2024 Annual Public Meeting of the Board of Directors
Hybrid Public Meeting
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Transcript

Welcome and Opening Remarks
Richard L. Schilsky, MD, FACP, FSCT, FASCO, Board Chair, Reagan-Udall Foundation for the FDA

Dr. Richard Schilsky (00:00:00):

Okay. Good afternoon everyone, and welcome to the 2024 Annual Public Meeting of the Reagan-Udall Foundation for the FDA Board of Directors. My name is Rich Schilsky, and I'm honored to be the chair of the foundation board. I do see in the audience here we have a quorum of our board members present, so I will call the meeting to order. We're pleased that so many of you are able to join us both in person and virtually. We welcome the opportunity to provide updates on the Foundation's work and to assemble key FDA leaders to share their perspectives from the agency. 2023 was a very productive year for the foundation. To better support the FDA's mission, which is our core business, of course, the foundation updated its strategic framework, which can be found on our website. We committed to a stronger focus on patient and consumer-centered activities in our portfolio of work.

(00:00:59):

That enhanced focus is reflected in much of the work of the past year. Our RAISE project aspires to improve the capture of race and ethnicity data in healthcare delivery work that should be an important step toward the development of safe and effective medical products for all people. Our regulatory science accelerator examined emerging technologies in the development and monitoring of FDA-regulated products.

(00:01:28):

At the request of Commissioner Califf, we initiated a project to advance our understanding of the opportunities and obstacles to greater evidence generation in the post-market setting. We're really pleased with the uptake and the potential impact of that particular report. This project, which examined both food and medical products, strove to identify gaps and propose recommendations to improve data collection to support regulatory decision-making.

(00:01:57):

I was honored to chair the expert panel that addressed the opportunities in medical product evidence generation and excited to see the emerging work from FDA and others that is consistent with our recommendations. We also addressed the challenge of providing accurate science-based information to the public. We engage with stakeholders and health research and communications experts through listening sessions, roundtables, one-on-one interviews, and polling. You can see what we've learned in our recommended strategies in the published report on our website.

(00:02:35):

We continue to build our expanded access navigator and the eRequest app to facilitate applications for expanded access. Last year, 25% of all expanded access requests came through the eRequest app and we plan to build on that success going forward. Our food and nutrition program explored front-of-pack labeling as part of an ongoing conversation about how to help consumers make healthier choices. Our portfolio of substance use disorder work continues to expand. We organized fascinating programs on xylazine exposure and buprenorphine use, and began examining online sale of controlled substances and barriers to prescription stimulant availability.

(00:03:23):

Building on our research and expanded access portfolio, we're now doing more in the rare disease space. We hosted a workshop at FDA's White Oak campus, or we will be hosting a workshop at FDA's White Oak campus next week on patient registries and natural history studies and rare diseases. Now my colleagues on the Foundation's board of directors provide invaluable guidance and leadership to all of these projects as we continue to expand the breadth of the Foundation's work. They are a fabulous group with enormous expertise. I want to express my sincere thanks to everyone on the board for their hard work and dedication. This year. The board welcomes two new members, expanding its knowledge base and expertise.

(00:04:07):

It's my pleasure to welcome the Foundation Board's newest members, Dr. Antonio Tataranni. Antonio, why don't you give a wave or something? There he is. Antonio serves as the Chief Medical Officer at PepsiCo, where he advises the company on key health science and medical issues. And Dr. Reed Tuckson. Reed, thanks for being here. Reed is the managing director and founder of Tuckson Health Connections, a private health and medical care consulting company currently Dr. Tuckson also serves as co-convener of the Coalition for Trust in Health & Science. I have to acknowledge the invaluable contributions of our outgoing board members as well, whose terms expired at the end of last year. So therefore they're not with us today. Founding board member and former board Vice Chair, Dr. George C. Benjamin, board member and former secretary-treasurer Alan Coukell and board member of Molly Fogarty, we're so grateful for their dedication and vision, which continues to guide our work.

(00:05:09):

And thanks to of course, to the fabulous foundation staff led by our exceptional CEO Susan Winckler for their outstanding efforts over the past year. We traditionally released the Foundation's annual report in conjunction with our annual meeting. Copies are available here today. I hope you all will pick one up and have a look at it, share it with colleagues, and point to it on our website. And for our virtual attendees, each of you will receive a link to the report, which is available at reaganudall.org. I encourage you to read more about our work over the past year in this report. So now it's my pleasure to introduce our foundation, CEO, Susan Winckler. Susan.

FDA Priorities Panel Discussion

Moderator: Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA
Peter Marks, MD, PhD, Director, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
Marta Sokolowska, PhD, Deputy Center Director, Substance Use and Behavioral Health Center for Drug Evaluation and Research, U.S. Food and Drug Administration
Jim Jones, MS, Deputy Commissioner for Human Foods, U.S. Food and Drug Administration
Jeffrey Shuren, MD, JD, Director, Center for Devices and Radiological Health, U.S. Food and Drug Administration
Michele Mital, Deputy Director, Center for Tobacco Products, U.S. Food and Drug Administration

William Flynn, DVM, MS, Deputy Director, Center for Veterinary Medicine, U.S. Food and Drug Administration
Douglas Stearn, JD, Deputy Associate Commissioner for Regulatory Affairs, U.S. Food and Drug Administration

Susan Winckler (00:05:54):

Great. Thank you. We have what I consider to be the most August and probably largest panel of speakers in the DC area today. So come on up. But thank you, Dr. Schilsky, for running us through some of the highlights of 2023, and thanks to each of you for joining us here today in person and for our hundreds of attendees who are joining us virtually. If you've been to an annual public meeting of this board before, we often hear from leadership at the agency, and that is what we are about to do this afternoon.

(00:06:28):

As our panelists get settled on the stage, I'm going to describe this session. We've gathered leadership from the agency for each regulated product area in the field force, and we asked you as registrants what you would most want to know from the leadership here. So I am not going to go through introductions. I'm going to fire off questions, and we have asked the leaders here to capture their eloquence and insight in three to four minutes per question so we can navigate a lot of territory in a short period of time.

(00:06:58):

And as a reminder, we will not be asking our panelists to address questions regarding any pending regulatory action or specific company products. So let's kick off the conversation. I'm going to start in the middle of the stage. Deputy Commissioner Jones. You are the first person ... Deputy Commissioner for Human Foods. I should say you are the first person to hold that title. Congratulations.

Jim Jones (00:07:21):

Thank you.

Susan Winckler (00:07:21):

And that comes with a lot, and that's true for the ambitious agenda of everyone at FDA. We can't talk about the whole scope of activity, but let's focus on nutrition. So front-of-pack labeling, definition of healthy, efforts to reduce sodium-added sugars, many, many other things on that list, but what are the key metrics you are using to define success for these efforts and how will it influence innovation? And what's the vision for the Nutrition Center for Excellence in continuing this agenda?

Jim Jones (00:07:56):

Thanks, Susan. I appreciate it. So you mentioned a number of the activities we have ongoing related to nutrition, and it is a very ambitious agenda. I'm going to talk about them somewhat in a reverse order because of the timing of our actions in the very near term. So sodium reduction, we made a sodium reduction. It's a voluntary reduction goal about two and a half years ago. That two and a half years just ended in April. We're right now tallying the results. It was basically we recommended a 12% reduction across 163 categories of foods. These are processed foods as well as food sold in a restaurant. There's about a year data lag. So we're now looking at data that is still a year from the original goal. And the results so far are very encouraging. They're encouraging enough that we are going to propose probably in the June-July timeframe, a second ramp-down of sodium in manufactured food And restaurants

probably be in the same ballpark, but you'll have to see the proposal before anyone can speak to it publicly.

(00:09:02):

So fundamentally, the way we're going to measure this is we're going to measure industry's ability to meet these goals. Like I said, we are about halfway through analyzing the first year and a half of the first two-and-a-half-year goal. And once we have enough data, we will actually put that out for the public to look at and we will do the same for the second goal. So again, there's about a year data lag in being able to measure. So the goal, the deadline just ended at the end of April. So about a year from now, we will have all of the data we need to see how well we did in meeting that first goal.

(00:09:41):

Again, preliminarily, a year and a half into the goal, it's looking very encouraging. We're seeing results that we were pleased with, pleased enough that we're going to recommend it. We're going to propose a second reduction. So that's how we're going to do it on sodium. Ultimately, over time, hopefully, we will be working with our colleagues at CDC, be able to measure changes and things that we really care about, which is cardiovascular disease, for example. Sodium, I think that's a little more straightforward than some of the other things that we're doing. But the second thing that we can expect to see from us is a revision to our nutrition ... what is a healthy food. And basically, all fruits and vegetables will be eligible. So really we're talking here about manufactured food. We are going to be capturing the revisions in the dietary guidelines for Americans to update a standard that was finalized about 25 years ago, which will lead a pretty significant change in how we define healthy and what foods can say they're healthy.

(00:10:35):

And probably as importantly, we're going to follow that with the development of a logo. So that right now, pretty much a company can, if they meet the criteria, they can say healthy, however, they choose, we're going to have a logo so it's standardized so a consumer can recognize it. And the way we're going to measure that is what's the uptake in the marketplace. Right now it's about 3% of foods currently meets the healthy definition that's on the books. We want to see that increase pretty significantly. And I have a feeling I'm getting close to time for you, but if-

Susan Winckler (00:11:02):

Well, and that was just really disappointing.

Jim Jones (00:11:05):

That is very disappointing.

Susan Winckler (00:11:06):

That means I probably didn't eat anything healthy yet today, but that's all right. We've got another minute for you.

Jim Jones (00:11:12):

All right. So front-of-pack labeling is sort of the third big agenda item that we've got. And this summer we hope to propose a regulation that would articulate how we want manufacturers of manufactured food to articulate on the front of the pack of their label in a very prescribed way, certain attributes of the product. And people who have followed this know the attributes we're fundamentally looking for relate to things that we are not that interested in people consuming a lot about antidepressants, sodium

saturated fat, and so consumers at a glance, because we know the way people shop, they're making decisions in seconds if less than seconds when they're grocery shopping.

(00:11:58):

So giving people information that's actionable in a very short period of time is our objective. We are a statutory authority around labeling, is that we are authorized to provide nutrition information that informs consumers about the nutritional characteristics of their products. So the way we're going to measure this is going to be do consumers understand what it is that we're trying to convey to them and do they convert that into specific actions. So that's the measurement approach for that.

Susan Winckler (00:12:28):

So really helpful on the metrics and that we will literally be seeing some of these things in the products and then tasting some as well.

Jim Jones (00:12:37):

That's right.

Susan Winckler (00:12:37):

At least in thinking through that. All right, so let's turn from newest member of the leadership team here to individual with the longest tenure in your current role. Dr. Shuren, you win that prize as Center Director for Devices and Radiological Health since 2010. And what we had submitted for you relates to the Medical Device User Fee program. So specifically the Medical Device User Fee program supports several device pre-market activities. One exciting development was the launch of the Total Product Lifecycle Program or TAP pilot just in October of 2023. What should we know about that pilot and what have you and the center learned so far?

Dr. Jeffrey Shuren (00:13:23):

Well, first, I wouldn't put in the bid for healthy because it tastes great and less filling too. So here's the good news. We are designating over 100 technologies a year as breakthrough. So it looks like a nice pipeline, really exciting things being developed. And most of the submissions we get for breakthrough devices, we authorize, here's the bad news. Most technologies with breakthrough device designation never make it to patients at all. And that road from concept to commercialization is aptly called the valley of death. There's really a lot of reasons to fail. Sometimes it's just not safe and effective technology and hey, we're done. But other times it can be FDA issues, companies not really thinking strategically taking advice into account, but it's for other reasons too. Not understanding the value proposition for key stakeholders, not including the voice of patients in the design development or evaluation, not understanding the needs of providers or the needs of payers if they're going to provide coverage and reimbursement.

(00:14:29):

And when you deal with the FDA, you know, traditionally we are reactive to what a company wants and we'll answer your questions for us. We offer the chance to meet with us on any issue, biomarkers, clinical trials. But you'll get that answer in about 70 days. You've got more questions, you can come back and a breakthrough device has four or five or more of those pre-submission meetings. Here's how we're changing things. That's where the TAP pilot comes in. So I brought into head this, a venture capitalist 30 years of setting up med tech and pharma companies and we have new positions called TAP advisors. They engage with innovators proactively and strategically. They help them do an analysis, understand

value proposition, identify the key challenges, what are payers thinking about, kind of a soup-to-nuts approach. And if they're interested, we'll connect them with the key patient groups and provider groups. That's TAP. To get in your breakthrough device. But you haven't met with us before. So really early in development, we rolled this out first for cardiovascular devices, next for neurological. Next fiscal year, it's going to broaden beyond that.

(00:15:43):

And to give you an idea of value, we're talking about not shaving off a few days on pre-market review. This is about months to years on the valley of death, make it predictable, efficient, and timely. So one company, after a few meetings with us already said they have saved over a year of development time and they're still early on. That's TAP.

Susan Winckler (00:16:05):

That is fabulous to then have just those conversations and knowing when and to come in and getting that guidance. So thank you, Dr. Shuren. And I'll hand that to you.

Dr. Jeffrey Shuren (00:16:17):

This is actually the way I talk. It's smart.

Susan Winckler (00:16:19):

[inaudible 00:16:20]. That's all right. Just in case.

Dr. Jeffrey Shuren (00:16:21):

And I don't even swear.

Susan Winckler (00:16:23):

It's a great timbre, but just in case. Let's turn to the field force. So joining us, Deputy Associate Commissioner for Regulatory Affairs, Douglas Stearn. I made it through that title, but every one of our attendees may not know exactly what that translates to. So what do you wish that people knew about the Office of Regulatory Affairs?

Douglas Stearn (00:16:46):

So I think one way to put it is that ORA is the boots on the ground. It's what most people think about in terms of their interactions with the agency from a field perspective or what happens out to actual facilities. We have investigators who do inspections across all the commodities that FDA regulates, all of whom are represented here. We have also an organization that focuses on having important operations in terms of what gets admitted into the country. ORA contains our Office of Criminal Investigations, which conducts criminal investigations. It may lead to prosecution. And we have 12 laboratories that do regulatory testing that the agency often relies on for food and for medical products. And then there's also some other adjunct groups that sort of work with states, and so on.

(00:17:40):

So I think the one thing I think people also should understand is just as FDA's scope is really broad, our scope ends up being really broad, that we have a lot of an enormous number of facilities that we're asked to follow up on and to inspect. In terms of things like import decisions, FDA makes over 15 million a year. So we regulate a lot of the economy that is the agency does, and there's follow-on actions from that that are required. So we have a big job to fill.

Susan Winckler (00:18:13):
Yeah, yeah. So is it 15 million?

Douglas Stearn (00:18:16):
15.

Susan Winckler (00:18:17):
50.

Douglas Stearn (00:18:18):
50.

Susan Winckler (00:18:18):
All right.

Douglas Stearn (00:18:19):
50 as in more than 40 and less than 60.

Susan Winckler (00:18:21):
50.

Dr. Jeffrey Shuren (00:18:21):
50.

Douglas Stearn (00:18:22):
50.

Susan Winckler (00:18:24):
Great. I knew I was not ... All right. Now I'll let-

Douglas Stearn (00:18:27):
[inaudible 00:18:27] my Philadelphia accent.

Susan Winckler (00:18:29):
Oh, that's all right. Now we have it. It's 50 million. All right. That's really helpful, Doug. Well we'll turn to tobacco products. Michelle Mital is the Deputy Director for the Center for Tobacco Products. I was going to say relatively new, but actually you're an adolescent center now, clearly an adolescence. And CTP issued a strategic plan fairly recently. What should we know about that plan and priorities for the rest of 2024?

Michele Mital (00:19:00):
Sure. Yeah. Thank you so much for this question. Yes. In December, CTP issued a new strategic plan intended to be our roadmap and blueprint for the next five years. This plan builds on past efforts that

the center has put together back in 2014 and 2016 where we had strategic priorities and also our 2017 plan, comprehensive plan for the regulation of nicotine and tobacco. And so this plan builds on all of that past work. We had a very iterative process in terms of developing the plan with lots of opportunity for feedback, both internally with CTP staff and with external stakeholders as well. Lots of opportunity to weigh in on the goals, objectives and outcomes to help us define what would be included in the plan. One of these tactics, we had a listening session. We had over 500 attendees, which was really wonderful. Anyone who registered and requested time to speak was provided time to speak.

(00:19:59):

And I think at the end of the day, we ended up with almost 60 folks providing their comments verbally during that meeting. So we took all of that feedback and we developed this new strategic plan. It has five overarching goals that really focus on our key programmatic and operational activities. So those are regulations and guidance, pre-market application review, compliance and enforcement, public education, and operational excellence. So in addition to those five key goal areas, we also have four themes that are interwoven and reinforce those that are woven throughout the plan. And those are strong science, health equity, stakeholder engagement, and transparency. So those are also key themes as we think about our next five years in the strategic plan. So that's a little bit about the plan itself. I'll now sort of turn to what's ahead in the coming year. The second part of your question.

(00:20:59):

So a lot of exciting work ahead. I'll just kind of go through the goal areas and give you a couple updates that I'll highlight things that we're working on. So starting with regulations and guidance, the product standards continue to be a priority for the center, as well as updating our regulations to reflect the change in the minimum age of tobacco sale of 21. So working on that.

(00:21:20):

We're also working on a rule for administrative detention and also continuing to work on the Tobacco Product Manufacturing Practice, our TPMP. I'm being mindful of on my acronym, Susan, rulemaking as well. It's a really important foundational rule for us. In addition, in terms of guidances, we're working on a new civil money penalty guidance that we will release this year. Moving over to pre-market application review, you will continue to see decisions come out of the center, including for some higher market share products in the coming months.

(00:21:55):

And also just yesterday we announced a Tobacco Products Scientific Advisory Committee meeting that will be holding in June to review a modified risk tobacco product application renewal. So this is the first time where we have products up for renewal. That'll be in June. June 26. Moving on to compliance and enforcement, a lot of work in that area. We will continue to take action across the supply chain to prevent the illegal importation manufacture, distribution, and sale of unauthorized tobacco products. So you'll continue to see escalated actions that we're going to take with our partners in ORA and other federal agencies to hold folks accountable and to take enforcement action for those who continue to violate the law. That'll be in the form of civil money penalties, injunctions, and seizures.

(00:22:45):

Public education. This year we mark the 10th anniversary of The Real Cost campaign. So we're very excited about that. Last month we put out two new ads aimed at preventing youth from using e-cigarette products. And we'll also continue to educate adults about the relative risk of tobacco products. Operational excellence. We're continuing to hire, we got direct hire authority approval from OPM in October, which is wonderful for us. That's good for two years. And the benefit of that is it'll really help us hire qualified candidates more quickly. So we're very excited about that. So that's just a snapshot of

all the work we have to come. We're really excited about it and we'll continue to keep the public updated on all of our actions.

Susan Winckler (00:23:28):

Yeah, that's great. You'll need the people to get all of those things done in the strategic plan.

Michele Mital (00:23:32):

Yes.

Susan Winckler (00:23:33):

So let's go to this edge of the stage. Dr. Peter Marks, director of the Center for Biologics Evaluation and Research. I have to give props to whoever submitted this question because it's very elegantly phrased, eloquently phrased, both. Although the North Star doesn't appear in relevant FDA law nor regulation, what is your North Star for navigating regulatory flexibility in accelerated approvals and how do you maintain the right balance of risk of a false positive conclusion versus delaying access to a beneficial therapy?

Dr. Peter Marks (00:24:09):

Thanks for a very good question about a topic that is so controversial that we could spend the next two hours having a debate.

Susan Winckler (00:24:16):

Yeah, four minutes.

Dr. Peter Marks (00:24:16):

And have to go to a bar outside to settle the differences. But in a word, it actually, I think the North Star is science. I think for us in the Center for Biologics, we are very lucky for the genetic therapies that we regulate. These are products that are generally based on a very good scientific underpinning. If you are giving a gene therapy, you generally have to know the gene you're actually giving someone. That usually means you know the gene product, you know where it's being expressed. You have a leg up on things that you just often don't have when you're giving a small molecule. It's not always the case, of course, because we have targeted therapies, etc. But the science that we can leverage here across any of our products is probably the most important here. And I think we want to leverage the science maximally as we did during the Covid pandemic, as we'll continue to do, to try to bring benefits to people as quickly as possible.

(00:25:21):

Even despite following the best science, you can make mistakes. But I think we have to balance that with the benefit-risk considerations so that particularly when we're dealing with smaller populations with very high unmet medical need, where there is a good scientific underpinning, I think the North Star is you follow the science, you take all the available evidence, and yes, you may use a biomarker or an intermediate clinical endpoint, but you try to get somewhere that brings forward a therapy to patients a little bit sooner using accelerated approval and you get the confirmatory evidence down the line. It does mean that occasionally something may have to come off the market because we won't get that confirmatory evidence. But as long as we're getting it right most of the time, I think the diseases that we're talking about, at least in our center, often are diseases that they kill people. Either kill people or

they make their lives so miserable, or they make their lives such that their parents of kids can't work. So things that could change that calculus, I think give us a North Star that look, we want to put science in the driver's seat to help us move that along.

Susan Winckler (00:26:35):

You made it under the wire, but we've got that science for the North Star. Thank you.

(00:26:41):

We're making our way through the stage. So I want to turn now to Dr. William Flynn, who is deputy director for the Center for Veterinary Medicine. So we'll turn to our animal health products. This question was clearly written with today's meeting in mind. So Dr. Flynn, what role can the Reagan-Udall Foundation and other stakeholders, including industry play towards accelerating innovation in the animal health industry and how do you prioritize innovation initiatives? And I did not write this question.

Dr. William Flynn (00:27:13):

Thank you, Susan. So we're excited to publish our, back in September of this past year, our animal and veterinary innovation agenda. And I think the intent with that agenda really was to look at ways in which we at CVM can enhance our scientific and regulatory preparedness, looking forward over the horizon over the next five to 10 years, what do we see in terms of dealing with new technologies that are evolving today and in front of us today as far as what we see on the horizon and what we see in terms of the landscape of the animal health sector and product availability.

(00:27:56):

I think that agenda really focuses on four key objectives. One is what can we do to help support development of new technologies or new products that can really meet critical needs? What can we do to modernize our regulatory processes? And that really means looking inward and reflecting on what's our policies, our regulations, and what statutory authorities are we operating under? And are we well positioned really to navigate or to advance new technologies that are coming? Or are we best positioned to deal with the gaps that continue to be there in terms of meeting animal health needs?

(00:28:40):

And thirdly is looking at our workforce. Do we have the right expertise to be prepared to deal with those new technologies? And then again, the fourth area really then is looking at reflecting on what are the most critical needs? What are the gaps facing animal health? I mean, we have the challenge of many, many different animal species cutting across the animal agriculture sector, companion animals, zoo species, miners, and it runs the gamut. And so a variety of diseases affecting those animals. And historically I've had a challenge with getting sufficient number of products in the marketplace to address all those needs.

(00:29:21):

So really assessing that animal health need and looking at what are the emerging threats over the horizon. And again, taking into account that this spans across both meeting animal health needs as well as public health implications in terms of managing disease in animals. So I think for us, this innovation generally was really a challenge to ourselves to look at how can we potentially do things differently? How can we adjust our practices and again, look towards what the future brings in terms of technology and what can we do to help infuse new products into that system.

(00:29:53):

Some of the things we put in that innovation agenda are intentionally aspirational in nature. We're pushing the envelope a bit. And so this is also I think a challenge or an attempt to prompt discussion amongst the industry. So in a sense, what we need is we need input. We need engagement from the animal health community, veterinary community, others about what are helping to fill this out in terms of refining that agenda. What is it that we need to focus on?

(00:30:24):

So I think from a standpoint of priorities moving forward, I think one is we certainly are paying a lot of attention to focus on what are some of the new technologies that are right in front of us now. We've made some important progress in terms of moving forward with intentional genomic alterations in animals and what potential opportunities are there in terms of animal health and human health. We have expanding interest in cell and tissue-based products in veterinary medicine. And so there's new types of work we're looking at there, new expertise and there's promise there for new products. And there's interest in the ag sector about new types of products that may be moving away from traditional antimicrobials, looking for other types of products that can help the ag industry in terms of addressing environmental concerns, food safety concerns, or even looking at alternative ways to enhance production.

(00:31:20):

So those are all things we're focused on now and need to move and react so we can advance those technologies. But the other main priority for us, looping back to Reagan-Udall, is we're really looking forward to this year to focusing on working in partnership with Reagan-Udall to really do an assessment of the animal health sector and reflect on what are those gaps, what are the challenges facing that industry now? And really help to formulate some recommendations for us that will again, help refine our innovation agenda and help prioritize what makes most sense to move forward with there. So I guess that's for us, we're excited about this and also very excited about working with Reagan-Udall.

Susan Winckler (00:32:09):

Fabulous. Well, we are looking forward to that as well. And I think we've all learned a lot more about the intersection in animal and human health and the One Health Initiative and just lots of things happening daily news-wise as well. Let's close out round one.

(00:32:27):

Dr. Marta Sokolowska, who is deputy center director for substance use and behavioral health at the Center for Drug Evaluation and Research. Are you ready? All right. Your area of responsibility within FDA is one where clinical endpoints are frequently discussed. How do you think about clinical endpoints as it relates to mental and behavioral health, including substance use disorder?

Dr. Marta Sokolowska (00:32:53):

Well, thank you very much for including me and thank you very much for this question. CDR's covering broad range of indications and topics and endpoints are frequently being brought up not only in mental health but across a different indications. But I'm really glad that you mentioned mental health because especially since COVID-19 the mental health crisis, it's something that we are all trying to address and well, we haven't solved the problem just yet. Needless to say, mental health, it's a really broad spectrum that includes overdose prevention, addressing drug overdose that we all having. It's peaking right now. And despite all the efforts as well as addressing substance use and substance use disorders. When speaking to our stakeholders thankfully to the RUF, frequently through your engagement and through your facilitation of engagements, we hear very frequently that despite the fact that we know that

mental health indications and addressing this problem is so critical, we have limited investment in this space.

(00:34:05):

And when we are asking why is there limited investment in substance use disorder treatment? Frequently endpoints, that's how I'm getting to the endpoints, are being brought up. So it's definitely one of the areas that we are very much focusing on trying to better understand how can we help to facilitate drug development with better understanding of the endpoints and aligning the endpoints with patient treatment goals, clinicians' treatment goals, health outcomes, functional health outcomes, and the drug development programs. So we've been working with our partners and colleagues from CBRH, for instance, on issuing guidance on endpoints. More generally for instance, in October we issued the guidance on multiple endpoints in clinical trials addressing not only endpoints for substance use but across the different indications. Most specifically for substance use disorders, we've issued number of guidances recently. Most recently we issued stimulant use disorder, treatment development drug guidance, but we have also issued final guidance for opiate use disorder a year ago or so.

(00:35:22):

And we have other guidance, for instance, for alcohol use disorder where again, most of the critical component of these guidances typically are focusing on the endpoints, emphasizing that abstinence is not the only endpoint the FDA would accept. Again, stressing abstinence is not the only endpoint that FDA would accept, there are other endpoints that we want to explore. We want to use the community engagement to understand how we can utilize change in patterns of use, for instance, as an endpoint or change in the disease stage of severity as one of the endpoints. There are a lot of opportunities thinking about accelerated approval programs, potentially there's additional potential in there. So we are very hopeful that with all that engagement, we'll be able to reach that goal very soon.

Susan Winckler (00:36:14):

As I hear you reflect on that, just the importance of knowing where industry and patients might be, healthcare professionals even thinking about what does improvement look like and what should we be thinking? All right, that was round one.

(00:36:28):

Labeling innovation and interaction with the agency science's North Star, 50 million, not 15 million. Lots of things in the strategic plan and hiring, innovation and getting better on endpoints. So now we're going to pick up the pace just a little bit for round two, but we will get through on round two.

(00:36:48):

Dr. Marks. I'm going to start with you. So this question does refer to both CDER and CBER, but we know you are just speaking to the CBER perspective, are CDER and CBER aligned on their approach to accelerated approval in rare disease?

Dr. Peter Marks (00:37:08):

Complex question again, but I think we can say that we are generally aligned and that we acknowledge that there are some differences. Look, any large organization has to acknowledge that you're going to have... When you have the Office of New Drugs is 1500 people. Our center's 1300, 1400 people. These are large organizations. Our Office of Therapeutic Products, which is the equivalent of Office of New Drugs in CBER, is about 350 people. You have to work to get people aligned. And I think there's an effort to do that and I think there's a concerted effort now to do all of the normal Cs that you have to in an organization to do this. If you're a CEO, you get to do other Cs, you have to make people communicate,

you have to get them coordinated and you get them to cooperate. And all of those things I think is work that is going on.

(00:38:03):

I think we are trying to decrease the number of differences that we have at CBER from how we approach things from CDER, and I think vice versa. But there may always be some remaining differences here that I think people are going to have to accept. There are endpoints that might be acceptable for a small molecule that might not be acceptable for a gene therapy and vice versa. So I think there may be product-specific differences in how we go about granting what we will grant an accelerated approval for, but we'll try to be transparent about that when it comes up and otherwise we'll try to align to the best extent that we can. So you'll see more effort at that.

Susan Winckler (00:38:45):

Yeah, well it must be challenging. Different products, different groups of people, somewhat different statutory authority even. And so your communicate, coordinate, cooperate.

Dr. Peter Marks (00:38:57):

Right. Yeah.

Susan Winckler (00:38:58):

All right.

Dr. Peter Marks (00:39:00):

Right, exactly. Because I think we do have different, it's a large organization and we try to give people basically as much freedom to, things have come up from the grassroots as they can, but that means that sometimes they can diverge, which means coordination and communication are very important.

Susan Winckler (00:39:22):

Yeah. Excellent. All right, we'll come back to tobacco and back to Deputy Center Director Mital. You talked about a lot of things in 2024 in that strategic plan and hiring. So this is a four-word question. Is CTP's, abbreviations for one word right? Is CTP's workload sustainable?

Michelle Mital (00:39:45):

Wow. Yeah, I mean, I'll just start by saying we have such a tremendous opportunity to impact public health by regulating tobacco products and that strategic plan that I spoke about earlier is intended to prioritize the work that we're doing to make the most impact as possible and maximize that. That said, in 2022, as you all know, Reagan-Udall Foundation convened a panel that made some recommendations for CTP, including the establishment of a new strategic plan. There were also some recommendations related to resources as well.

(00:40:19):

The panel recommended that the Center improve its ability to recruit higher and retain staff and also to secure user fees from all sectors, including e-cigarettes. Right now we do not have the authority to collect user fees from e-cigarettes despite spending a significant amount of our time regulating those products. So as I talked about earlier, we've made some really good progress on the hiring with the direct hire authority and we are maximizing that to higher up. And the budget request that's under review now by Congress does include both the request to assess and collect user fees for all regulated

tobacco products as well as an increase in our user fees. So with more we can do more and manage that workload that we're really excited about.

Susan Winckler (00:41:07):

All right, thanks. Actually, as you mentioned budget hearings, I'm struck that actually this discussion is kind of like a budget hearing in that it could be anything on any topic.

(00:41:18):

So let's turn, we're going to come back to you, Deputy Commissioner Jones. What is your perspective on the acceleration in legislative activity at the state level to prohibit certain ingredients in foods on safety grounds, which would typically be the role of the FDA, and how do you envision balancing the work to assess chemical safety and also to continue to support innovative ingredients?

Jim Jones (00:41:42):

Thanks, Susan. So it is the work of FDA to evaluate chemicals that are authorized for use in food. For those of you who don't know, we have a pre-market review program for any chemical that you want to add into food, preservative, a colorant, an artificial flavor, all kinds of other chemicals you may want to put into food. And also for indirect food additives that can leach in from packaging. And that's a very robust program. It's very predictable. We have authority to evaluate chemicals that have been on the market, a post-market review program. However, for the last, really since its existence, FDA has not put much energy into the post-market review process. As a result in the last five or six years, we've seen a lot of attention in the public interest community on the issue of post-market review by FDA.

(00:42:33):

The agency has not really stood up a post-market review program. So the NGO community basically went to states and said, "FDA is not doing it, you'll need to do it." And a couple of states have been quite receptive to that message. California last year passed a law that banned for authorized food additives. Authorized by FDA, they are now going to be prohibited in the state of California. New York has taken up similar legislation. Illinois the same. From my perspective, the only way to influence this is for us to have an ambitious post-market review program, which is part of our commitment. It's captured in the reorganization Dr. Califf articulated about a year ago. Our chemicals program in the Office of Food Additive Safety will have a pre-market review group and it will have a post-market review group. Right now it's not a post-market review group. Every once in a while a chemical will get enough attention that resources will be cobbled together to look at it, but we need a sustained, predictable post-market review program.

(00:43:36):

And once we get ambitious enough and we're evaluating enough chemicals in a post-market context following the science and taking regulatory action when warranted, allowing the authorization to remain if there isn't a risk, restricting the chemical, however, if there is a risk, the states will, in my experience, stand down and I have a little bit of experience in this space. There are really only two other chemical pre and post-market review programs in the United States. And both of them went through this phenomenon, pesticides and commercial chemicals. And it wasn't until the federal government got ambitious enough in its agenda to start assessing and regulating as appropriate chemicals that the states just kept cranking away at state legislation.

(00:44:17):

Once the government got ambitious enough on it, the states backed off because they're like, "I have other things to do on my legislative agenda. You seem to have it under control." This does seem to be

getting traction in both the business community and in the industry or in the NGO community, I think this message is getting through. A rather large coalition of NGOs and industry have gotten together. They are right now advocating for a $35 million increase in our chemicals program for post-chemical review work. I know it's a very tough environment, but I think it is an indication that there's a sense that in the civil society that there's an acceptance that, you know what? FDA's got to be more ambitious if we're going to have uniformity in chemicals, which is really hard to operate in business without uniformity when you're selling things in commerce. So those are my views on that.

Susan Winckler (00:45:05):

So activity is what will change it.

Jim Jones (00:45:08):

That's right.

Susan Winckler (00:45:09):

More federal activity. All right, I'm going to come back to you, Dr. Sokolowska You mentioned the opioid epidemic and that it continues. So this question relates to that while there are medications to treat opioid use disorder, there are medications available, it doesn't appear that the available treatments are sufficient, or at least they aren't used by as many people who might be helped by the product. What can be done to help advance the adoption of medications to treat opioid use disorder and to develop additional treatments for other substance use disorders?

Dr. Marta Sokolowska (00:45:43):

Loaded question. Thank you. As you pointed out, and we discussed earlier, the overdose crisis continues and the substance use disorder, we still have a crisis and we cannot make a dent. Based on recent data from CDC and NIH one in five of people with opiate use disorder actually receive medication for opioid use disorder.

Susan Winckler (00:46:07):

So only one in five?

Dr. Marta Sokolowska (00:46:09):

Only one in five out of the 2.5 million people who have opioid use disorder. So what can we do? Number of things have been done. For instance, the moving of X waiver, which facilitates or broadens the number of clinicians who can prescribe a buprenorphine for opioid use disorder is increased now. There's no longer of a mandate that you need to have a special training and DA designation in order to do it. Hopefully, that's going to make a difference. And we see some fairly early reports that actually in Oregon for instance, it does make a difference. More prescribers are now prescribing, so that's outside of FDA though. We are working with our HHS partners to help to facilitate a lot of these actions.

(00:46:51):

But within FDA we are working on approving additional products. So we know that access is an issue. We have approved another injectable product. BRIXADI very recently we have approved a first generic version of injectable naltrexone products. Vivitrol was the brand name. Hopefully, with all these investments and developments as well as our work in supporting the development of endpoints,

potentially accelerated approvals, we'll be able to have more treatments, which will be hopefully also will make them more accessible and more associated with what people want.

Susan Winckler (00:47:35):

It sounds like I heard some similarities in those efforts with what had been mentioned for the device program as well and that conversation and thinking through what you need to stimulate innovation and development. All right, I'm going to turn back to ORA. Are you ready?

Douglas Stearn (00:47:51):

Ready.

Susan Winckler (00:47:51):

All right. Now this is a really big question. Not that any of these have been small, but this one, how will ORA be affected by the pending reorganization? And if you want to narrow that back to the two more important components, that might be an easier way to do it.

Douglas Stearn (00:48:09):

Maybe I'll just start with the name. So ORA will be the Office of Inspections and Investigations, which is a better reflection of what we do. So regulatory affairs raises questions about what we do because obviously there's a lot of parts of the agency that are engaged in regulatory affairs. It's really more of a historical accident that that's its name. And the focus really is on what we call sort of the three I's, which is investigations, inspections and import operations with emergency operations coming in as an overlay to those activities. So some of the things that are changing is that we have some places in our organization where there's some level of overlap with components in the centers that will be leaving ORA and be under one roof. And that includes compliance officers. So there's compliance folks in ORA and there's compliance folks in the centers, and they're going to be under one roof.

(00:49:03):

So they're going to be moved out from our current organization. And as well for our Laboratories, our laboratories are going to be moved out. So each of the centers has their own lab capability and tend to focus a little bit more on method development, but there's often a lot of overlap there as well because there's some issues in terms of testing that involve method development and some of the equipment or technical issues involved require center involvement and regulatory testing. So those are moving out. So we're having the food labs are moving into the human food program, and our medical product labs are moving in with the Office of Chief Scientists. So we will have a little bit smaller organization that will be focused on those activities that I've mentioned.

Susan Winckler (00:49:51):

That will still be a lot to do.

Douglas Stearn (00:49:53):

There'll be plenty of work.

Susan Winckler (00:49:54):

Yeah. And so OII?

Douglas Stearn (00:49:56):

Yes.

Susan Winckler (00:49:58):

And that's how we should say it.

Douglas Stearn (00:50:00):

Well, that's a good question. I'm not sure we have...

Susan Winckler (00:50:03):

I'm down the marker. It is OII.

Douglas Stearn (00:50:06):

It sounds better than OI.

Susan Winckler (00:50:07):

I knew somebody was going to go there. So we'll put it down to OII. All right, let's do our rapid-fire return to CDRH, real world evidence. For many years, CDRH has actively supported the development of real-world data sources like Device Registries and the use of fit-for-purpose, real-world evidence to support regulatory decision- making. I'm told that today manufacturers of more than 100 medical devices have used RWE to support FDA pre-market review decisions or to meet post-market requirements. What are your recommendations for manufacturers who are interested in using real-world evidence for FDA regulatory purposes in the device space?

Dr. Jeffrey Shuren (00:50:52):

Well first off, we're even seeing a continued uptick in the use of real-world evidence. In fact, now we're probably authorizing about 50 devices a year that are using real-world evidence to support that decision-making and of course a whole bunch of potential benefits from it generating evidence from real-world data, getting it more efficiently, having a better reflection of the true benefit-risk profile of that technology and able to better understand things going out in the post-market setting. But challenges too because that data may be incomplete, not standardized, poor quality. So if you want to leverage it, first of all, come talk to us. Take advantage of those meetings that we give out there to make sure if you're going to do it, it's going to be fit-for-purpose. Two, we've issued guidance back in 2017, but we just updated it late last year in draft. We'll finalize it probably in the coming year with more best practices and examples. Take a look at that.

(00:51:48):

And then we also help set up the National Evaluation System for health Technology or NEST that's being run by the Medical Device Innovation Consortium. And they've got relationships with 19 data partners and growing to like 220 million patient records, hospitals, clinics, doctor's offices, and they bring in, they're essentially a general contractor bringing in subcontractors who do data extraction, aggregation, encryption, analytics. So basically go to them, they'll look at the data source, they'll generate the evidence for you and determine is it going to be fit for purpose. For us, it means we have higher confidence in what's developed. And already last year, we had a company got their device authorized based on their study, came out of NEST. I've got another one we'll be authorizing soon, a third one to follow not long thereafter and several other companies are using it. And we're leveraging it now for

getting post-market data, and we're looking to build out an active surveillance capability. So heady times.

Susan Winckler (00:52:53):

Yes.

Dr. Jeffrey Shuren (00:52:53):

So here's my slogan. Get real.

Susan Winckler (00:53:00):

And that whole learning system, right? I am struck that there's ways for the agency to learn what's happening in the real world and then to generate the information that you need about those pending products. All right, I think if I counted right, it's last question in second round. Turning to CVM, so you mentioned this a bit, but CVM recently issued two final guidance documents that related to, and I quote "heritable intentional genomic alterations in animals." So gene editing in animals. Is that fair? I know that OCC won't let you say that. Can I say that?

Dr. William Flynn (00:53:40):

Yeah, intentionally genomically altered alterations in animals.

Susan Winckler (00:53:44):

All right. That's what I said, right?

Dr. William Flynn (00:53:47):

We can say IGA for short.

Susan Winckler (00:53:49):

All right, so intentional genomic editing. What's changed from the previous versions in 2017 and which category of products do you think the FDA is most likely to receive from industry?

Dr. William Flynn (00:54:03):

Well first, we are extremely happy to get those guidances out. I would say one is final and actually one's in draft. So one is actually available for public comment and obviously a really important milestone in terms of getting these guidances out in terms of clarifying policy and clarifying for developers of these products a pathway. And so these two guidances work hand in hand. One is more overarching policy and outlining our risk-based approach for regulating these products. And really that's premised on this framework that provides for a risk-based pathway to market categories. And so running the sort of spectrum of a category where essentially based on what we know through exercising enforcement discretion, those products without a consultation with the FDA could go directly to market. On the other end of the spectrum where the third category would be products based on what we understand about risk or maybe don't understand about risk for those products, they would come in the expectation there would be an application submitted for us to review prior to making an approval decision.

(00:55:18):

In the middle is a second category, which is a category where there would not be an application that they would need to submit and us review prior to products going to market, but there would be an expectation that they provide information to us in advance of going to market for us to assess risk. And once we've assessed that information, then make a determination that those products could go to market. So that is the overarching framework.

(00:55:46):

The second guidance really delves into more of the details of technical guidance for those developers that say fall in the third category that would need to submit an application. It outlines what that is and what that would look like for these kinds of products. So those two guidances sort of work hand in hand. What's new really is, I mean one is a reaffirmation for our commitment to work across the federal government on this issue, including as part of that establishing a new MOU with USDA to help facilitate information sharing and collaboration on this issue. When it comes to the guidances themselves, I think some of the key differences from the perspective of the developers is one, I think just overall clarified what this framework looks like for them in terms of the different pathways, clarify the timelines for review. And also, which is one of the more substantial changes is expanded that second category, that middle category in the terms of the types of products or types of IGAs that potentially could qualify for that second category.

(00:57:06):

And then really for farmers who would have these animals potentially on their farms and that raised some concern is clarifying that if they're not involved in developing IGAs but they have an animal on the farm that contains an IGA, they can go about their normal business and handle those animals as they normally would including breeding because there was some misconception and confusion around that point. So those are some of the key differences, and I think answering that second point question about what do we expect to see most of not surprisingly is things that fall in that second category that we've expanded. And that opens up the door potentially even to certain IGAs involving food producing animals. And some examples of that would be say alterations that could be obtained through this intentional genomic alteration process that you would expect to perhaps see through conventional breeding.

(00:58:09):

And in other words, if you can accomplish that same kind of change through conventional breeding, then that may be one we would look at for that middle category. Essentially we would evaluate information upfront in terms of assessing risk and then make a determination whether the product, that use could go to market.

Susan Winckler (00:58:26):

Yeah, yeah. Fascinating in just thinking about the scope of activity and what that might mean. Well actually, I would say Commissioner Califf, you have conversations like this all the time where in 54 minutes you hear everything from science and accelerated approval for rare disease and aligning between CDER and CBER, you hear about clinical endpoints as it relates to substance use disorder and what more can we do in stimulating product innovation to how CDRH is getting real, and the success of the TAP program and what you're seeing in the innovation space to all the changes that we might see on products in labels from healthy to not only then in their labeling but to what's contained in them and some more activities it relates to chemical safety.

(00:59:22):

All that's happening with CTP and your strategic plan and the daunting workload that you are going to continue to navigate and address hopefully with using that new hiring authority to what we just heard on genomic editing for animals, and I really will memorize the name of the guidance before I ask you about it again, but then all of CVM's activity as it relates to innovation in animal health and finally to our field force that is changing names to OII and your 50 million import operations. I think we need to thank this group for sharing all of that insight in that short period of time. So thank you.

Commissioner Remarks with Q&A

Robert M. Califf, MD, MACC, Commissioner of Food and Drugs, U.S. Food and Drug Administration

Susan Winckler (01:00:12):

And so we'll let you all leave the stage as we welcome to the podium, the Commissioner of the FDA. I am sorry that all of their productivity was focused here for the last little bit of time, but it was really, really helpful I promise. But we want to turn this over to you. The foundation was created to work with the agency and the Commissioner to address regulatory science challenges. And I often say we have one of the best roles in the world, so Dr. Califf, you may have the podium. I will step away, and we're looking forward to hearing from you.

Commissioner Robert Califf (01:00:49):

Okay, thanks Susan. Good to be with you and it's good to hear all this. I have to admit my head is exploding right now. If you think about all the questions they answered, this is my Senate Appropriations Hearing book for tomorrow's hearing, 220 pages, single space. I remember every single word of it of course. But it was good to hear at least I think I knew the answers to all the questions that were asked or at least part of it, but these people obviously know a lot more about every element of this. I thought what I'd do is just give you a brief update on priorities as I see it for this ongoing year and then have as much time as possible for a Q&A because I'm sure you'll have some interesting questions. As I'm sure it hasn't escaped your attention, there is an election coming up and I learned in 2016 that that's a particularly interesting time to be at a place like the FDA as you're trying to anticipate what needs to get done, what might change, and a new administration of either party and how to deal with it.

(01:02:05):

So I'll start out with just what I see as some top priorities that we're working on now, and you've actually discussed a lot of them right here. But number one on my list is the reorganization. This is the largest reorg in the history of the FDA. As far as we know, it's involving 8,000 people. The status right now is we've been through HHS, the executive branch of the government, and we've notified Congress. We're not quite all the way through Congress yet. We'll be discussing that tomorrow at the hearing I'm sure. And assuming that that goes okay, technically we're not required to get permission of Congress, but given the dynamics that we operate in, it would obviously be kind of stupid to try to proceed without reaching an agreement with Congress that this is the right way to go. And then assuming that we get through that, then we have a final step with the unions.

(01:03:04):

About 80% of our employees are unionized, and so we have to make sure that we have agreement on how to proceed there, but I'm assuming all that goes okay, which I'm confident it will. Then we got everybody a mass at the gates ready to go, and we literally have hundreds of people that have volunteered within FDA to be change agents basically to lead the change across every single aspect that needs to be involved. And as you've already heard, that not only involves the human foods program

where we started, but also OII reorganization and creating the Office of the Chief Medical Officer, which is really combining things that already exist into a more efficient organization and a few other key issues. Number two on my list is tobacco enforcement, and I'm getting my body armor on for tomorrow.

(01:04:03):

I would say the amount of pressure on the Center for Tobacco Products that I saw when I came in, when people ask me what were you surprised by when you came back the second time? No one told me actually what was going on in CTP. And it was quite a shock for me to realize that there were over 26 million applications for vaping products that had to be dealt with. And when I came in, the center was right in the midst of trying to really recover from this staggering amount of work that had come in that had not been really expected. And I do want to thank Reagan Udall on obviously the reorg is largely following a report that came from the Reagan Udall Foundation. And in the same way, the CTP report that you all did has been extremely helpful to us and I feel like we're well on our way now.

(01:05:00):

We've gotten through 99% of the applications. I say we, I haven't done any of the work. It's a huge amount of work by very hard-working people, and we really now need to turn our attention to the enforcement part of what we do. And it's a focus of Congress. Simple-minded way I look at it, right now, the majority of our vaping products that are coming in are made in China. These are products that are not legally sold in China to Chinese people. And so we've got to figure out how to deal with this in a much more efficient way. We have 300,000 retail shops selling these products, and the idea that we're going to have an FDA person in every one of these shops is obviously not feasible. So we got to have a way of stopping this stuff at the border. And so there's going to be some discussion about that tomorrow and I won't get into more details about that, but enforcement I think is really a key thing now.

(01:05:58):

I do want to note that the number of combustible tobacco users is continuing to decline. The mortality rates are continuing to decline. At least as best we can measure it, teenage vaping is actually declining. Having spent some time with family teenagers last weekend, it's hard to know exactly how accurate those numbers are. But I believe we can really stem that with better enforcement. I also want to point out that the residual combustible tobacco users are a great concern to me. I spent some time studying this at my time at Alphabet, and these are in general, not people that are otherwise doing well, a very high rate of serious mental illness, a very, very high rate of living alone and being uninsured. Or another way of thinking about it, if you're hanging out in places like the FDA or university faculty lounges, no one is using combustible tobacco. But if you go to parts of society that are different where people are having a lot of trouble, that's where you'll find combustible tobacco use. And I probably don't need to tell you that our health systems are not exactly focusing on this part of the population. And so getting rid of combustible tobacco use in the residual 30 million people that are using it is going to be a major effort that's not just FDA, but we have a role to play. Number three for me that has risen recently to the top of my list is rare disease. It's not something new for me to think about. I've been involved on the development side of treating, developing treatments for rare disease, but the big change now, which I'm sure you talked about maybe a little bit before I came in when we get to CDER, CBER is the science is explosive right now and offers opportunity for families that have previously been consigned to no effective treatment and despair in very difficult circumstances.

(01:08:06):

Now there's real hope because the technology is here. Interestingly, the same technology we're discussing in animals for there. It's the editing of the genome and the ability to directly affect gene function by small molecules now, which is evolving. So thus the CDER and CBER collaboration is critical.

And I can't say a lot about the details of that, but it's an area of great ferment. And I'll also add very important from my experience in developing these treatments, we can't talk about just in the sense of drugs and biologics, the diagnostic assays and the assays for biomarkers in drug development are very important. So we got to have the device part of the FDA in this effort also. Then the fourth area is one I didn't expect to have to spend so much time on. I did not think I was going to become an expert in supply chains for generic drugs, but this is a big problem. It's not going away. There's a really important report from HHS put out about a month ago I would urge people to read if they're interested in this topic. We're still experiencing over 200 threatened shortages a year. The less expensive the drug, the more likely there is to be a shortage. And it's really fascinating for me to try to get politicians to understand. We essentially have two different industries. The innovator industry, where at least in my view, prices are too high. One can argue about that. And then the generic industry, where actually US prices are lower than Europe, significantly lower. And in fact, so low for some of these particularly injectable staples that we need every day in the running of our hospitals and routine care. So low that you can't even make them in India with the cost of Indian labor and make a profit.

(01:10:07):

And I don't know, some of you have run businesses. If you want to sign up to be CEO of a company guaranteed to lose money, I welcome you to enter that particular business. So there's a lot the FDA can do to deal with when there's a threat and shortage. It's really plugging holes in a system which is a market failure. And in order to solve this, we've got to fix the market. But in the meanwhile, FDA has got to plug the holes as best we possibly can and keep as many of these products coming in as possible. And then I'm going to add a little one here because there seems to be just extraordinary interest in this, and I'm personally interested too because of my history. It's the advisory committees. You may have noticed, we just put out a notice that we're going to have a meeting about advisory committees.

(01:10:58):

Every time we say the least little thing about advisory committees, there's an avalanche of press and people with interest. And for me, I have to say my time on the Cardio Renal Advisory Committee was really the epitome of my academic career. Because it's in that setting that all the information comes together about a topic in a way that you never see in the world of traditional academics or clinical medicine, but how to conduct those meetings, how to get the most out of them, how to use committees to get the advice we need without creating spectacles of people rushing. I still remember in the old days before cell phones, there would be the rush of everyone to the pay phones when the committee voted. I just heard about a very important committee that may not take a vote, which warms my heart. I know a lot of people love the votes and many of our own FDA people want to have as many votes as possible.

(01:11:54):

My view is we want advice. And I was just at Harvard, and almost everybody in the audience thought the advisory committee actually made the decisions, which just shows how we've got a lot of education to do. All right, so then we have these overarching things that we've been working on with your help. Misinformation. I don't know what you think. I still think we're actually losing ground to misinformation, but we are. It's sort of like we're going against the tide. And I think thanks to you all, we have a very active three-part program within FDA now that we're working on, following advice from the Reagan-Udall report. But it's much bigger than FDA and there's a lot of work to do there. The general talk of evidence generation. I like Jeff's motto of, "Get real." Your report there is very useful. There's a cross-HHS effort now underway. As someone who's worked on this for my entire career, I have to say I'm so frustrated it's still hard to really get traction on making the progress we need.

(01:13:12):

And a real theme for me is that if you look at FDA approval, every product coming through has a very high standard of evidence that's needed to get on the market. But then there are a whole bunch of questions that come after that that are not addressed by the FDA and for which the FDA doesn't have authority to require that the studies get done. And so this is a space that's not owned by anyone and this is really why all of HHS is involved. And there's a lot of interesting possibility there to create a system of evidence generation in the US that answers questions of comparative effectiveness, value. Remember that in the IRA, CMS now has an official statement, they are going to use real-world evidence in the price negotiations on drugs that come under the IRA. And then we've got the issue of computing internal data, AI within the FDA.

(01:14:15):

I won't talk much about AI outside the FDA, it's an enormous area that's transformative. But within the FDA, if you want to look at productivity, you've heard about the overwhelming amount of work. There's no way that the people we currently have in an increasingly complex set of things that we're regulating can get all that work done unless we figure out how to embrace the use of artificial intelligence and not only using the data that we are generating in the traditional way, but also bringing in external data that can help us have essentially a continuous surveillance of all the quality of the products out there and then focus our human work where it's going to be most productive. It's another thing I'm getting ready for tomorrow. I have to keep reminding a lot of people that we don't make the products at the FDA. And so I still maintain that we're most like referees.

(01:15:18):

We don't play the game. The game is played by the industries that produce the products. It's their obligation to produce safe and effective products. Our job is to call the shots as we see them to the extent that we can. And for example, we don't test every generic drug that comes in the US. It's a requirement that whoever makes the drug has to test every lot that's made. And we have to figure out how to use the resources we have in the most intelligent way to oversee the quality of the system. And then I'm going to mention in closing three or four areas that I think are interesting. I could go on forever, if you could tell.

(01:15:58):

But dietary supplements, I still have a great hope that one day we'll have a rational system of dietary supplements in the US. I don't expect that to get done this year. I'm looking at Jim. But what I want to have is a rational approach that we can at least begin to put into play for people to think about how to regulate the $60 billion industry more effectively so the supplements that are effective get used more often, and those that are ineffective people don't waste their money on them. We need pathways for hemp, marijuana. Janet coined the term Center for Bad Decisions as a need for a new center. But these are products that have no medical benefit for the most part except under very specific situations. Our society has decided, Kratom is another example, has decided that people are going to use these products in large numbers. And in our view, there needs to be a systematic approach to regulating harm reduction, essentially.

(01:17:07):

For example, we do take enforcement action now when we find someone selling gummy bears full of Delta 8 marijuana type product, which can be extremely dangerous to children. But there are all sort of variations on that theme right now where we need to work with Congress to come up with a better pathway. I'm obsessed with nutrition right now. I sort of have a recurring nightmare. My great grandkids are going to read a history book that said there was a time when the Food and Drug Administration was led by this guy named Califf, and the whole goal of society was to produce a diet that would increase the

weight of every American by a pound per year. And then in order to deal with that, he helped the industry develop a drug that cost $20,000 a year to try to reverse engineer what we had created in the first place.

(01:18:08):

And I think ultra processed food is clearly a target. Not a target for it to do something about this year, but to understand better. And it's a theory with a lot of observational evidence that there's a direct relationship between ingestion and of large amounts of ultra processed food and weight gain and diabetes and other bad outcomes of almost every type causal inference about exactly what it is. I think there's a real need for research there because we can't take action without consensus in the field about what the exact issue is and what needs to be done. And last thing I'll mention is international strategy. We're working on an international strategy.

(01:18:57):

Our supply chains are diversified and global. We have enormous national security threats from the fact that our key starting materials for drugs is coming from China in a setting in which there's tremendous adversarial situations. But that's only the start of it. If you look at our recent applesauce problem, things are happening in countries that we can oversee, but we can't have the same level of intense oversight that we have on products that are wholly made in the US. And I'm not advocating to reshore everything, but we got to have an international strategy that has more than just a few FDA people out there. I mean, imagine yourself as the FDA investigator going to inspect a firm in China right now, what's involved in making that happen, the cost of it and the personal risks that people are taking, given all the things that are going on there. So stay tuned for that. That's a brief summary of a few priorities.

Susan Winckler (01:19:59):

Do you have time to take a few questions?

Commissioner Robert Califf (01:20:06):

Yeah. Oh, yeah.

Susan Winckler (01:20:08):

All right, so you got cards when you checked in if you want to write a question on there. I have a couple that came in and this one, well, they reflected that they imagine your job is a lot of firefighting and that you don't get to reflect on maybe things that went well. So this was an open question to say if you had to reflect on something that has gone well in the last year, what might that be?

Commissioner Robert Califf (01:20:35):

I mean, I had a list of 30-something priorities. I think I talked about them last year with you all and we just looked at them again. I think pretty amazing progress has been made in almost every one of those priorities. I've already talked about CTP. Yes, we have problems, but if you look at the progress that's been made in the organization, the effectiveness, the rigor and discipline involved in getting through all those applications, I think that's a really good example. Let's look at the pandemic and the choice in dealing with vaccines and antivirals. Now the issue of uptake of those things, that's another issue. It's almost like this is the kind of thing where everything we do well on is going to create a new set of questions that have to be dealt with. But cosmetics, we're ahead of schedule in terms of things that we're doing in cosmetics, don't say this too loudly, despite budget allocation that matches. So we're

hoping that Congress will see the way to allocate more money to cosmetics because it's a really significant need. I can go on and on.

Susan Winckler (01:21:50):

Well, so a question that just came in has to do with cosmetics and it says, "What role might digital tools play in helping cosmetic manufacturers navigate this new regulatory landscape like GMPs?"

Commissioner Robert Califf (01:22:06):

That's really interesting. I see it the other way around. The question is what are we going to do to keep up with the use of AI in cosmetics? I learned that at the big cosmetics show this year, the main plenary session was entirely on AI because of the transformative capability that now exists to look at yourself in the computer and talk to the computer and have cosmetics applied and see what you're going to look like. You can add in a little cosmetic surgery along with it and get that looked at. So I think the cosmetics industry, I've also heard that teenagers right now are completely obsessed with Sephora, which I don't understand very much.

Susan Winckler (01:22:54):

Yes, they are.

Commissioner Robert Califf (01:22:55):

So I think the question is more how are we going to regulate the explosive growth of AI in every industry, including this one. And I would say use of AI by the cosmetics industry is not high on my list of things that I worry about the industry in that regard. I think it's going to take off, and I'll just mention one thing that I do think about periodically is a potential for asymmetry. We're getting all of our applications now have something that you might call AI somewhere along the development pathway. And the companies we're working with are using AI increasingly. We've got to be able to match that capability in order to just deal with the applications, for example, in an effective way.

Susan Winckler (01:23:46):

So there's AI within the agency and then thinking about how it's coming in the applications to the agency and how industry is using it?

Commissioner Robert Califf (01:23:55):

Yeah.

Susan Winckler (01:23:55):

All right.

Commissioner Robert Califf (01:23:56):

A lot of different segments there.

Susan Winckler (01:23:57):

Well, as you might expect, I think 50% of the cards I got had AI on it. And the one piece that I think was untouched here was any thoughts on how AI use in medical devices might be different from what you've already said about AI?

Commissioner Robert Califf (01:24:16):

All right, I'll unload here for just a couple of minutes, if it's all right from your... First of all, you talked about achievements. We had a record number of biologics, drugs and devices getting on the market through the FDA this past year. And again, we are not producing these products, they're being produced by the industry, but just the work it takes to make good choices and review the applications is quite a bit of work. And I think good decisions are being made. When it comes to AI in devices, again, the least of my worry is AI in what I would call traditional devices for serious medical illness. So for me as a cardiologist, it's easier to talk about defibrillators being an example. The regulation of AI there looks to me pretty much like the regulation of anything in a defibrillator. You've got to show the darn thing works and if there's a hint of a problem, then you're going to have to start over and prove that what you're producing actually has the benefits that you're claiming it has.

(01:25:23):

The thing I'm most worried about is one that is really at the gray zone interface of the FDA with society decision support and the use of generative AI in clinical practice and in interacting with people at home is an enormous area. It was the main focus of my visit to Mass General Brigham in understanding the way many smart people there are looking at it. My big worry is that if we're looking at the criteria being used by health systems right now to purchase, I'll just call them AIs. There are all these different tools that incorporate AI. It's almost completely a financial lens. So it's, "Can this produce a better margin for my health system," or a margin where one doesn't exist because they all feel under stress.

(01:26:16):

When the main use that I see is if, I'll guess all of you have had relatives or yourself go to a clinic in the last year and have witnessed a really good doctor, nurse, pharmacist typing into a computer, unable to look up and even think about what's going on with you. And all those people are spending hours now in the evenings trying to catch up with their epic billing. Generative AI should fix that. And then the question is, is it going to be used by the task masters that are financially running the systems now to give you time to interact with patients or is it going to be used to see twice as many people. MGB right now, like our leading academic biggest NIH conglomerate, 100,000 people in that system can't get primary care appointments right now.

(01:27:09):

And yet, I see the potential. Let's just take a patient with rare disease comes into St. Vincent's in some city that's a good hospital but doesn't have the specialist you would need to diagnose a pediatric rare disease. I mean, you would hope as a parent that that system is connected with all the other systems using generative AI to identify, "Hey, this child needs a specialist and we can figure out where the specialist is." And that encounter is combined with all the other children like that one so that you're learning as you go along. There is no technical impediment to that. Now, it could happen today, but we exist in a world where there are barriers that are going to keep that from happening unless we figure it out. Now, what does the FDA have to do with all this? I'm looking at Dr. Sherman.

(01:28:12):

This is a blessing for us in many ways. We are prohibited from looking at the finances as the issue. Our mandate is safe and effective, and I'm hoping that we can somehow get in requirements that force the health system to do what they should have done in the first place. For example, if it's a generative AI, and I learned a lot about this at Alphabet, if you stick that in a system and don't continuously update it and look at its operating characteristics, it can either get a lot better, it can get a lot worse, and you don't know which it's doing unless you're constantly essentially doing the same study over and over. And so this is something called local recurrent validation. Something to remember. If health systems

have to do that, that means they're actually going to have to be able to follow people over time and be accountable for their clinical outcomes, which would achieve some other goals. I know you didn't ask for all that, but that's...

Susan Winckler (01:29:08):

But that was perfect, and that gets us to time. If we were on a zoom, we would all be saying, "Oh my gosh, I've got to log off and go to another one." So Commissioner Califf, thank you so much for joining us today.

Conclude

Richard L. Schilsky, MD, FACP, FSCT, FASCO, Board Chair, Reagan-Udall Foundation for the FDA

Dr. Richard Schilsky (01:29:20):

So that does bring us to the end of our open public meeting. I want to, again, thank the Commissioner. I want to thank all the center leaders who are here. I want to thank Susan for doing a wonderful job as our moderator and thank all of you and all of you who are online and who've been listening in to the meeting today. So thank you all. I will now declare this meeting adjourned. And for our board members, we are going to adjourn to another room to finish our day's work. Thank you all very much.