Mary Dwight: Hello. Welcome to this webinar of the Alliance for a Stronger FDA. We're so pleased to have so many people join us for today's webinar with Dr. Patrizia Cavazzoni, director of the FDA's Center for Drug Evaluation and Research. My name is Mary Dwight. I am the Alliance's Vice President and also Chief Policy and Advocacy Officer at the Cystic Fibrosis Foundation.

As I hope you know, the Alliance was founded in 2006 and is composed of a broad cross section of FDA stakeholders, who are bound together by a common commitment to strengthening the FDA through increased appropriated funding. Our ranks include consumer and patient groups, research advocates, health professional societies, trade groups, industry, and individuals.

While Congress has granted substantial increases to the FDA over the years, the demand on the agency continues to grow and become even more complex and apparent every year. This should not be a surprise. No federal agency's mission and responsibilities are more affected by changes in science, technology, innovation, commerce, and social trends, than the FDA.

Co-moderating our program today with me, will be Ron Bartek, the Alliance's President, and also the President and Co-Founder of the Friedreich's Ataxia Research Alliance, or FARA. He also serves on the board of the National Organization for Rare Disorders, and the Alliance for Regenerative Medicine.

Also, Julie Anne Zawisza, a member of the Alliance's Board of Directors, and the Director of Global Regulatory Policy at Merck. Before joining industry, Ms. Zawisza served in a variety of roles at CDER and also as the Assistant Commissioner for Public Affairs.

Our guest of honor and speaker today, is Dr. Patrizia Cavazzoni, the director of the Center for Drug Evaluation and Research (CDER) at the U.S. FDA. Her job is to ensure that safe, effective, and high-quality drugs are available to the public. CDER regulates medical products under its jurisdiction through their lifecycle, including pre- and post-market surveillance, conducts research to advance regulatory science, and takes enforcement actions to protect the public from harmful products.

Dr. Cavazzoni joined the FDA in January of 2018 and has held a variety of posts in her capacity there. We particularly want to congratulate her on her recent appointment to be the permanent director of CDER, after serving a year as the Center's Acting

Director.

Dr. Cavazzoni received her medical degree at McGill University and completed a residency in psychiatry and a fellowship in mood disorders at the University of Ottawa. During her training, she was a clinical investigator working on trials of novel antipsychotic and antidepressant medications.

She subsequently received a full-time appointment to the Faculty of Medicine at the University of Ottawa, where she treated patients suffering from severe mood disorders. She taught students and conducted research on genetic predictors of bipolar disorder as part of a multidisciplinary international collaborative effort, authoring numerous peer-reviewed scientific publications.

After her tenure in academic medicine, Dr. Cavazzoni worked in the pharmaceutical industry for several years and held senior executive positions in clinical development, regulatory affairs, and safety risk mitigation in large companies across multiple therapeutic areas, until she joined the FDA. She is board certified in neurology and psychiatry, and was recipient of the American College of Psychiatrists' Laughlin Fellowship.

Dr. Cavazzoni we're delighted to have you today and look forward to you remarks.

Dr. Cavazzoni: Hello everyone. It's a real pleasure to be here today. Mary, thank you for that kind introduction. I'm really delighted to be able to spend an hour with this group today.

I will actually endeavor to do my very first self-interview and go through a list of questions that Reed and Steve sent me ahead of time. They are quite all-encompassing. So, I really look forward to these questions, to give you a robust update to the priorities for CDER, and the work that we have done over the past year and a half or so, and what lies ahead.

So, the first question is: What are CDER's long term budget priorities, altogether and by major types of drug products?

So, I will give you a bit of an overview of what we see as the areas that, from our perspective, continue to warrant more effort as well as potential incremental investment.

So, first and foremost, I'm going to start by talking about the

opioid crisis. So, during the pandemic we have seen unfortunately, an increase in opioid that's due to overdose. Largely as we felt – or overwhelmingly, as a result of fentanyl overdoses. So, this data has certainly reinforced, even more so than before the pandemic, the importance that CDER plays in the opioid crisis. So, we're doubling down on policy initiatives that are pointed at fighting the opioid epidemic. This is an area which obviously, requires more effort. Where we have, from my perspective, we could certainly benefit from additional resources that are fully dedicated to this effort across the Center.

Another area of focus for us is drug safety surveillance. When it comes to drug safety surveillance, obviously we are dealing with increasing work. Certainly, we have seen that happen during the pandemic. Where not only did we have to continue our drug safety surveillance work, but also, we had to put in place – as I will speak later on when I talk about real-world evidence, we had to put in place active surveillance systems for authorized COVID-19 therapeutics.

In addition to this we have started a fairly ambitious project to modernize how we do post-market safety. That entails obviously, doing a multi-prong approach where we are looking at how we can develop more integrated cross discipline teams. So, all the way through how we use technology to support drug surveillance work.

Other long term budget priorities for us, and these reflect areas where we anticipate incremental effort, are the advancement and acceleration of the delivery of therapies for underserved populations with unmet medical needs. That includes some rare diseases, many rare diseases, as well as non-rare diseases such as Alzheimer's for instance, and so on.

So, we are very aware of the fact that there is a lot of demand out there for us to be more engaged in thinking about novel approaches. So, both when it comes to clinical trials, when it comes to policy, or regulatory framework, and so on. For that to happen, we need to start thinking about how to put together a program. Given that our resources, particularly in the offices that review applications, are very much focused on reviewing specific applications, and meeting the next goal dates, and so on.

So, we see the need to develop – to enhance the review work, by having additional scientists who can have more time to actually think about how we can accelerate the delivery of therapies for

unmet medical needs.

The other areas that we are continuing to focus on are the modernization of how we do the work at CDER. This has been a multi-year effort that actually started thanks to a very substantial appropriation we received in 2019. That gave us the resources to undertake a multi-year roadmap to modernize how we do review of new drugs, as well as generic programs. This is an area obviously that continues to deliver, but we also know that we have a few years ahead.

Enhancement and modernization of inspections is also an area of focus and anticipated incremental work, and therefore obviously part of our budget priorities. This is an area where we obviously work very closely with the Office of Regulatory Affairs.

Last but not least, we are going to continue to pay a lot of attention and build out our surveillance program, to strengthen the drug supply chain. We started this work during the COVID pandemic as a way to expand our well-established drug shortage surveillance program. We started focusing on a relatively small number of critical drugs that are used to treat or support patients with COVID-19, including drugs that are needed to maintain a patient on a ventilator. This is something that we're definitely going to continue to build out after the pandemic. So, obviously we anticipate that this would be an area of ongoing need for incremental resources.

When it comes to the next – the sufficiency of CDER's budget, obviously we have received, and we're very grateful for having received, one-time supplemental funds over the course of the pandemic and more recently as part of the American Rescue Plan. These funds are very helpful in turbocharging some of these activities. For instance, in allowing us to accelerate the build out of drug supply chain surveillance. At the same time, the limitations of these one-time appropriations, is that we cannot use them to hire permanent staff. Therefore, obviously it is one-time appropriations that can be very complementary to strengthening the base appropriation that supports these areas of priorities.

The next question is: "What sort of new demands is CDER facing in 2021 and 2022?"

Well, I can tell you that the pandemic has placed tremendous, enormous resource demands on CDER. When it comes to the

people side of things, we have absorbed the incremental demand with the resources that we had in place already. We have, despite that, obviously we have been very fortunate to receive the supplemental appropriations. We have put them to very good use.

As I said earlier, we have applied them to building out and conducting surveillance of the pharmaceutical supply chain. We have also invested in an advanced manufacturing program. We have applied these funds to support the pre- and post-market work on therapeutics both when it comes to some of the review work and also utilization of real world evidence to understand COVID and understand standards of care. Also generate hypothesis when it comes to therapeutics, and also as part of our need to conduct more real-time surveillance for authorized COVID therapeutics.

Last but not least, these one-time appropriations are going to support the recovery from COVID-19, including many areas for instance, the recovery of our inspection program for medical products. Obviously restarting inspections and doing what we need to do to catch up on inspections, after obviously the challenges that we have had over the past 18 months, due to travel restrictions.

Next question: "What are the most important needs and largest budget requirements in the area of inspections? Do those priorities sign into a plan for restarting the full range of inspections?"

Yeah, absolutely. This is a big area that requires incremental resources. We are – obviously we have – we try to continue to evaluate facilities by leveraging alternate approaches to on-site inspections. For the most part we have been surprisingly successful. Having understanding that obviously there are instances where there is no option but an on-site inspection. There are times where we obviously cannot make it to the facility.

Having said so, we need to continue to build out the infrastructure that has supported, and will increasingly support, the modernization of inspections, including the IT infrastructure that allows us to more seamlessly collect data. Also, the infrastructure that has been supporting the remote evaluation of facilities which we have started over the past few months, and in fact have supported recently by issuing guidance.

Now let's switch to hiring and recruitment. This has been an area where there has been – I noticed this group has followed closely. I

remember the first time that I came to speak to this group downtown back in 2018, and one of the questions was about the large number of vacancies at CDER at that time. I'm very pleased to report that our hiring – our ability to hire and retain talent, has improved since then. In fact, it has continued to improve during the pandemic. Which is almost counterintuitive to some extent, but I will offer some potential hypotheses for why that happened.

To give you an idea, back in Fiscal Year 2019, we had a little bit over 20 net gains. By net gains we mean, net gains of employees that actually increase the net count of employees at CDER. In 2020, we had over 100 net gains for our employees. In 2021, we are actually tracking to potentially exceed that number. So, this represents a major turning point for us. What we have seen during the pandemic, if anything, hiring picking up and attrition going down. Attrition has been lower than the historical trends.

We don't know why that happened. We think that the greater flexibility with working remotely, not having people all move to Silver Spring, and so on, has made a difference. Not only in our ability to hire talent, and also to retain talent. So, we're very interested in exploring, obviously within the limitations of the government rules, how we can get to a new normal where employees have more flexibility to work remotely and so on. Obviously, there's some things that we need to do to facilitate that.

One of the things that we need to facilitate obviously, that we need to do, is like many other businesses right now who are dealing with these issues, is making sure that we have the technology in place on campus to accommodate for instance, hybrid ways of learning. Where we have some people at home, some people in the office, and we need to make sure people can hear each other in meetings and all of that. So, we're doing some work right now to think about what the new normal will look like, understanding that employees have told us loud and clear that they enjoy the greater flexibility in how they work.

The next question is: “Has the 21st Century Cures Act provided you with needed recruitment tools?”

Absolutely. It has been a real godsend. The advances that we have made since 2018 clearly could not have taken place, had we not had decent 21st Century Cures authority. It’s not a perfect solution obviously. We were never going to be able to pay talent as much as the private sector does. Having said so, we are more

competitive, and we are also able to hire faster thanks to this direct hiring authority. There is approximately 20% of our workforce that is not covered by this authority. This creates a bit of a have and have-not's situation. Obviously, what we also have to contend with is the inherent challenges in hiring in government. So, periodically we have to address a few glitches here and there, and problem-solve. But overall, the Cures authority has been a game changer. CDER has entirely pivoted to using that authority for all eligible positions, into which we are we are hiring for new hires.

The next question is about employee retention. "How is CDER able to adequately retain employees? And how would you describe morale within CDER?"

So, I spoke about our attrition, which is lower than historical attrition. Over the past 18 months, it has hovered around five, five and a half percent, which is better than what we have done previously. When it comes to morale over the past 18 months, obviously people have worked very long hours and very hard. We have absorbed, at a minimum 250 full-time employee equivalents worth of work, as part of the pandemic response. As part of our time reporting, we have seen that close to 40% of CDER staff have reported time against pandemic response activities.

Despite this, I think that our staff are doing relatively well, morale-wise. Obviously, we are a mission-oriented organization so staff tend to rise to the challenge when public health is threatened. Having said so, the pandemic is turning out to be quite a marathon as opposed to a sprint or even a middle-distance race. So, I am personally paying a lot of attention to staff work-life balance, burnout because I know that we have people who have been going nonstop, for close to a year and a half. I think that we have to pay attention. We have a number of initiatives within CDER around morale, to try to do everything that we can to make sure that staff remain centered, and morale remains as high as you can realistically be.

Let's switch now over to some program questions. So, the first question is: "How is CDER doing on its own non-COVID-19 responsibilities? Generally, how have you prioritized the workload to keep activities going?"

So, overall, we have kept all the balls in the air. We don't have the luxury to say, "Well, we are responding to the pandemic and we are going to stop everything else." No, our programs need to

continue. So, despite the challenges that we have had with the ability to travel to do onsite inspections, right now we are on track to meet our user fee goals for our three programs. I'm not speaking about OMUFA, the brand-new program. Certainly, our staff have been covering all these areas.

Obviously, there are some things that are taking a little bit longer because our staff is so focused on the pandemic response, and also the user fee goals. So, there are some guidances for instance, that are taking longer to be developed. There are some meetings that are either taking longer to be granted, or not granted, and so on. Obviously, we tried to do everything, but as I said, we have absorbed a lot of pandemic related work.

The next question is about CDER's work in promoting advanced manufacturing. So, we have a lot of activities here. This has been a program that was seeded by Dr. Woodcock well over 10 years ago. We're firing on all cylinders when it comes to this program. Our emerging technology program has now accepted more than 100 proposals, where sponsors are proposing to use some form of advanced manufacturing or continuous manufacturing. We have a pilot plant, where we are expanding our laboratory capabilities to study and understand and new technologies, so that we can determine how to regulate them. We are obviously continuing to work closely with sponsors on development and implementation of these new manufacturing technologies.

I think that next goal for the program is to evolve from a startup, to becoming broadly part of the fiber of, when it comes to regulatory decisions. So, the next area of focus for us will be, to double down on defining the regulatory framework around advanced manufacturing. Having spent a lot of time so far to work out the technology aspect, we're at the point where the technology is not a barrier, and we need to make sure that there is clarity in our minds, and in the public's, and sponsors' minds as to what the regulatory expectations are, and what the framework is.

The next question is about drug shortages. "What is the Center doing to address drug shortages?"

So, we're doing lots of work there, as I mentioned earlier. We expanded our well-established drug shortage surveillance program, which cut its teeth during natural disasters such as Hurricane Maria for instance, to build, to establish, or begin to establish a supply chain surveillance system. That is very much modeled on the logic

of what is done in safety surveillance. I have a lot of background in safety surveillance, so I'm influenced by that.

So, beginning with these critical drugs to treat or support patients with COVID-19, we established a system whereby we defined datasets that we wanted to monitor, to understand whether potential emerging supply chain disruptions, are due to increased demand or decreased supply. We use those data to raise flags as to potential signals. Then we evaluate those signals systematically. We think about ways to manage the risk, or mitigate the risk, of supply disruption. We intend to continue to expand this program going forward, and we view it as being part of an element of what we do at CDER.

The next question, we're moving into technology. "What is the status of the knowledge management system project?"

As I mentioned earlier, we have been undertaking an ambitious modernization project for CDER that focuses on what we consider our main clusters of activities. So, those include taking in information from the outside, then managing the workflows, and moving this information along workflows. If you think about an application review, that's what it is. It's a train that moves from one place to the other within the Center until such time as we need a decision to determine how we handle data, and what tools, and analytics we bring to bear to understand the data.

All the way to, how we better support our administrating activities, such as hiring for instance and how we put in place a system that allows us to see where a hiring action is, along the workflow at all times. So that we can also start to easily measure metrics and so on.

So, all of this has been taking place for the past three years. We have made considerable progress on all fronts. Some examples are for instance, adopting an enterprise workflow management system, which consists of software for services and a best in class platform which is cloud based, which is also something that we have decided we are going to be adopting. This platform is now supporting the review of INDs. We have a roadmap to expand the support to NDA and BLA review, ultimately to expand it to the review of, and this is one of many examples, we're using the same platform to manage safety signals.

We have rolled out an application that allows us to track safety

signals and see where they are in the signal management, the signal evaluation process, and so on, which is something that I know many pharmaceutical companies have, and we now currently have at CDER. So, lots of work there.

We have been very lucky, and we're very grateful for the appropriations that we received in 2019, which are now part of our base. So, year over year, we're able to plan this multi-year roadmap using those funds.

Next question is: "How can the existing Sentinel platform be improved?"

So, I'm sure that many of you are aware of the five-year plan that we have that we published back in 2019 and it seems like a long time ago. With this new plan and this new contract, we have not only maintained an Operation Center, but also established an Innovation Center that is looking at deploying innovative technologies to real-world evidence, and to leverage electronic health records data to put greater extent. But also, we have established a Community Building and Outreach Center, which I think is very important, particularly important for Sentinel.

If I had a couple of hours, I could go through all of the list of things that we're doing in Sentinel. There's a lot of work there. I'm going to highlight Sentinel's role during the pandemic. So, we use Sentinel as a contributor to the COVID accelerator. So, what we have seen during the pandemic, through works such as the one that was done by the COVID accelerator, was real world evidence coming into its own. Showing us how much we can do, when it comes to understanding using real-world evidence, to understand a brand-new disease.

We knew nothing about COVID initially, to understand very rapidly evolving standards of care that we saw during the pandemic. Remember we had nothing, and then we had dexamethasone, and then we had antibodies, and so on. Also, to test hypotheses as to potential therapeutics, that may have utility in treating COVID-19. The pandemic has given a real impetus to the utilization of real-world evidence.

When it comes to Sentinel, what I find I've been thinking a lot about is, the fact that from my perspective, Sentinel could benefit from a greater, more reliable funding, and resources that are built into our base appropriation. Well over half of the budget that

supports Sentinel is actually coming from user fees. It's actually close to 3/4. So, given that Sentinel is meant to be a national utility, and certainly we have seen this during the pandemic, from my perspective there is room too to strengthen the base of Sentinel. Including obviously, its resource base.

Next question. I am sure that it would be a great interest and I get this question a lot these days. "What have we learned about remote and decentralized clinical trials during COVID-19? Do we anticipate to make it permanent?"

The short answer is we have learned a lot. We have issued guidance. We have issued Q&As. We try to take an approach to guidance during the pandemic that was not monolithic, but rather recognize that we were learning along with everybody else. Including obviously the drug developers. So, we took this Q&A approach, which was very dynamic both for guidances around clinical trials, inspections, and so on.

So, we have clearly increased our level of comfort when it comes to decentralized trial designs. Obviously, I view digital health technology as being an enabler of decentralized clinical trials. We certainly view this as being part of the new normal. We are obviously thinking of how to issue more guidance around this post-pandemic.

I think that it will also be some work however, for the sponsors as well because trials will need to be carefully designed to minimize variability in remote assessment. There will need to be robust training for team members, who will follow a unique uniform set of instructions, and so on.

Having said so, it is very clear, and also the patients have spoken, that decentralized clinical trials are easier for patients including the reality of not having to trek to investigative sites as much as patients used to, being able to do some of these assessments at home, having a study drug delivered at home, and so on.

A word of caution, decentralized clinical trials are not going to work for every single clinical trial, for every single therapeutic area, or every single research question. But certainly, we view them as being part of our permanent tool belt.

The next question brings us back to post-market safety and pharmacovigilance. So, "…what are we doing to improve post-

market safety and pharmacovigilance?"

Well, I have a spoken a little bit about this. I will add a couple of things. We are well into the implementation of FAERS II. FAERS II is going to represent a major improvement over FAERS. We expect that our goal is to launch the new system in the fall of 2021. It will have a cloud-based component, which is again consistent with our desire and our strategies to adopt a cloud-based solution. It will also have a much more a powerful analytics suite, that is going to be part of FAERS II. That will support our scientists, both in the Office of New Drugs and in the Office of Surveillance and Epidemiology to analyze the data and manipulate the safety data to better understand whether we're seeing some new safety signals.

I have spoken to this new system that we have. We actually call it LIST, which is the signal management and signal evaluation system, that allows us to track and follow the workflow of evaluation of new safety signals, in a very transparent way.

We also realized that automation, artificial intelligence, robotics, are here to stay. We know that many companies now are embedding these new technologies in their case management and case processing system, and in their transactional adverse event databases.

So, we want to re-envision investing more in this area including maybe, taking some lessons learned from our emergency technology programs around advanced manufacturing to accelerate this work in recognizing that there are a lot of answers that companies have. Some of the answers are also very relevant to inspections, in our need to better understand the performance characteristics of these automated adverse event case processing approaches.

Next question is about our new OMUFA program, and also about complex generics and biosimilars.

So, obviously we talked a lot about prescription drugs, but the OMUFA program is one of many programs. When it comes to the generic program, we view the complex generics as being an area of increasing focus. Obviously, we have already a lot of work around complex generics. We have the pre-NDA program. We have the research program, which is a prime example of applied regulatory research, to provide very practical answers to developers, who

want to develop complex generics.

At the same time obviously, we are doing all of this within the very real constraints of a statute. That was written at a time where complex generics weren't even envisioned, and was put in place fit-for-purpose, to ensure the public that simple drug formulations were the same as prescription drugs and of equal quality.

So, some of the challenges that I recognize we are having, as an ecosystem including obviously companies, are very much tied to some of the inherent constraints of a regulatory framework. That probably has not kept up with the advances in pharmaceutical science, and obviously increasing prominence that we can expect and focus on complex generics.

When it comes to OMUFA, this is obviously a program that is in its infancy right now. We are focused right now, in addition to obviously having gone through very important steps, such as finally publishing the FR notice and setting our fees for the program to build the program. Bring the people in, hire the people, and also put in place the technology and the IP aspects of that are needed to support the program, including a portal and so on.

This is where those technology platforms, that I was alluding to earlier, are also helping us. Because having put in place these enterprise IT capabilities, it makes it easier for new programs such as OMUFA to get the support that they need. Rather than having to build everything new, every time, for each program, from the ground up.

Staying with technology, this is probably the last question that I will cover, so that we have a couple of minutes for Q&A. It's about the Data Modernization Action Plan, and the Technology Modernization Action Plan, that the agency has rolled out.

The question is: "How dependent is CDER on these initiatives? And how dependent is CDER on the legacy hardware and software? And does this, at the agency level, pose any problems?"

So, clearly there is an intrinsic dependency between the agency's modernization activities, when it comes to technology and data, and what CDER and the work that CDER is doing around modernization. We need to advance those hand in hand. We have been very fortunate to have strong leadership at the agency level first. What I mean, Amy Abernethy as the acting CIO over the

past two years.

So, we are working very closely with the agency's IT groups. In fact, within CDER, almost three years ago, we established governance and a structure around every single technology data analytics activity. Very early into the process, we asked the agency's Office of Information Management and Technology to be part of that governance, so that from the top-down we work together hand in hand, understanding the interdependency of our work.

So, I'm looking at the rest of the questions and I think that I probably have, if not directly, at least laterally answered additional questions that I was provided on technology and so on.

I will close with probably my favorite question which is: "What lessons have you learned from COVID-19? And how do you expect those to impact the agency of the future?"

This obviously, could take a long time to go over every lesson learned. I would preamble that, at an agency level, we have undertaken a process which was recently published to take stock of what we have learned during the pandemic. You have also probably seen the recent report on inspections and so on. So, there is a lot of soul searching, which I think not only the FDA or CDER should be doing, but the world should be doing to capture the learnings.

I think the biggest learning from CDER's perspective, is first and foremost, the fact that we begin with our staff and we end with our staff. Our strength is in our people, and our people have really risen to the occasion in a way that would have been difficult to imagine two years ago, as I said earlier, taking on a huge amount of work and so on and maintaining focus on the mission.

I think that the other big learning for us, is that we need to continue to maintain the crisis response infrastructure, and make sure that we don't let that go. We're able to, yes of course ramp it down a little bit. But at the same time being able to very quickly reactivate it, because we know that this is not going to be the last crisis.

Last but not least, we have made some huge gains when it comes to leveraging technology. In meeting's such as this one, despite the fact that I was cut off by my shaky Wi-Fi, all the way to remote evaluations of facilities using live cams. I mean, who would have

thought about that three years ago?

So, I think that we need to consider these new tools as a permanent part of our tool belt. Obviously, when it comes to inspections, we will go back to doing on-site inspections to the same extent that we did before. At the same time there will always be situations in the future, where for some reason we cannot make it into a facility. Depending on the situation, having some alternative tools would be very important. I'm using that as an example obviously, and there's many more.

I'm going to stop there, and turn it over to Ron, Reed, and Steve. Hopefully, we'll have time for one or two questions.

Ron Bartek: Thank you so much Dr Cavazzoni. That was a terrifically informative presentation. It spurred good number of questions, but we'll only take two in the couple of minutes we have remaining. I'll offer you one and then Julie Anne another.

The first one is based on your very encouraging presentation, regarding programmatic efforts to accelerate treatments for underserved populations, including rare diseases. That sounded really encouraging to us. Wondering if, that's especially encouraging given the fact that in the rare disease community, currently there has been some discussion regarding the amount of flexibility the FDA is currently willing to demonstrate regarding approvals and rare diseases, based on the traditional and well controlled study and confirmatory evidence, versus requiring multiple clinical studies.

That question might stem from the pandemic's additional strains on the FDA, having limited such flexibility. Whether or not that's the case, your indication would be that CDER plans to provide sponsors and advocates some additional advice or guidance on such flexibility in evidence, or otherwise advancing that kind of flexibility. Can you respond to that?

Dr. Cavazzoni: Yes of course. So, let's start with underserved populations with unmet medical needs. So, obviously as everyone knows in this very knowledgeable group, we have a finite set of regulatory tools, approval pathways, and so on. So, that's what it is. Having said so, I think that where we have the flexibility, depending obviously on the situation and in cases where there are big unmet medical needs, is the extent of flexibility that we use as we deploy those regulatory pathways. Also, the speed with which we deploy them.

So, I think that's where we need to focus, thinking about how we can use what we have with greater flexibility and agility. Obviously, I know that there's questions thrown out there. Do we need additional pathways? I'd rather start from, are we leveraging the current pathways with the optimal level of flexibility and speed? That's something that I think should be the first step.

When it comes to the question on further flexibility there are several aspects of it. It's going to take some time for the clinical trials to recover. Right? We're beginning to actually see the readouts of the clinical trials that managed to make their way, and continue, during the pandemic. So, if anything we're now seeing what we tried to anticipate by issuing guidance, let's say on statistical consideration, missing data, how to amend protocols, and so on. Now the rubber is hitting the road. So, I think that's where we'll have to walk the talk. I hope it would be a positive experience for all, but let's face it, we're all facing the unknown to some extent.

There is one area that I think that we can also think about when it comes to efficiency. We have developed quite a bit of comfort with remote meetings. Right? The ability to talk to sponsors like we're doing now, or over the phone, and so on. Of course, we're going to, as a society, go back to in-person meetings and so on. At the same time, there may be some advantages for certain meetings to use some of these more remote approaches, to make them more efficient for us and for sponsors as well. They usually are the ones who have to travel. So, I think that those are the two areas.

Then last but not least, as I said earlier, we're very interested in retaining these additional tools, continuing to talk to sponsors about decentralized clinical trials. I didn't mention platform trials, master protocols. These are all things that have come to age during the pandemic These are things that are not going to go away. We want to use what we have learned during the pandemic as a springboard, to continue to evolve these modalities.

Ron Bartek: Well, thank you again for those very encouraging comments. Julie Anne, for the last question?

Julie Anne Zawisza: Hi Dr. Cavazzoni, thanks for your time today. Our last question ties very nicely to what you just said. It relates to regulatory science. What I wanted to ask you is that: Of all the many projects that CDER is involved in to advance regulatory science, and to

harness that technological capability, and so on. Do you see one or two of these projects or activities, that might actually be transformative, whether it is a master protocols or innovative trial design, or new endpoints, things like that, biomarkers perhaps?

Dr. Cavazzoni: So, this is clearly an area that I think is a focus. When I'm thinking about unmet medical needs and underserved populations, I think that the regulatory science – the first step in thinking about a more fit-for-purpose approach, and I'm using it as an example, is thinking about: "What is the regulatory framework?" Right? Then what is the regulatory science and then we'll anchor the deployment of that regulatory framework.

So, everything that you have mentioned, such as thinking about biomarkers, thinking about how we can, for certain diseases, how we can improve our understanding of the molecular biology. So that drugs are developed against an actual known target, as opposed to throwing something against the wall and hoping that it sticks. All the way to, they're really not novel trial design, but greater deployment of platform trials, to decrease exposure to placebo for instance. Master protocols, and so on. Using more Bayesian approaches to statistics and so on.

These are all a suite of tools that, from my perspective, anchor a more fit-for-purpose framework to advance or accelerate the development of therapeutics in general. Even more so, therapeutics for unmet medical needs or for populations where there are unmet medical needs.

Julie Zawisza: Thank you.

Mary Dwight: Dr. Cavazzoni, I just wanted to say thank you on behalf of the entire Alliance. We so appreciate your time and really thoughtful robust comments about the breadth of CDER's work. We so appreciate your leadership and really look forward to working with you collectively over the years. So, thanks everyone for joining us, and again we appreciate everyone's time.

Dr. Cavazzoni: It was my pleasure to be here.

Mary Dwight: Thank you all. Buh-bye.

[End of Audio]

Duration: 64 minutes