Tom: Good afternoon, and welcome, Alliance members, media, and Alliance guests, to our webinar with FDA Commissioner Dr. Robert Califf. I'm Tom Kraus, Vice President of Government Relations at the American Society of Health System Pharmacists. I'm joined today by our co-moderator, Kyle Kinner, Senior Government Relations Officer with the Pew Charitable Trusts. Kyle and I are both Alliance board members, and excited to support the work of the FDA.

First, just a quick word about the Alliance. We are a multi-stakeholder coalition that advocates for increased appropriated resources for the FDA. We have been an important force in doubling FDA's budget authority funding from $1.6 billion to $3.3 billion. Our other mission is to educate policymakers, the American people, and the media about FDA's growing mission and responsibilities. We're the only advocacy organization that focuses on resources for both the food safety and medical products missions of the FDA, as well as the other components of its mission.

Our members include consumer and patient groups, research advocates, health professionals, societies, trade groups in industry. We have about 150 members, and we welcome new members to further strengthen our advocacy and our educational efforts.

So, for this webinar, Dr. Califf has agreed to respond to questions from our moderators. We've planned some questions to ask him, and you may submit questions by clicking on the Q&A button at the bottom of your screen. Please don't click the chat box for that; just do it in the Q&A, and we'll do our best to get the questions to Dr. Califf.

Before I do introduce Dr. Califf, I want to send a special thank you to Chrisy Goldie and Dayle Cristinzio, Tristan Colonius, and Julia Tierney from FDA. They worked closely with us to make this webinar happen, so thank you to all of them.

It's now my privilege to introduce Robert Califf, the Commissioner of the US Food and Drug Administration. So, Dr. Califf was confirmed this year as the 25th Commissioner of Food and Drugs. He is a distinguished physician and researcher, and a leader in the fields of science and medicine. He is a nationally recognized expert in in cardiovascular medicine, in clinical research, and a leader in translational medicine, which is key to ensuring that

advances in science actually translate into medical care. As I think everyone knows, this is Dr. Califf's second stint as the Commissioner. He also served as the 22nd Commissioner, and before assuming this position at FDA, he was the Deputy Commissioner for Medical Products and Tobacco.

Prior to joining FDA, Dr. Califf was the head of medical strategy at Alphabet. He joined Alphabet in 2019 after serving as a professor of medicine and vice chancellor for clinical and translational research at Duke University. He also served as the director of the Duke University Translational Medicine Institute, and the founding director of the Duke Clinical Research Institute. So, Dr. Califf, welcome to this conversation. Thank you for joining us.

Dr. Califf: Hey, Tom. Good to be with you. Good to see you.

Tom: Excited to have the conversation. So, Dr. Califf, I think, as I mentioned in that intro, the Alliance for a Stronger FDA, we want to make sure that people understand the responsibilities of the agency, new authorities, and requirements placed on the agency, and want to know how that translates into resource needs for the agency. And we also want to make sure that you are able to execute on your priorities and have the resources to do that.

So, maybe just to get us started, can you tell us a little bit about your vision for the FDA in the next three to five years, and what does the agency need to start doing now to achieve that vision?

Dr. Califf: Well, Tom, you spent your time here. So, you understand this quite well. The FDA is a decision-making machine, and before coming in for the second time, for some reason, I ended up following Louis and his work on The Fifth Estate, but also, a really interesting podcast on referees in our society. And I actually think the analogy is, really, quite excellent.

The FDA, in essence, is a referee, and it plays by a set of rules. The referees have input into the rules when the rulebook is made. Once the rules are made, like good referees, the FDA is judging based on that rulebook. But in order to do that, you have to have a lot of expertise in the area that you're working in, and you have to be aware of the environment in which you're working.

And so, when I look at the FDA, I think its fundamentally a

refereeing job, particularly on the medical product side, and is robust, and bolstered by decades of precedent and the building of machinery, which is highly effective, and now, super bolstered by the 21st Century Cures bill that you and I had the chance to work on together. Didn't start out looking so good, but I think it finished up being a tremendous asset in the medical product side because of its hiring authority, the fact that people get paid more, the movement to things like real world evidence, which are really important. I think it's been a tremendous asset.

On the other side of the ledger, on the food side, it is well known, and much discussed, that we've got work to do, but there's also been massive underfunding over the years, because it hasn't had the benefits that I just described. And so, as I look at it, three to five years, I'd say, in addition to sort of fixing up the parts of the FDA which haven't gotten the attention they deserve – and we'll talk about tobacco later, which is another area where I think, it's not quite the same as the issues in food, but there's work to be done there. What I'd say is, we've got to focus on some meta issues, which are going to have a big impact over three to five years. And two of them that are at the top of my list, no surprise to anyone. I think, number one is misinformation.

We are losing the battle on misinformation. Now, it's not just an FDA issue; it's a science issue in general, and an issue for all of the federal agencies and clinical practices that – people are being distracted by mis- and disinformation. We can cover that in more detail if you wish. But also, the evidence generation system.

The FDA does really well when it applies a set of rules to a set of data, which is high quality data, when the evidence is good. We still have arguments about how to interpret it, but it's entirely different than when the FDA has to make a decision, let's say, with a court mandated date or a user fee mandated date. The evidence is not adequate, to be entirely clear, and yet, a decision is still needed. That's when we really have a whole different kind of argument, which is not beneficial. And I think it's, I believe – and this is an area I've worked in for, I can say this now, over four decades, I would say that our delivery of evidence to support decision making is a fraction of what it ought to be, given the technological expertise that we have globally, and in the United States.

So, those are sort of the meta issues that I want to bring along. So, five years from now, let's say three years from now, the next

election, which is sort of the timeframe that I'm looking at, I want to turn over an FDA which is bolstered by much better evidence, and with a winning strategy on how to counter misinformation. And then, having bolstered these areas which have not gotten adequate attention, where work is needed.

Tom: I think we're going to have some specific questions about that misinformation concept and the hiring authorities that you mentioned, and I know Kyle is going to take us through some questions on funding and appropriations, in general.

Maybe, just before we do that, can you just say a little bit more about evidence generation, and kind of, what you think is – what would good look like? It's already good, but what would great look like? How do we actually get there?

Dr. Califf: I mean, by my standards, it's not even good. I'd say it's mediocre, at this point. I think we do a really good job of developing medical products up through the early phases, and that system works well. It's very expensive, but it delivers a quality product. If you ask the question, do we understand what the right doses of drugs are, how to use devices, how to combine and compare choices that we have to make with medical products, I'd say we're doing a lousy job of generating that evidence. And yet, everyone in the United States has an electronic health record packed full of data that could be used to do studies, very inexpensively.

And this is especially important on the medical product side, at a time when more and more of the approvals are accelerated, which means, by definition, that it's only reasonably likely that the benefits outweigh the risks. That's yet to be proven by the follow-on studies. And I think it was a signal to the very broad community when the initial statement was, it would take nine years to do the follow up study on **Adulheim**, and people said, wait a minute, that doesn't sound like the timeframe that's reasonable. And you've to to ask, what's the system that would generate the evidence that we need for those sorts of post market studies? It's simply inadequate.

But as I've been thinking about this, let's just look at food. We're discovering PFAS in our food. How do we understand what the risks and benefits are of taking things down to certain levels? And we've learned a lesson, over and over again, that what looks like the right decision from the point of view of health, in an industry, which is essential – and I'll just talk, I can mention infant formula

here. You take out one element of it, and you have, now, some essential food, which is not available.

So, everything that we do is in a balance, based on science, and 15 years ago, it was impossible. You had your best guess. Now, with big data, and all the technology that's available, we can start generating pretty high-quality evidence on the food side that we just didn't have before. I could go on and on about this, but that's sort of a flavor of what I think.

Good would look like, every time there's a medical product, we would understand the benefits and risks, and understand how the product should be used in practice, so that the labels were actually informative to the people that have to make the decisions.

And I'll cap it off just by saying, when we're talking about US specifically, who would've thought we'd have to depend on Israel to give us the information about the decision on the fourth dose of vaccine. We just didn't have the data in the US to inform that decision. We've got to do better.

Kyle: Dr. Califf, kind of in line with doing better, just a couple of questions around appropriations. Obviously, the Alliance itself is keenly interested in making sure that FDA has the resources to fully execute its regulatory mission, and I'm curious, from your perspective, does the FDA currently have the resources it needs in FY22? As you look at FY23, The appropriators are gearing up to move their bills. what are some of the most pressing funding requests, from your perspective?

Dr. Califf: Well, the most pressing areas for us, first of all, is making sure we can pay the salaries at a level which is competitive, and that's a significant area of consideration. Secondly, is bolstering the food side of the FDA. And again, it's not optimal, or very suboptimal, to have a situation where the same person doing essentially the same job would be paid different amounts of money, depending on which part of FDA they work in.

But underlying that, also, is the need for better information technology, having worked at Google for five years between the two stints at the FDA. And Tom, I certainly don't need to tell you this, but federal computing is not quite the same as what I got used to in my Silicon Valley life.

Tom: I'm sure that's true.

Dr. Califf: So, imagine FDA employees who had access to the current type of technology so that, for example, rather than entering data when you do an inspection, you just take a picture, and use standard AI to fill in a lot of the characteristics of what that item is in the audit. And these technologies are becoming available, but it's going to take funding. We got all these legacy systems at the FDA. You can't just do away with them, as they're being used every day. There's a cost of making that transition. And I think all of you know that Janet agreed to stay on, Janet Woodcock, largely because she had this list of things she wanted to take care of, and this is one of them. It's not just the technology, it's also the human systems. It's a transformation of the efforts. So, that's very important.

And then, I would just say, the infrastructure, in general, is in constant need of upfitting, whether we're talking about buildings or technology. Those are really the top priorities that we have in the upcoming budget.

Kyle: And kind of an extension of that question, it's increasingly looking like the FDA's FY23 funding is going to be dependent on a continuing resolution that will take us into, probably the last part of the year. From the agency leadership perspective, what are the implications for the agency to live on a CR, and how it may affect your operating capabilities?

Dr. Califf: Well, it just puts limits on what we can do. And I don't need to tell you, we're dealing with a set of industries which are expanding and becoming more multi-dimensional and complicated and global. One of my favorite book titles is Predictable Surprises, and we're going to have a growing number of predictable surprises if we don't have the flexibility and the ability to grow and start new programs, which under a continuing resolution, are very, very difficult to do. So, I hope that your prediction doesn't come true, but if it does, we'll be constrained in what we can accomplish on behalf of the public.

Tom: Maybe a question about where there have been some resources allocated. So, FDA, obviously, has played a central role in response to COVID-19 and the pandemic preparedness plan, and the FY23 budget requested a substantial allocation of new resources, I think $1.6 billion to support FDA's contributions to

the bio defense and pandemic preparedness. Can you tell us about the goals and timelines for that initiative, and what it would look like, if fully funded, to enhance those particular responsibilities? And maybe just a follow-on question, what did COVID teach us, in FDA, about what we need to know to prepare, going forward? And obviously, that ties to resources, as well.

Dr. Califf: Well, this gets us back to the predictable surprises theme. As we went through Ebola and Zika, that we could see what happened with a global pandemic, and a lot of work was put into sort of having the playbook ready to go. But there was just so many deficiencies in the readiness that we had. The National Strategic Stockpile was in disrepair. I don't know about exactly what you were doing in private life, but I was sitting out there at Google, helping people find ventilators all over the world, because a lot of the ventilators we had actually weren't functioning. They hadn't been kept up. And PPE, we can go on and on.

Tom: From the pharmacist perspective, we were scrounging for products, and including from the SNS and elsewhere. Yeah, you're right.

Dr. Califf: And tied into all that, of course, something that's near and dear to the pharmacist heart, is that supply chain in general. I think one of the lessons from the study of what happened in COVID was supply chain; was the realization of what was already obvious, is that we were having supply chain problems before COVID that are related to this combination of lack of resilience in the supply chain due to just-in-time approaches, linked to large single source contracts, which make it almost impossible to change if something goes wrong.

And so, to be ready for a pandemic or super hurricane or some, you know, I can think of a number of global catastrophes – we're at higher risk of nuclear war, now, than we've been since the days of Khrushchev. I know, Tom, that was before you were born, but I was around for that. So, there's just a host of things that we need to be ready for.

Of course, there are many other lessons from COVID about how public and private systems can work together to achieve common goals, when we actually identify the common goals and have ways of working on them. But in terms of the funding, it's really so that we can be ready for what is predictably going to be an increased number of natural global problems that could be very disruptive to

a normal and happy life for Americans.

Tom: And maybe just one more global budget question. Obviously, user fees are an important component of FDA's ability to do its work. And obviously, we're almost to the August recess in Congress. User fees are kind of moving along, but not yet passed. What are the implications for the agency if the user fee legislation isn't passed by August?

Dr. Califf: There are enormous implications for the agency. As you know, in the medical product side, this is a very significant part of funding, and basically, we'd have to lay people off if the user fees don't go through. And even if we approach that cliff, we are very dependent right now on hiring people. We're in the period of the great resignation. I don't know about your generation time, but I've noticed that, certainly in my life at Silicon Valley, people came and went, fairly rapidly, from one organization to another. And who wants to work in an organization if you're afraid that these jobs are not even going to exist in the next short period of time? So, we really need to avoid that.

But in addition to that, we've got to consider the consequences for the public, for the American people. If the user fees are not funded, we can't – we'll review products as quickly as we can, but the timelines go away, and the commitment to the timelines goes away, because there's no way we could meet those commitments. We wouldn't have the people to do it.

So, it's just hard for, I think, anyone to believe that the user fees wouldn't get passed, but it's really important that we get them passed so that the transition into the next phase can occur without disrupting employment and function at the FDA. If you had a rare disease, imagine that there was a drug that was invented that could save your life, but it didn't get on the market because there was no one in FDA to review it. It just seems like that would be unacceptable and should be unacceptable. So, we need to get the user fees done. We've reached agreement with the industry, that's well known, and we're in this final negotiation phase now.

Kyle: Dr. Califf, just a couple questions about foods. And particularly, you said earlier, in appropriations, food appropriations is one of your priorities. Talk a little more about what you view, from CFSAN or CVM's perspective, as important priorities, whether they be in the foods arena or whether they be in veterinary

medicine, cosmetics, dietary supplements. We just talked about user fees, so there's also lab diagnostics being discussed in the context of the user fee legislation, but I'm curious how you view the agency's priorities for those key areas.

Dr. Califf: Yes. First of all, let me just make a small technical point about what you said. I noticed that people tend to throw CVM in with foods, and I think a better way to think about CVM is, it's like a smaller FDA for animals that encompasses all of FDA. So, if you talk to people at CVM, they got a lot of work to do on medicines for animals, and devices for animals. And so, there's a whole part of CVM which is not food. But in a food program, that part of CVM is obviously an important component.

Perhaps, I've learned – I knew that, coming in, I got a lot of phone calls saying, you've got to do something about foods. The F in FDA stands for food. And of course, the infant formula crisis hit. So, I have gotten a lot more detailed knowledge of the food side than I had expected to. And I think, there's just no question that over the years, because the user fees essentially picked up the medical product side, the commensurate appropriations for the food side didn't keep pace. And yet, the industry, 80% of food, the industry is enormous. Farms, restaurants, all the importation, it just – the issue of toxic substances in the food, and then, nutrition itself, it's an enormous portfolio that's inadequately funded at this point.

And so, the things that you think about are, we've got to have more people, and they need to be highly technically qualified people, because the technology related to food is every bit as complicated as the technology related to drugs. We've got to have the information technology under guarding it. Which, again, I'm coming from Google. So, I think about Google Earth and what I saw when I was there, and what's possible.

It's not an imaginary thing. It actually exists. There is an image of the whole world, everything on it, and the water supply to all the farms on the face of the earth that exist, on Google Maps, for example. And we've got to be able to have information technology at the FDA, that enables us to keep track of all this and do an inferential job of regulating this enormous industry and all its components.

And then, I think, there's obviously the sort of organization and

culture underneath that require some work, because when people are overworked and under stress, it's hard to do all the things that you'd like to do.

And one of the main things about the food side is, 70% of the funding goes to ORA. And rightfully so, in terms of the function, because the security and safety of the food supply has an enormous component of the states, and of international cooperation and information exchange, from imports and all that, which requires, very much, an outgoing, user-friendly interface for the agency. So, all those things are in play.

I think we will have a good plan, I think we will – I think the mood is good, that people recognize that more funding is going to be needed, and we sorta have to bring the plan and the funding together into something that's a great place to work and that gets us ready for the future.

Kyle: Thank you. And no shade to the Center for Veterinary Medicine. I feel like Dr. Solomon's probably going to call me after this and tell me I forgot about their important mission. But I agree with you, absolutely. Animal health is critical.

You mentioned a little bit about maternal health. We've got a question from the audience. Let me just ask, you're seeking additional funding for maternal and child health and nutrition programming. There's obviously been a lot of focus by FDA in this area lately, both kind of on the infant formula side, but also, just in general, how do Americans maintain a healthy diet, avoid obesity and nutrition related chronic disease. What's your vision for this area? How do you want to make that happen, and the question from the audience member, how do we encourage innovation, in the area of nutrition, to improve US maternal and baby health outcomes?

Dr. Califf: Well, I'll start, sort of, with where we are right now, which is one of the highest infant mortality rates in the world, certainly the highest among high income countries, a five-year shorter life expectancy than our peer countries. We passed the five-year mark. I mean, I would've never imagined. I'm used to playing on the winning teams. I'm a sports person, I like to win. We are losing right now, in the life expectancy comparison. It's not just infant mortality, it's also common chronic disease.

And so, when I look at it, you're absolutely right. We need to figure out how to change the way we approach diet, which is so much at the core of common chronic disease, but also, the healthy growth of infants and children.

So, some of it comes back to the basics. We need more people. It's well known, we had nine people dealing with all of the processing of the information needed in the infant formula area. We eked out four more spots in last year's budget,. think we'll do better this time, due to the crisis. But that's just the start. The question of, what is a healthy diet at different phases of life, starting with before birth, is something where, we know a lot, but there's a lot to be learned with the advent of big data and the ability to do population studies in a much more refined way. So, I expect to see that get better.

But one of the themes that I've had, that I haven't mentioned yet, FDA has a core mission, and then, there are connections between FDA and the rest of the world, where the FDA is sort of a foundational element. But in order for the foundation to be useful, it's got to connect to these other areas. So, the supply chain, and the actual availability of healthy food, is an important component. But when you say available healthy food, you've got to say what healthy food is, and of course, there are a number of long-awaited judgments by FDA on things, such as, what does healthy mean? What should go on a label? So, this is a multifaceted issue.

And just while we're on infant and maternal health, I'll also mention that I think a big area where work is needed right now is on the issue of studying medications in pregnant women. It's been understandable why this is sort of the last area to get attention. We had to work through the children's issues. But I have a daughter who had congenital heart disease, she's doing well now, and I've got a granddaughter, who's 18, as evidence that treatments do work. But my daughter had to take medication when she was pregnant, and there were no studies to really inform the right dosing and the essential effectiveness and safety of those medicines. And I think, now, we've got technology that can really help us do the right studies, and I think that's an area that I hope will make some progress in the near future.

I mean, the great news is, we've got millions of women who wouldn't have been alive if not for treatment of rare disease and congenital disease, which is allowing people to live into adulthood

and have children. Now, we've got to figure out how to optimize their care in this next phase of life.

Kyle: Last question, again, about food, and particularly, food safety, which we know is central to FDA's mission, and a safe and nutritious food supply, obviously, critical to every American's day to day life. But the agency's role on the food side is not, maybe, as widely understood as USDA or CDC, for example. Is there anything more you think that FDA can do, or will do, to engage the public, and the food industry itself, to build on FSMA's orientation toward prevention, and to reinforce a shared commitment to a culture of food safety?

Dr. Califf: I think you just answered the question. There's a lot that can be done. And I think the New Era of Food Safety has got all the right ideas in it, and the ideas are relatively easy to come up with in a more digital world. We can connect supply chains, we can identify outbreaks earlier, we can localize the identity of the cause of the outbreaks much earlier, if we get the right technology and systems in place.

But also, I meant what I said before, you said culture. For this to really work, there's got to be a really good connection across the federal, state,and county systems, all the way to the level of the farm, and that takes a lot of human interaction. And I keep trying to make this point to Congress. The right technology should facilitate those interactions because this is such a complex and fast industry, there's no way that just flying to a place and shaking hands is going to take care of it. We've got to use all of our technology, and our human skills, to make this happen.

Kyle: Thank you. Tom?

Tom: So, Dr. Califf, you mentioned chronic disease as an area where there's a lot of need for attention and improvement, and I'm wondering if you can just kind of apply a little bit of your comments about evidence generation to chronic disease. I know in the past, you've talked about data reporting that occurred during COVID-19, tracking of the spread of COVID-19 and variants, and what's the analog in chronic disease, to get better visibility, and what would FDA need to be able to undertake that kind of an effort?

Dr. Califf: Well, so, my thinking on this right now – first of all, I'll come back

to the evidence – there's several pieces of this, but one is, the evidence generation piece. So, as we let more and more innovative therapies out on the market, we need a system that generates the evidence about what really works, and in which people, interventions, are most effective, so that they can be applied.

We know that when we turn something loose on the US market, it, preferentially, goes to those who are highly educated and well to do. Particularly, in recent years, rural Americans have largely been left out, because they don't live next to the big centers and have access to the greatest technology. So, if we actually look at this decline in life expectancy that we're seeing, particularly the big difference, growing difference, between us and other high-income countries, it's largely driven by these disparities that we talk about. Not only race and ethnicity, but also, increasingly, rural location is a huge factor.

And so, we need the evidence generation to occur, not in specialized research centers, but in places where medicine is actually practiced. And of course, now, with the technology we have, there's so much more that we can do as we bring that technology to bear. That's where the foundation of 21st Century Cures, I think, is great.

But in addition to that, we need population data, for public health purposes now, where it's like, we're driving down the road and we got mud all over the windshield because we can't see exactly where we're going. And yet, I know, from my recent experience, that it's entirely technically feasible to have tremendous data that tells us exactly where our resources should be concentrated to have the biggest impact on chronic and acute diseases.

At the core of this, Tom, is a fundamental American issue of individual freedom and privacy, versus the benefits of your data being used for your own benefit, by combining it with other people's data. Whether the company, PatientsLikeMe, is the right concept, I'm not commenting on, but the phrase is basically essential. The only way that your doctor can know the right treatment for you is if your data is combined with other people like you to figure out what actually works, and for some reason, the focus on privacy has overridden the need that exists for public health.

We're going to need to address that, and it's not something you can

just do by fiat, because people are not trusting of government, for example. So, it's going to have to be done carefully, over time, but I think we can work our way out of this problem if we put these different elements together.

Tom: One of the, maybe, implications of what you're describing, is that there's a gap in development of innovative products that we know are effective, at least in some populations, and actual application and use of those interventions in practice, at scale. What's the role of FDA in addressing that delta? And we're going to talk about how we could address that.

Dr. Califf: A lot. I think, first of all, is being more clear about what we think about the data. And I'll just pick on vaccination right now. I mean, if you look at vaccination, COVID vaccination, and antivirals, almost no one should be dying from COVID now, in the United States. But yet, we have a significant mortality, about 300 people a day right now, almost all of whom have either not been vaccinated up to date, or didn't get an antiviral, if they were unfortunate enough to get infected.

But I'd also point out, Tom, like I said before, this is an area where the FDA, alone, it's just not in our lane to cover this on our own, because we don't, you know – the practice of medicine is not our purview. But it's where we need linkages, and I've described what we need as sort of like a relay race, where the US approach up to now has been, FDA runs its lap, and then, it drops the baton, and then, the payers and CMS have to pick it up and figure out what's going on, and then start the next lap. We ought to be running side by side for 30 or 40 yards before handing off the baton. And that means, in the design of late phase studies, for example, making sure there is a connection to what the payers are going to need to understand about you, in comparative effectiveness.

This is easy for me to talk about. It's been my career. But, actually doing it within the constraints and the issues that we face is going to take some time to work out. But let's look at the amazing things that could happen now for things like neurodegenerative disease, for rare genetic diseases, where the intervention can be early on and preemptive, but we don't know the long-term consequences. We've got to have a system which measures the long-term consequences, because sometimes, we're going to think it's going to be great, and it's going to turn out not to be great. We need to be able to find out about that.

So, we need a system to do that. FDA can't do it alone; it needs to work with CMS and with the clinical community, and awaken people to these needs.

Tom: So, in your response there, and some of the questions before, that you – I heard a couple things you talked about, kind of, Americans' interest in privacy rights. You've talked about distrust of government, gaps in the applicability of new information, and application for certain patient populations. I think a lot of that can be a recipe for breeding of misinformation and distrust.

You mentioned misinformation earlier. Where do we go from here, with regard to misinformation? Or what are we getting wrong, and what is the way to do it in a way that, actually, would foster trust from patients to communities?

Dr. Califf: Tom, and I'm sure all pharmacists, your friends, can relate to this, I was mystified early in my career when I would make rounds and I would hear two doctors, next to each other, seeing different patients who had the same problem, recommending entirely different treatments. And it always struck me that it would be so much better if doctors had high quality evidence, so that they would understand what the best recommendation is. Both of those recommendations couldn't be right because they were different. And so, I always believe that evidence-based medicine was the best way to do things.

And then, I ended up at FDA, certainly, in the fabric of FDA. I went to Google, and when I left FDA, I sort of worked halftime at Google, halftime at the university, and I spent a lot of time on misinformation because it became clear that was a growing issue. Then, at Google, I saw it firsthand, and there was a lot of effort at Google to deal with it. And then, I ended up back at FDA.

And what I'd say is, we know a lot about misinformation, we know how it's generated, we know how it spreads. It really is a fact that, for the most part, misinformation travels faster and further than truthful information. I haven't found a single expert, and I've had access to all of them, who has a solution to the problem that they think will work, at this point. And we are losing that battle, and the best evidence is our situation with COVID, where we're number 67 in the world in vaccination status, right now, just behind Iran, which, I got nothing against Iran, per se, but I think most

Americans would sort of be mystified about how that can be the case.

And so, we've got to come up with a strategy. We're going to be working on this, and all the federal partners are interested, but I'd also say, one thing that all the experts agree on is that the federal government cannot solve this problem. There's too much mistrust already in the government. We have a significant, and very important, role to play, but we need all of you to be activated. We need a network of people who are committed to the promulgation of reliable, truthful information.

And remember that the best antidote to someone who's been misled by information is an interaction with another human being that they trust. So, physicians, pharmacists, nurses, teachers, really need – we need to develop a strategy to get unified, and that's realizing, there's some information that, really, is reliable and truthful. There's some information, and particularly – now, remember, there's disinformation, which is purposefully intended to harm people, a significant part of it now being state sponsored, essentially, cyberwarfare.

Then, there's a large body of information where we don't know their opinions, and it's legitimate for arguing. But as long as all we do is argue, and then, we have a very concentrated group of people promoting this information, it's no wonder that the public is very confused.

So, is this an FDA alone problem? No, but it's in the mission of FDA, right, about the safety of medical products, but also, in teaching the public, and prescribers, about the appropriate use of medical products, and we've got to have a strategy to deal with misinformation.

The one other thing to mention, as it relates to the way I think about it, in the good old days, when I was making rounds, there was sort of a very comforting structure to things that many of us grew up with. Which is, companies develop products, if they pass the FDA test, a label is written, the FDA, essentially, makes sure that the label is a means of transmission of knowledge about that product, the transmission goes to learned, intermediaries, physicians, nurses, pharmacists, and then, it's transmitted to the public.

Well, I mean, we now know that actually left out a lot of people. It was not perfect. But now, what we have is, the FDA makes a decision. It might put out a labeling thing, but there's an avalanche of information on the internet that has nothing to do with what we regulate, and that's often very misleading and listened to by a large part of the public, more so than what's in the label. We have to do something about this.

Tom: Well, maybe a different variation on engagement of individuals, and with their own health and generation of information, is use of emerging technologies, including health-related software tools. 21st Century Cures actually spoke to some of these challenges, as well. What resources did the agency need for regulating these kind of new, emerging technologies, that I think, I've got to believe, will be a key component of managing chronic disease and other diseases in the future?

Dr. Califf: I think there are two fundamentals here. Within each Center, where an emerging technology is particularly relevant, for example, digital therapeutics might be in CDRH and regenerative medicine, technologies, or in CBER, just, as examples, we need those, we need those areas to be bolstered. And then, the user fees, for example, CBER is getting a healthy infusion to deal with this amazing opportunity of regenerative medicine. And I think CDRH is doing pretty darn well with digital implantation into devices, and other technologies.

But we also need a function across the agency, about how to put these things together. Because there's a concept that I love, it's relatively theoretical, called convergence, and this has been a main theme at the National Academy of Sciences for a decade now. And because of the digitization of information, the difference is, that used to exist across the boundaries of science, like chemistry, physics, biology. They're going away, because it's all digital information, and it also means that the information that our centers use is merging. We're going to have more and more complex technologies, one that I had a chance to work with on the outside platforms for a robotic surgery driven by digital technology.

So, I mean, a simple way to think about this, let's imagine that you're a teenager, I've got teenage grandkids now, he's off in a rural place doing a hike, he gets run over by a car and ends up in a rural emergency room needing emergency surgery. In the near future, we should be able to have the expert surgeon scrub in from

the trauma center, rather than having to transport the person, and particularly, now, with the new allocation of money, and laws about expanding our digital presence. But that platform, if you think about what's in a robotic surgery platform, as a whole, it's like, dozens of devices, all at one time.

And so, we've got to have the talent and the technology to regulate this, because it can do amazing good, but it could also do profound harm if it's misused or inappropriately develop.

Kyle: Dr. Califf, in your prior tenure, you made workforce recruitment and retention a priority, and it sounds like you still view that as a really incredible function of your role. We are curious as to how you view the authorities from the 21st Century Cures Act, and how they've affected the medical product side of FDA, and how discussions around expanding those authorities might strengthen the food side of FDA.

Dr. Califf: I really appreciate that question. At the core of everything FDA does is the people in FDA. It's obvious, but I don't think we can state it enough, because sometimes, I think people sort of view the FDA as an inanimate object that sends out messages. It's really full of people, and their skills and knowledge and wellbeing are so important to the industry. I think the people that know that the most, actually, are the regulated industries, who constantly want to meet with people at the FDA, and they want to meet in person whenever possible, something I'm very aware of right now.

So, I knew 21st Century Cures was important, but now, looking at it now, it's had a huge impact on the ability of the medical product side to do what needs to be done, to get the right people, and to hire people in a reasonable period of time. Simply put, we need it on the other parts of the FDA, and I hope we get it, for the same reasons.

We're in a period of climate change. We could have an argument over what's causing it, I don't want to get into that, but I don't think, almost no one is denying the fact that we're going to have many more natural stresses on our system. So, we're going to have food technology that could really make the difference in feeding the world. And now, you add in war to it, the impact of the Ukraine war on the food supply, we really need to sort of amp up our ability to adapt the food industry to the needs of the world.

We're facing the risk of starvation in Africa, right now. We could really help, with the resilience that could be grown into plants, with the technologies that are available. But you've got to have people that understand the biology, the digital technologies, the data science, and the human interactions, in order to regulate that.

Kyle: Further, sort of expanding on FDA's workforce, the budget and others, FDA has talked about the importance of embracing and advancing diversity. I'm curious if you have any thoughts on that. And you also talk about, in the budget, the importance of addressing health equity issues, which connects more broadly to priorities in the administration. I'm curious if you have thoughts on that.

Dr. Califf: So, just to mention three things about that, as I mentioned already, our national malaise, in terms of health, is evidenced by life expectancy, but the (?) of the population matches the life expectancy data. It's driven by disparities. So, there's a human reason to deal with these disparities. So, it's pretty obvious, from my perspective, but even if you didn't believe in that, as a matter of national strength, we need to deal with the equity issue.

Second thing I'd say is, there are areas that are essential within FDA, in that regard, the nutrition and tobacco areas, I'll particularly mention. For example, menthol flavoring of tobacco has a very disproportionate effect on African American populations, and there was targeting of advertising involved in that. So, we are taking that on, Tom, this year. We tried in 2016, we didn't quite get it through, but we're now moving along with that.

But in addition to that, we have, of course, diversity in clinical trials, something I've worked on for a long time. But a caution there. I worry, sometimes, that the focus on diversity in clinical trials is really a sort of, a distracting maneuver from the underlying issue of lack of equity in our healthcare system. Because I'm pretty sure that if we fix the lack of equity in our healthcare system, the clinical trials would follow suit. But having said that, we're going to, you know, I'm all for it, and we'll work hard on helping to increase diversity in clinical trials.

And then, the final thing is, within FDA, we have work to do on equity. We have a shortage of people of color, and Hispanic people, in the leadership roles at FDA. And so, watch for this, it's

going to be a very active effort on our part to diversify the workforce. And as we're now living in a hybrid work environment, means we can recruit from other places, and include people who might not be able to move to Silver Spring, for example, and include them in the workforce. So, we've got some real opportunity there.

Tom: Dr. Califf, one last question, just to wrap up. You talked about evidence generation and leveraging machine learning. Is there potential to apply those tools to repurposing of drug candidates? I think that's something that the House appropriators were interested. What are your thoughts on that, and what would you need, to do that?

Dr. Califf: Well, I think there are three or four different angles on what to do with old drugs that might have multiple purposes, and I'm hyper aware of the fact that when one discovers a pathway and goes to start a company, there are actually, often, many options, in terms of therapeutic targets, you might pick. And all too often, those targets are some combination of likelihood of success and likelihood of financial return. So, that means a lot of drugs that are on the market might have other uses, and you're also well aware that most drugs that have really hit the jackpot, been highly successful, were developed for something different than what they ended up being useful for.

So, the combination of real-world evidence with large datasets, and AI machine learning algorithm applied to biology, and the intersection of those two leads to the opportunity to develop new uses for all drugs.

But this is not child's play, Tom. I think you talked about lessons from COVID. I mean, there were so many false starts, people claiming that old drugs work for new purposes in the COVID era, but there are a few that look like they may pan out. And so, this has got to be done by people who are competent, who understand causal inference and statistical and machine learning methodology, so they don't end up with false positive results. But yes, overall, really exciting area.

You mentioned machine learning and AI, I think one of the biggest uses that FDA, in the near future, is going to be to help us with inspections. We simply can't just physically inspect every place at the rate that would be optimal. But as we get more and more access

to data, we can have the inference about where to go for inspections, based on where the risk is. And that's sort of underway, but it's a standard part of business now, and I think it's going to become a standard part of FDA.

Tom: Great. Well, thank you, Dr. Califf. You've been very generous with your time. So, we certainly appreciate it, and we look forward to supporting the agency, going forward.

Dr. Califf: You bet. Great to see you all, and happy to talk anytime you want to talk. Take care.

Tom: Thanks, Rob.

Kyle: Thank you, sir. Take care.

[End of Audio]

Duration: 60 minutes