over a three-week period than a two-week period? Yes. Fewer visits to the hospital is a good thing. Well, can we actually think of a different burden of proof to demonstrate that that's safe for patients? Yes. I think there's a lot of pragmatic things like that, that we've got the opportunity to align around. And I think that we can do it through your convening force in the way that you're doing here.

Alice Park 00:28:17

Okay. John, I want to ask you about two things. One is, you know, we've heard today about the clinical trial enrollment process. And one of the things that we saw come out of COVID was the piggybacking on existing—an existing network that was established during the HIV epidemic, right, with institutions and participants. How can we make something like that a little more standardized and more routinized so that we're not starting from scratch, essentially, right, for every institution, as one of you mentioned, with separate IRBs and really starting from zero with trying to enroll patients with eligibility criteria? How can we create a more systematic way of doing that? That's, of course, more efficient, too.

John Halamka 00:29:11

Well, of course, a couple of thoughts. So, academic medical centers typically have been the place where you enroll patients in clinical trials. They are not representative of this country. That is, when we start to look at rural areas, we look at all of the heterogeneity of demographics across this country, we need to enroll patients at the point of care in rural areas. The tools aren't there to do that. As you say, they may not have human subjects, IRB; they may not have the alignment of incentives to participate. They don't have the electronic health records that are in their workflow that enable it. So, Mark McClellan and I, you know, a fine colleague, former FDA commissioner, spent some time figuring out how to do this. And it's early days. But because of the work that has been done by the Office of the National Coordinator, there are now more standards, more interoperability, more technical capacity to plug functions into the existing workflow of electronic health records. So, imagine this: you are a point-of-care delivery physician or nurse, and you are simply told the person in front of you right now is qualified for a really important trial. Push this button, and the process starts. Because today, that's not what happens. And so, instrumenting the electronic health record with frictionless tools and making the process—I know this isn't a word—"automagical" will then get us—

Jacob Becraft 00:30:41

It is now.

Alice Park 00:30:41

It is now, yeah.

John Halamka 00:30:41

Okay, perfect. Will get us that heterogeneity of much larger enrollment, and we need to do it at the point of care.

Dave Fredrickson 00:30:51

I was going to make just a small point on this. So, Alex asked a question of me in terms of how we think about the investments that we make in clinical trials. And so, we've got six major research hubs across the globe: two in Europe, two in China, two in the US. And so, why is that? Well, we're going to go to wherever the science is most breakthrough, most leading. We also are investing in clinical trials in the places where the science is best. And it does, to this point, follow where the phase 1 and phase 2 is best, but also where we get the most value for our medicines. And again, here, that's a huge strength of the US. We want to enroll more patients in clinical trials in the US, and we can't enroll as many patients in the US as we would like to enroll in the US. And so, the opportunity that exists in that—and I think it connects to what John's talking about—is how do we get more than the low- to mid-single-digit percent of total patients who are eligible for trials into trials, right? So, two to five percent of patients who are eligible for trials are actually in trials. Yet the appetite for industry would be to enroll many, many more of those. And how do we do that? I think we have to get into the community. In addition to the large academic centers, we've got to get into the community. I think that that, as a goal of whatever industry policy could look like within the US of a thriving US biotechnology, would be a very tangible goal. And I think that it would open up capacity for clinical trials, improve outcomes for patients, improve the health systems that are enrolling in those trials. I think it would be very virtuous.

Grace Graham 00:32:31

And I'll just add, I think two of the things announced at the TrialBlazer launch in June directly relate to both of those points. First, the Office of Inspector General. You might not think, what is that relevant? Well, if there's anti-kickback concerns, or how do we remove friction? When does a payment to a patient to help with time off work, to help with the time it may take to get to a trial—what are the rules around that? People take a very conservative approach, and it is something we got a lot of feedback on from patient groups, that there is more we could clarify from the federal government about how companies, doctors, others, academics could help provide and help facilitate patient enrollment. And then, if you think about, are the investigational new drug requirements—that regulation, the last time it was touched was in the '80s, which is when all the clinical trials were at big academic centers. So, when you're thinking about the responsibilities of some physician in the community setting, what is their responsibility with respect to the trial? Validating the data? There's not a lot—our regs are a little bit ambiguous, I should say. It's a nice way to put it. And it's an active work stream, and we hope to get something on that, too, for folks to comment on as part of the rulemaking process, to do the first very substantial update to those rules in over 40 years.

Alice Park 00:33:38

Okay, fantastic. I think ambiguous and probably outdated, I'll add that. John, the second part of my

question to you was the digitizing of health, right? Speaking of data, and speaking of being able to reach out into the communities, what role is that playing in helping us to be able to rethink, as Grace was saying, like modernize the clinical trial process, both in enrollment, in reaching more people and also in terms of the types of data that regulatory agencies like the FDA might accept and start including in its review?

John Halamka 00:34:14

Well, excellent question. So, over the course of my life, when I was growing up, the most advanced technology in my house was a Smith-Corona manual typewriter. I know what a carriage return is, right?

Alice Park 00:34:27

You and Tom Hanks.

John Halamka 00:34:27

And so, think about it. So, medicine was an entirely analog profession. There was absolutely no way, unless one did case report forms and manual creation of registries, to be able to understand postmarket surveillance or nonobvious associations, what works, what doesn't work, et cetera. So, as we look at these last couple of decades, we have standardized the way many data elements get into an electronic record, and therefore we can start building these different tools. What's happened in the last couple of years is an amazing explosion of the breadth of data types. Let me give you an example. So, Mayo has 22 million pathology slides fully digitized. And so, that means I have the lifetime medical record and the tissue fully stained, and AI can go look at every piece of tissue and say, "Ah, I see that marker. Oh, I see the stage. Oh, I see that this drug worked or didn't work." And so, wow, if you now have millions of people and you have every image, every bit of telemetry, every bit of tissue, genomes, et cetera, you can suddenly use these novel tools that are emerging in the 2020s to find nonobvious associations. Let me give you a quick example. Glioblastoma is a very bad disease. People with brain tumors don't usually have longevity or quality of life. So, our chief of neurosurgery simply went into this large corpus of data and said, "How many patients does Mayo have that have all the images and have all the tissue and have all the genomes?" And it took about an hour: 8,000. So, imagine that you had a registry that was rich in birth-to-death information on 8,000 patients, and it took one hour to create it. So, then she started asking questions. Who lives? Who dies? And she found some pretty remarkable things. If you have a colleague, a family member with a brain tumor, probably a very effective drug to give them is a GLP-1. Like, what? How could that be? Well, it turns out brain tumors grow with glucose. And if one reduces the fasting glucose, the brain tumor is much slower growing. That was found in an hour by looking at this rich data that we now have available. So, early days, and again, that's not an RCT. But at least it gives us a sense of signal and points us where to investigate. Last thing I'll say, there are some—I mean, Alex, you will remember this—some unintended consequences of digitizing the US health-care system. We created some burdens for our doctors and nurses. And so, here's what I tell them: We now have enough data to give you something back. Right? We're going to give you decision support, clinical trial enrollment, and new cures. Thank you for spending the time entering the data.

Alice Park 00:37:31

All right. Alex, I wanted to ask you about the looming threat from China, of course. And what, in your view has led to their dominance in the phase 1 area? Like, if you could point to the factors that have really driven their dominance in the last few years?

Alex Azar 00:37:49

So, they've had a very coherent plan to do it. So, second habit of highly effective people: begin with the end in mind. If you don't have a goal, you're not going to achieve it. I used to get attacked because I would say, with Warp Speed, I would say, that you fail to achieve 100 percent of the goals that you don't set. And a member of the media came up to me at one point and said, "Hey, dummy, that's Wayne Gretzky." I'm not a sports guy, so I'm always careful now to cite the great business thinker Wayne Gretzky. *[Laughter]* But they start—Xi has an agenda. He wants to dominate global biopharmaceutical innovation, production, and ownership. Because he knows, first, he's got a population problem. He's totally—You think we're upside down? They're upside, upside down on population. So, he's got a big health issue himself. But it's the dominant economic engine of the world. I mean, it's the centerpiece of the American economy right now, is the biopharmaceutical industry.

Alice Park 00:38:43

But is it recognized as such?

Alex Azar 00:38:45

I don't think it is or is valued. I was at a meeting—I was at an investor kind of meeting where I speak at. I do a lot of paid speaking. And I was at one of these big analyst meetings, and somebody asked the question. They said, "You know, it is interesting that we dominate for decades now. We have—we took from Europe, we dominate the global biopharmaceutical industry. And right now, China is sort of nipping at us, you know, sort of grabbing at our heels on this to take it away. And instead of us fighting back and sort of coherently leading the way we would with Sputnik or, you know, getting to the moon before the Soviets, sometimes it seems almost as if we're saying, 'Here, would you like it? Have it? Do you want it?'" And so, what do we have to do? It's not—this is not—it's not rocket science. It's not rocket science. We need to keep investing in our PhDs, our fellows. We've got to get NIH and the rest of our programs back on the human capital. We've got to be the—we have to be the magnet for talent and human capital around the world. We have to have our regulatory processes get incredibly nimble and flexible. The Chinese have done that. Now, listen, I'm not—I am not saying the Chinese and their ethical standards and regulatory standards are the way we necessarily should be going. But the flexibility, nimbleness, et cetera, that we know we can have because we did in Warp Speed, we should have. And this was part of Warp Speed that is often overlooked. It's the unsexy part. It was a recognition of manufacturing. That's one of the biggest barriers to trial initiation in the United States, is the number of offices at FDA that have to touch manufacturing before you can get into the human.

Alice Park 00:40:14

Well, I think most people don't know it's part of the application that you have to have. Right, Dave? And he can attest to that. You have to have that plan in place before you even produce a single product, right, for market?

Alex Azar 00:40:24

And this is the thing, because making 1,000 doses is radically different than making 100 million doses. So, going to commercial-scale manufacturing and being able to invest and get to that point takes a lot of effort. And it's not necessarily needed to initiate first human doses. Other countries are more nimble at this than we are. But it's not the—it's the thing that takes real insight into how the drug industry actually

works and what the real barriers are. The Chinese, Australians—especially the Australians—have figured this out. Grace is trying, but this is massive organizational transformation. And, you know, it's like the government's not different from big corporate America. It's very hard to do transformation of behaviors and mid-level managers in the sense of inertia. It's not liberal or conservative; it's just people don't want to change. And it's a tremendous skill to try to break that. China can—has the mechanisms to change behaviors a lot faster than we in free democracies and free-market systems have, so it takes even greater skill here to do that. But it's those kinds of things: the nimbleness, the focus, the end in mind, the deep, empathetic understanding of what your regulated entities have to go through and how they interact with you, and really process mapping that out and finding out what those barriers are. But start with a goal. Have a goal. Is it to first human dose within nine months? Is that the goal? Is it six months? And then work backwards from that to see what we can do to achieve that. And fund it and staff it and resource it. Poor FDA. I mean, there's still—Grace and the team are still leading through a lot of the recovery post-DOGE. A lot of disruption that they're still trying to have to reconstruct and build up there.

Alice Park 00:42:03

Okay. Speaking of working backwards, Grace, I want to ask you about the Commissioner's National Priority Voucher, which is one very concrete way, I think, that the agency is trying to shorten that review period and bring drugs to market quicker. Seven approved since 2025, if I'm not mistaken, and 20 vouchers have been issued. So, tell us a little bit about that balance between speed and safety. And, you know, we've equated speed with lack of safety. How do you find that balance, especially under this program? What's been the experience?

Grace Graham 00:42:39

Yeah. To date, this program really also focused—some were given early. Some—it does focus on shortening, again, that six, eight, nine, ten months once we get the application. And I think part of the goal of all of our programs, look at breakthrough drug designation or others, is we're talking about how do we shorten before it gets to FDA's door. But that doesn't—and it doesn't sort of end up with more questions and delays in that six-, eight-, ten-month period. So, the commissioner's program was a pilot started to think about how we could reimagine it for certain priority products. You went through the stats. We had a public meeting to hear how the pilot was going, what worked, what didn't. Career staff are informing us who've had to, you know, maybe they had to put other piles aside to work on those in that short time frame. How did that trade-off work? Could we do the inspections of the manufacturing facilities in that timeline? So, it was a great pilot, I think, to learn a lot, to pilot a new mechanism, and we're continuing to review those comments and think about whether it goes to a full program that's permanent and, if so, what that looks like. So, there's a lot of ongoing discussion about that program internally. And the one thing I was getting on to Alex's point is it's not just change in the agency. So, even if tomorrow every manufacturing person is on the same page about what it is we need, everyone out in the world has to believe it. And they have to believe that there's not one reviewer who will give you a different ask or ask for another piece of information that would delay you two months. Because you would much rather send us a huge—way more than you need to—and know you're going to get it in 30 days and you're going to get a yes, than leave out one chapter because it'll save you one month here, but then somebody asks you for it in that 30-day time period. And so, it's a lot of what we are doing. And what I was surprised coming to the agency—not surprised, that's probably the wrong word—but, you know, on the Hill, people are not shy about coming to complain to you about the agency or decisions or processes or inconsistencies from the agency. And so, when you get in there and I say, "Here are the common complaints we get, or are we flexible about this requirement?" I mean, routinely the answer from the experts there, they've been

thinking about it a long time. They say, "Yes. And here's in these cases where there's public health need, where it's a rare disease, where it's this, we've waived that or we've had flexibility here, or the sponsors ask and we're happy to work with them." So, a lot of it is also a communication problem about how do we make sure the world knows and trusts that the agency will be flexible and apply that flexibility consistently?

Alice Park 00:44:47

So, for Jake and Dave: Earlier this year, the FDA made an announcement about being more open to alternative ways to conduct preclinical testing. And we've got, you know, as John mentioned, we've got data, we've got digital models now. We have potentially computational models that can emulate and perhaps simulate some of the things—not everything, of course, but some of the things—that we might see in a preclinical phase. So, I'd like to hear from both of you your perspectives on that and whether that's something that's welcome or concerning.

Jacob Becraft 00:45:27

I think it's a fantastic step forward to say that publicly. But to what Grace just said, I mean, there's all sorts of guidances that the FDA has even issued on any number of things, manufacturing included, that I'll show to my team, and they'll say, "Yeah, but we were already doing that." Or, oh, but, you know, I don't think that—like, a regulatory expert might say, "Yeah, but I don't know that every reviewer at the FDA will be on board with that." And so, it'd be fantastic if there was a mechanism for higher levels of communication and earlier interactions with the FDA that could have binding feedback as well, where we say, you know—oftentimes we do the one meeting, the pre-IND meeting with the FDA. You submit an entire briefing book: This is what our IND is going to look like. This is how we're going to do this. This is how we're going to do the manufacturing. What do you think? And some of the answers you get back are, "You could do it that way." And you just have to go, "That's not exactly an answer." And so, like, I'm aware I could do it that way. I could do it a whole ton of ways. I could submit a six-page IND if I want. Nothing's stopping me from doing that. But, you know, the problem, the toxicity, especially for an early-stage biotechnology company doing your first IND or your second IND, a clinical hold because you didn't have something in your IND, it can kill your company. If you're public, it can sink your stock price, like, immediately. You don't have the room for error. And so, you err on the side of caution sometimes. It would be—I am very much on board with that. We have an entire division of my company that just builds organoids and organs-on-a-chip so that we can study our drug in all sorts of settings. We have all of that data, and if I could use that to accelerate the FDA's review or get an IND faster, that'd be wonderful. But I can't necessarily count on that unless there is an open communication that comes with, like, a full commitment and a binding decision from the agency that they will accept something in a certain way. So, I welcome it. But it's going to require communication and higher levels of communication, like Grace just said.

Alice Park 00:47:33

Okay. And Grace, just very quick on, specifically, on like organoids and some of the approaches that Jake mentioned.

Grace Graham 00:47:39

Yeah. Human-based science, a top priority for us to move away from animal models where we can. We also regulate veterinary medicine, which people sometimes forget. We'd like to know the flea and tick products work on dogs. So, we do need to study products in dogs sometimes. But I would say we are

working collaboratively, all the centers, whether it's devices, even the food program, cosmetics, across with our NIH colleagues. What they have. What data do you need? Cross-training reviewers. I mean, it's a top priority. We've changed how CDER works operationally, too. So, we now have a review team within the drug center. So, when an application comes in with NAMs, they have—they call this one center to try to embed that consistency across the center on the drug side. So, there's a lot of work going on. Top priority.

Dave Fredrickson 00:48:23

I mean, I think the two things that I'd add to this, and John speaks to this, is I think that the advancements that are happening with technology allow us to be able to do exactly what Grace is talking about. And there's a level of confidence that can be had within this area of preclinical. We need to be recognizing what the technology and the data are unlocking that previously was not possible, and so therefore we had to go through the steps that we did. I guess I'd like to also maybe use the opportunity to put a fine point on two things for me that are a little different than preclinical. But I do think that we need to be very specific about what some of the goals are. I like what Alex was saying on this. I think that the US, and any country for that matter, should set an objective that being leaders in cell and gene therapy is a goal. Cell therapy, in my view, once it moves from where it currently is, which is autologous, into in vivo or something that's allo, is going to be truly transformative in hematology, solid tumors, and autoimmune. Right? What isn't great about being able to envision a world of curing across those areas?

Alice Park 00:49:33

So, the body becomes its own—

Dave Fredrickson 00:49:35

Yeah. And I think that's something where I'm excited, we're excited by where the science is going in that space. To not be leading there, I think, would be just an enormously missed opportunity. And so, tackle the question on what would it mean to facilitate as rapidly, without compromising and cutting any corners, the path to be able to be leaders within that space. I think that would be a remarkable area to focus in on. I think also, if, you know, obviously I spend my time in oncology, but I think late-stage also, there's modernization that needs to take place. We need to, in the late-stage space, combinations is how we will get to cure. Do we need, though, to have contribution of every component in the combination? I understand why we do it, but are there alternative ways? Can we use synthetic data? And I think there's an openness at the agency to do that. And how we begin to now align on what that looks like. Because now I'll get to the right, the ice hockey: we skate to where the puck is. You've inspired me in all this, Alex. But where's the puck going? It's going to combinations. It's going to cell therapy. It's going to *in vivo*. Let's make sure that we're anticipating that and building the systems to enable that. I think that's really how we should be focusing.

Alice Park 00:50:57

Okay. I just want to remind everyone to scan the QR code, if you have a question, which we will get to in a bit. John, before we do that, I wanted to ask you, coming from academia, when you look at the system now and you look at the potential of having synthetic data, computational models, how comfortable are you with that? Are we there yet? And how long will it take us to get there if not?

John Halamka 00:51:21

Sure, I think it's early. So, what was very common is that pharma will come to an academic medical center and say, "We have some questions. We're going to try to figure out potential uses, potential new drug targets. Can you look at this giant corpus of data and guide us?" And so, in effect, it reduces a lot of the time and error rates because at least there's some guidance. But one has to be a little bit careful about just looking at real-world evidence and deciding that there is causality. So, this is a kind of awful example, but I want to give you an issue that just shows you how complicated the data is. A young engineer who knew nothing about health care came into our de-identified dataset and said, "I have found a remarkable way to solve a health-care problem. Do you know readmission rates are very high, especially in things like congestive heart failure? And what I found in my looking at the data, if every patient is admitted to a palliative care unit, they don't have readmission to the hospital." *[Laughter]* Okay. True. Not clinically useful. Right? And so, let us answer the questions. Let's speed up the process. Let's use control arms that are using real-world evidence. But also, let's be careful.

Alice Park 00:52:47
Okay, on that note, I'm going to turn to—I am going to turn to questions from the audience here. Interesting one on AI: "On the topic of competition with China, are there any obstacles to AI adoption and integration in the United States? And what, if any, policy changes would you recommend to address them?" And I think the FDA recently had a policy about dual use technologies and knowledge?

Grace Graham 00:53:18

Yeah, I can jump in. And FDA recently now, you know, I think AI so permeates everything that is going on, whether it's how you're using it in manufacturing, how you're using it in clinical trials, how we're using it to look at real-world evidence, and how are we thinking about it. How are we using it to better target where we're inspecting? So, there's so much going on. We now have a deputy commissioner for Tech and AI, who is also coordinating a lot with HHS and the administration, both how we can use it and give confidence, again, a theme of the day, to the external parties who may want to use it and may see benefit to it. Where does FDA need to know that? Where don't we? If you're using it to come up with what your molecule looks like, we don't. We don't need to know that; we don't care. And we have some guidance on this that's draft, continue to review comments, and work through to give more external folks ideas about where FDA's head is thinking when it comes to sort of regulated entities using AI in their development process.

Alice Park 00:54:08

Okay. Anyone else?

John Halamka 00:54:11

I mean, just, as we embrace more and more AI technologies, that public-private partnerships coming together to decide quality, safety, guidance, and guardrails is important. Because, as I say, AI can produce remarkable findings, but we will together have to decide when we trust them and when we don't.

Dave Fredrickson 00:54:31

Yeah, and I guess the question on that, John, I think it's a good question that's being asked. I mean, I guess we could envision a world where foundation models and AI should be used to agentically perform synthetic controls, build protocols, run them through. Well, let's agree on what validation of that would

need to look like. And I do imagine that that's something that we need to get in front of. The other place, by the way, that has nothing to do with trials, but where I think that we need to have concerted effort: I believe that AI can be of tremendous value just in ensuring that we deliver guideline-concordant care at the provider site. But how do we incorporate that into payment? How do we incorporate that into liability? I think those would be some very good topics to be tackled to help unlock what AI could make possible in terms of improving outcomes for patients.

Grace Graham 00:55:26

And depending on what that's doing, you start crossing into a medical device lane. And our device center recently put out a discussion paper about clinical AI and how it's used, and sort of a concept about competency-based framework to regulate it. Do we think about regulating more like a doctor? You'll never be able to validate every single output from a generative AI medical device. And so, how do we think about that? And are really excited and got a lot of great comments and further work there at the agency to try to clear the path.

Jacob Becraft 00:55:54

One other piece on it, and just because I think it relates to outside of just, like, the FDA, but still within the government. How are we going to solve another huge limitation, which is multiple people on this panel have mentioned our need to get clinical trials into the community health setting. That's not just about getting community health centers excited about being part of clinical trials. There's an infrastructural gap where community health centers are not currently resourced. I think we need to think about, when we're talking about scientific funding and mechanisms, whether it's NIH or NSF or other mechanisms through the government, we have to build that infrastructure, both training and really just, like, medical infrastructure. Because if there's an iPad that tells a community health doctor, "This patient is eligible for this trial. It's only 2.5 hours away." They'll be dosed every week, and they need to come in for biomarkers. That's a five-hour round trip for this probably rural—I grew up in rural America. My family lives there. They are not going to be able to participate in those trials necessarily at a major medical center, even if it's only 2.5 hours away. We have to meet the patients where they are and get them into these trials and build the infrastructure to do that.

Alice Park 00:56:59

Okay, we've got an interesting question about the fact that we have different approval systems around the world. And an interesting query about whether we still need that? And is there any effort, would it make sense to have a more harmonized and uniform drug approval process—regulatory process?

Alex Azar 00:57:20

Certainly, with countries with whom we share a real value structure, like the European Union, UK, Japan, I don't know why we wouldn't have a much more harmonized structure. At least, even if it's not complete reciprocity, at least systems where you get 90 percent of the way there.

Alice Park 00:57:38

Or could we use their data?

Alex Azar 00:57:39

Right. I mean, there are some reasons, obviously, for Japanese requiring Japanese clinical trials because of different, obviously, genetics, metabolic, metabolic PK/PD issues. China, I think, same. I think we have elements of the same. Just make sure clinical trial diversity fits the population base, et cetera. But no, I think it would be nice to get there. The challenge is, I mean, we're having—we have enough trouble reforming our own systems. I'm not sure if we get there. Maybe it's a way to leapfrog. I mean, maybe the fast way is to not reform and just co-opt someone who's gotten there faster. I don't know.

Dave Fredrickson 00:58:14

I think. Sorry, Grace, please.

Grace Graham 00:58:16

No, go ahead.

Dave Fredrickson 00:58:16

Are you sure? Okay. I mean, again, in oncology, I think that Orbis showed very much this path. And Orbis has been an excellent way of being able to harmonize the process without having any compromise on standards. And I think that extending that to more countries and extending that to more therapeutic areas would be good. One of the chief questions is that, well, does that mean that there's going to be a lack of security on datasets or concerns there? And that's a very reasonable concern. Though we remind that these same datasets we send to these other countries anyway. So, it's just about syncing up the timing with which we're doing that. It's not sharing any information that wouldn't already be going. It's just making sure that we're streamlining the processes. So, yes, is my emphatic answer, that I think it would be good to do that.

Alice Park 00:59:13

And better coordination. Yeah.

Grace Graham 00:59:14

Well, and I'd say, you know, 70 to 80 percent of medicines, roughly, are approved first in the United States. And FDA is a leader in all—there's sort of two pieces. There's what are the standards? And a lot of multinational forums, whether it's ICH, IMDRF, work to set standards for what is submitted. We have a common application platform. Sets the foundation for reliance models, and it's something we're working closely with and doing in a lot of cases. We have clusters with the EMA on pediatrics or on rare disease, especially. And I think it is a goal and something we worked—if you look at some of the agreements on reciprocal trade last year, their work piece is about reliance on FDA decisions because of the value of that FDA decision. We are often first. And we should unlock it for American companies and for the public health benefit of the world, to try to get access to those innovative medicines more quickly.

Alice Park 00:59:58

Okay. And finally, we've got a question, obviously, about the—related to the midterms. We've seen some huge reductions in R&D in the United States biomedical industry. And the question is, do you feel those

impacts individually? Like, if any one of you wants to address that, like how it's impacted your program specifically? And are you optimistic about the results of the midterms, that those challenges will be addressed in coming years? Everyone's looking at you for some reason, John.

Dave Fredrickson 01:00:36

I mean, our investment levels are set by what we think we can achieve, whether—whomever is in office. And so, I—we, obviously, it's a reality of what we need to navigate, but we're a global company. We spend 20 to 25 percent of our turnover in R&D. We continue to do that. And so, I think in that regard, I would just say that I remain optimistic just because I think that we are in this golden age where science, technology, data are coming together. I think maybe to get to the heart of this, one of the things that I do think, though, that is important is we need to continue to make sure here in the United States that there is incentive for talented scientists to come here. And I think that is something that I see. The more that we can ensure that it's easy for skills-based individuals to see the United States as a destination, I think that is good for the ecosystem here in the US.

Alice Park 01:01:38

Okay, great. Well, I want to thank you all for a very lively discussion. I think bottom line message is if you want to do a clinical trial, move to Australia?

John Halamka 01:01:49
Oh. *[Laughter]*

Alice Park 01:01:49
Just kidding, just kidding. Thank you all. Thank you.

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