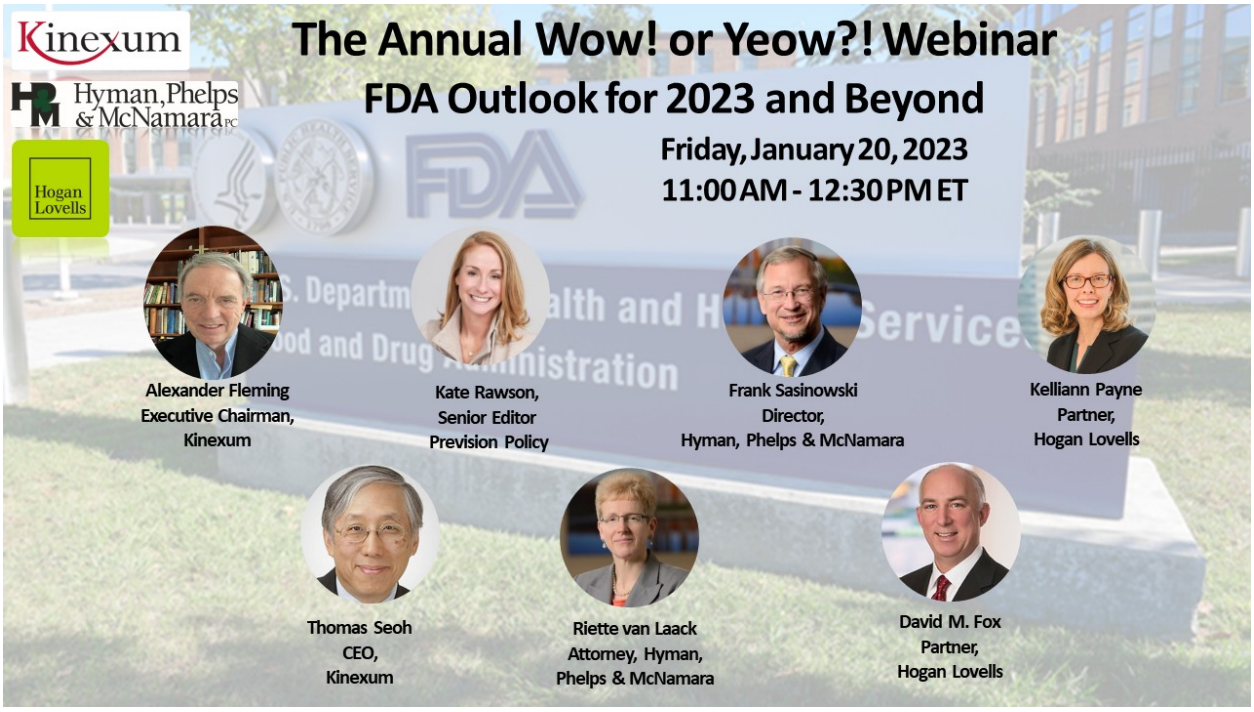
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The Annual Wow! or Yeow?! Webinar
FDA Outlook for 2023 and Beyond
Friday, January 20, 2023
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Alexander Fleming
Executive Chairman,
Kinexum
Kate Rawson,
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Prevision Policy
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About the Panelists:

Alexander Fleming is Founder and Executive Chairman of Kinexum, a strategic advisory firm specializing in regulatory, clinical, CMC, and other translational aspects of life science product development. During his tenure at FDA, Dr. Fleming led reviews of landmark approvals, including metformin and the first statin, insulin analog, PPAR-agonist, and growth hormone for non-GH deficiency indications. He helped shape FDA policies and practices related to therapeutic review and regulatory communication. Dr. Fleming is also founder and President of the not-for-profit Kitalys Institute, whose mission is to accelerate the translation of emerging advances in the biology of aging into public health, the prevention of chronic diseases and the extension of healthy longevity for all.

David M. Fox, a Partner at Hogan Lovells, and formerly an Associate Chief Counsel for drugs at FDA, advises management teams from start-ups to the largest global pharmaceutical and biotechnology companies on matters before the FDA and DEA. Mr. Fox previously led Hogan Lovells' Pharmaceutical and Biotechnology practice group and now serves on the firm's global Life Sciences management team.

Kelliann Payne, a Partner at Hogan Lovells, drafts premarket submissions for diagnostic and therapeutic medical devices, evaluates and formulates applicable regulatory strategies, and reviews the accuracy of marketing claims. In her role as Assistant General Counsel at QVC, Inc. from 2013 to 2014, Ms. Payne counseled internal clients on FDA and FTC regulations applicable to health, wellness, beauty, and cosmetic products.

Kate Rawson is a senior editor at Prevision Policy LLC, a continuous information service. She has more than 25 years of experience covering FDA-regulated health care industries, primarily pharmaceuticals and biotechnology. Kate co-founded the annual FDA/CMS Summit for Biopharmaceutical Executives and the Biopharma Congress. Kate also helped launch and was a senior editor for "The Pink Sheet" DAILY, and served as Managing Editor of "The Rose Sheet," which covers regulatory and business news of the cosmetics industry.

Frank Sasinowski, a Director of Hyman, Phelps, & McNamara, has helped secure FDA approval for hundreds of new drugs, including more than 100 new molecular entities, often for serious and rare diseases. Mr. Sasinowski has been involved in many of the recent drugs FDA approved by way of its accelerated approval process. He is involved in many cell and gene therapies and aided on the first approved systemic gene therapy, Zolgensma. Mr. Sasinowski joined FDA in 1983 as regulatory counsel in the Center for Drugs and Biologics, where he was key to implementing both the 1983 Orphan Drug law and the 1984 Hatch-Waxman law.

Thomas Seoh is President and CEO of Kinexum, a strategic advisory firm that provides regulatory, clinical, CMC and other translational guidance for life science product development. He is an entrepreneur/executive who has held senior leadership positions in public and private pharmaceutical, biotech and medical device companies for over 25 years.

Riëtte van Laack, provides regulatory counsel on OTC products, including foods and dietary supplements, OTC drugs, cosmetics, and animal feed and drugs on a range of FDA, USDA, FTC, and CPSC issues. Ms. van Laack has experience with food and dietary supplement issues, labeling and advertising. Ms. van Laack also has s experience with regulation regarding labeling and advertising of OTC drugs and cosmetics. Ms. van Laack has degrees in Nutrition and Meat Science and was a professor at the Dept. of Food Science and Technology at the University of Tennessee.

Webinar transcript:

Thomas Seoh:

We're delighted to have you join us. Delighted to have you join us for the 2023 edition of our annual Wow or Yeow, FDA Outlook webinar, jointly organized by Kinexum, a regulatory and clinical consulting firm, Hogan Lovells, an international law firm with a large food and drug law practice, and Hyman Phelps & McNamara, a specialist law firm with the largest dedicated FDA practice in the US. We have a chock-a-block set of topics to cover, so I just want to remind you to enter your questions in the chat column. The panel will try to get to as many of those as we have time for in the last segment of the webinar. Just to warm up the chat function, those of you who are willing, please say hi in the chat and from where you're logging in. A recording of this webcast will be posted over the weekend and a transcript will follow. I'll now turn the mic over to our moderator, Dr. Zan Fleming, Kinexum Founder and Executive Chairman and an FDA alumnus. Zan?

Alexander Fleming:

Thank you, Thomas. And we do have a Wow panel and much to cover, so let's do dive in. It's a tradition for us to start with Dave Fox, FDA's year in review that he does so well. Dave Fox is a partner at Hogan, and he and I go way back to early days where he was Associate Chief Council, charged with keeping me out of trouble. I'm sorry, just kidding. But we, or at least I, enjoyed working with Dave a great deal back then. Dave is a master resource and my go-to expert for a very broad range of drug and biotech product development and approval issues. Dave now serves on the firm's global life science management team. So Dave, take it away.

David Fox:

Well, thank you Zan, we appreciate it. I'm going to start as I do every year by apologizing in advance for what you're about to hear. I'm speaking only for myself, which is a good thing because this is, I will say, an approximation of the truth. It's shaped to meet the irreverent spirit of Yeow or Wow, and Zan and Thomas's drastic time constraints. So here is one year in hopefully, 10 minutes. So, into the numbers, 37 approvals from CDER, 8 from CBER, a total of 45 new approvals. I imagine you're all close readers of the trade press, so you've seen the headlines. This is about a 25% drop in the numbers from what we've seen in recent years. If you look at it the way the Pink Sheet looks at it with a 15-year lookback, this is a straight on regression to the mean. 37 CDER approvals is right on point. That's about the average over 15 years. If you look at it the way CDER does in its annual report, over a 10-year period it's about 15% off the mean. And if you look at it the way I do, which is over the last five years or roughly the last PDUFA cycle, it's about 30% off the mean.

So, 37 CDER approvals, a pretty weak year by the numbers, but let's dig a little deeper. About half of them involve novel mechanisms of action. So about half first-in-class products, not bad, more than half, as always, rare diseases, significantly more than half use an expedited program, priority review, fast track, breakthrough, accelerated approval, all in line with the usual numbers. Oncology as always, drives the numbers. 13 approvals this year versus 17 last year. Not really a material difference. We did see a spike in approvals in dermatology. That was the standout. They were second to oncology. So again, those numbers are all strong and an even distribution if you look at some of the major therapeutic areas, hematology, neurology, infectious disease defined broadly, even ophthalmology. **So,**

a good spread of approvals, but nothing in pain, nothing really in allergy, nothing in psychiatry, very little in imaging. So those were weak.

The inventory, however, as again I think this is aptly captured to the trade press, was there for a strong year. There were 70 applications up for approval in 2022, but only six in 10 actually made it over the finish line. That is pretty troubling. Half requested a new clinical study. And that, I think, is really startling. It wasn't just inspectional issues, it wasn't just COVID legacy inability of FDA to do a preapproval inspection that drove those numbers, there were some very significant disagreements between the agency and sponsors over the adequacy of the data, which I think it could be a variety of things. It could be the targets are getting tougher. It could be novel clinical study designs, interpretation of data, but it also may be a comment on the status of the interactions between the agency and the industry in terms of getting feedback. We're seeing just this continued trend toward written responses only, for sponsor meetings.

Maybe we're seeing the effects of meet from home as opposed to the old line, suiting up and going to the White Oak, and maybe without the urgency of COVID when FDA wasn't particularly productive. Without that urgency, maybe **we're starting to see the effects of a little bit of distance between the principles at FDA and the principles in the industry. Now, what could change some of that? We have a new mechanism under the new PDUFA. If you haven't looked at it, I strongly recommend that you do: type D meetings, which is an effort to allow sponsors to get three questions answered from a limited number of disciplines on a short time span.** A targeted feedback mechanism has been added, which I think is helpful.

We are going to see now the implementation of accelerated approval reform. I should have noted **accelerated approvals were cut in half in 2022. So only six accelerated approvals versus historical norm of about 12 per year**. Now the chatter is that the trend away from accelerated approval or the lower numbers is going to continue because industry will be scared off by the new requirements, which are essentially, that you must have your confirmatory study set up before you get your accelerated approval, and that FDA will have more rapid means of withdrawing your approval. But it could be that strengthens the accelerated approval program and makes it more attractive and more open with the assurance that you have a study already underway. So, we'll see. And then the last I'll note, continue to be down for the year, and I think continues to be troubling, are advisory committee (Ad Comm) meetings.

We're still in the low tens, 10, 11, 12 advisory committee meetings per year for novel therapeutics and significant supplemental applications. I think what we've seen is that everyone benefits when the agency goes to an Ad Comm. We saw Ardelyx get a serious Complete Response Letter turned around through an Ad Comm and an appeal process. And then of course, and we'll talk about this a little bit more, I'm sure many of you followed, Amylyx had two advisory committee meetings in the span of one review cycle with the second Ad Comm essentially reversing the first Ad Comm. More or less the same panel but reaching a different conclusion. So, I think Ad Comm is another component to try to maintain the numbers that we've gotten used to.

In terms of other notable upswings, I'd be remiss if I did not mention biosimilars. We're really seeing the maturation of the program. We're now up to **a total of 40 biosimilars approvals, 7 in 2022 against a total of 5 reference products.** All big-name targets, Avastin, Lucentis, Neulasta, Eubera and Neupogen.

And then we had two more interchangeable biologics. These are pharmacy substitutes in the biosimilars area, one against Lantus and one against Neupogen for a total of four categories of interchangeable biologics. That program continues to grow slowly, very slowly, very deliberately, but that is the big story ahead. And then last, what's going to drive the numbers? What's going to change the numbers materially, going forward? My own takeaway from what I'm seeing, and this is no great revelation, but it's RNA Therapeutics. RNA Therapeutics are just bursting. As a regulatory geek, I think the interesting question is **what numbers will the RNA Therapeutics affect? Are they drugs? When are they drugs, and when are they biologics? That's a very interesting regulatory question that we're going to be confronting.**

Let me move now to stand out approvals for 2022. I always like to pick out a few for this group. A standout approval really depends on your interests. There are some wonderful new products in the rare disease space just everywhere, and I can't cover them. So, what I try to do is I pick out the ones that would be most interesting to the real regulatory nerds. So, with that in mind, let me tell you about a few. For semi disclosure, I was involved in a few of these, but I won't tell you which ones to protect the innocent. So first on the list is Ferrings or Rebyota, which is fecal microbiota live transfer. This is the first true therapeutic in the microbiome space, and another area that I think we're just at the beginning of seeing the industry come through with some remarkable therapeutics. **This is essentially a human fecal transplant to repopulate the microbiome after aggressive antibiotic therapy to address a recurrent *Clostridium difficil*e infection**, essentially a traveler's diarrhea. These types of products that are derived from natural sources and retain all of the complexity of a natural product are always of interest to the regulatory types. I strongly recommend that you look at the labeling and the review documents. This product also went to an advisory committee. It's an orphan product, and there are others who are also seeking approval in this space and that's going to raise some very interesting issues.

Second, Amylyx's Relyvrio for ALS. Any ALS product is a headline. It's such a tragic, serious disease. From the regulatory perspective, can't miss the fact that it went through two advisory committee meetings in the same review cycle. What's very interesting if you dig in, is to see how the regulatory question as posed by the agency in the two advisory committee meetings changed over time, from the initial meeting, asking whether a single study was highly persuasive, to the second meeting, asking whether the single study plus confirmatory evidence was persuasive. There was a very marked shift in the way FDA defined the regulatory question. That in turn, you could see how that drove the debate of the advisory committee and potentially drove the outcome. **In addition, the confirmatory evidence came from within the single pivotal study, which was a very interesting development, as well as some really sophisticated analysis on the natural history of the disease in comparison to what was seen in the clinical study. So, lots to dig into on that approval. Just really a fantastic accomplishment all around.**

Third, and this is not so much a regulatory geek one, but I'll get to it in a second. In the endocrine metabolic space, only two real standout approvals in that space this year, but one of them**, Lilly's tirzepatide, is probably the product that would be the game changer for the largest population of the products approved. A remarkable product, dual mechanism, product building off of what we've already seen in the GLP-1 RA. The GLP-1 RA class was kind of the flashiest story of the year with weight loss indication.** All I hear about from my friends and friends of friends on the West coast is everybody is on a GLP-1 RA product. That's the hot new thing. And I'll leave that alone.

But the complement to that approval which is interesting is, and apologies if I'm not saying this correctly, Tzield from Provention Bio, which is a product that is approved to delay the onset of stage three serious type I diabetes. I'm drawn to this from a regulatory perspective because **anytime FDA approves a product to delay or prevent the onset of disease as opposed to treat the disease, is a signal moment.** Very, very tough risk benefit proposition from when you're treating people before they actually have the disease. This one we could debate for a very long time. I know Zan has strong feelings about it, and this is really in Zan's wheelhouse, so I'll leave it alone. But for those again, who are looking for those unique stories, I would look at the record for that approval.

Next up, we couldn't get through this without talking about Lacombe and Alzheimer's disease. Last year's session everyone was talking about Aduhelm. Everyone had very strong feelings about it. What stood out to me, was something that Frank Sasinowski said last year when everyone was really in a lather over Aduhelm, is he said that the amyloid story has not been fully written yet. He told all of us to calm down and watch. Now we have a new approval, same endpoint. Very quiet, not the same uproar. But then, I had this written. And then yesterday I think Kate Rawson pointed out Lilly's product was not given approval, and I think we're going to talk about that. So as Frank said, the amyloid endpoint story has not been fully written. Where that story takes us remains to be seen.

Two last ones, these are not NMEs. So, this is a little bit off the topic, but I just want to point them out. One is Xeloda capecitabine, which was the first product that fell under FDA's Project Renewal Program. So, this is a program led primarily by the Oncology Center for Excellence to go back and try to update, bring current older oncology labels. So Xeloda historically was approved for colon and breast cancer in fairly narrow segments. And middle of December, FDA approved 8 efficacy supplements all in the same day, all based on literature to significantly expand the labeling to include now pancreatic, esophageal, and gastric cancers, and significantly broaden the colon and breast cancer indications, as well as make some changes to dosing. They're all based on essentially input from experts and interpretation of published data, much of which is not even explicated in the labeling of the product.

So again, for the regulatory nerds, I highly recommend you look at that. That's very interesting. **Is that the beginning of a trend of going back now and modernizing labeling based on published literature?** And then the last one, this is a really obscure one, but I took a look at the supplemental approvals, most of which are for relatively new drugs where another indication was added. But I went back and looked at the oldest drug that fell into this category. It's a drug from a company called Fennec Pharmaceuticals. **Drug is Pedmark, sodium thiosulfate, which was approved originally for cyanide poisoning and now has been repurposed in 2022 for hearing loss in children on platinum chemotherapy. I thought that was a wow.** I think that's just great, and I think a good place to end. So, thank you everybody. And again, as much as it was a low year in numbers, once you dig into the approvals, you can always find some really exciting, really interesting, and some real Wow candidates.

Alexander Fleming:

Wow. Well thank you, David. We'll be coming back to some of those topics in a moment. But let's go on to Kate Rawson, who is one of the most astute and up on everything analyst and observer of FDA that I know. She's Senior Editor at Prevision Policy and brings more than 25 years of experience covering FDA-regulated industries. Among the many things she's done is to help launch and be a Senior Editor at the Pink Sheet, and she did serve as the Managing Editor of the Rose Sheet, which though was not around, is

aptly named because it covered the cosmetic industry. So, Kate, give us your take on some of the big picture issues for the agency.

Kate Rawson:

Yeah, absolutely. And thank you, Zan so much for that introduction. I hope I can live up to it. Just to pick up for a minute on what Dave Fox had said, the advisory committee meetings are always really interesting for us. That's our bread and butter at Prevision Policy. Just **what you've seen over the past couple of years is a real drop-off in the number of products that are going to a committee, which is too bad because David, as you said it's a lot less transparency as to why the agency does or doesn't approve something.** I was just looking back at the last few years, this is the third year where if you don't include the EUAs, more than half of the products that went to Committee were rejected by the committee. That's historically pre-Corona or pre-COVID, you're seeing more of a 70% yes rate.

So, I think FDA is being really particular about the products that it brings to Committee. I think a lot of that has to do with just, as we know, those committee meetings take a lot of time and energy. That's a trend that we're going to watch. The other thing I'll just mention about that, and then I'm going to get into what I am going to be covering as well, is that one thing that Commissioner Califf has talked about for 2023, is an update to the advisory committee process. One of the things that he has said might be included in that is a re-review of products that go to Committee, get a no vote, and then instead of being approved anyway, or for FDA issuing a complete response to bring it back to Committee again.

So, we might start seeing more committee meetings in the future. I just wanted to respond to that because I do like to geek out on advisory committee meetings. So, I'm going to go even bigger picture and step out just a minute and talk for a little bit about what the midterms mean for FDA, the elections that we just had, and then focus a little bit on what Commissioner Califf's priorities are going to be for the next couple of years that he had said he has left at the helm of FDA. So, the midterms, we didn't see that red wave that a lot were predicting, but there were still enough changes, certainly with the change in party on the health side as well as the Senate committee level to shake things up for FDA.

I think most obvious, if we're starting in the Senate is that **despite the fact that the Democrats retain control and even picked up a seat, there is likely to be a tougher oversight climate for FDA. And I think this is most obvious in the change of leadership in the health education, labor and pensions, or health committee with Vermont's Bernie Sanders as the new Chair. We all know Senator Sanders is the de facto leader of the progressive wing of the Democratic Party. He's also at the top of the list of some of the most vocal critics, a brand-named drug pricing and industry commercial practices in general.** While the former chair, and that was Washington State's Patty Murray who's moved over to chair the Appropriations Committee, she was certainly no industry ally, but there is going to be still a pretty sharp change in tone with a Sanders-chaired committee. In addition to industry commercial practices, Senator Sanders is also a critic of FDA Commissioner Rob Califf. He voted against Califf's confirmation in both cycles, and as chair of the health committee, he's going to have a ready platform to press his concerns about industry influence over FDA should he choose to do so. **On the Republican side of help, you have Louisiana Senator Bill Cassidy as the new ranking member. He's certainly not afraid to criticize FDA, but he generally fits within the Republican consensus that the agency is for the most part on the right track in its approach to drug regulation.**

So, you probably won't see much heat from Senator Cassidy, but of course it will be Senator Sanders who will be setting the agenda with the Democrats for the next couple of years. On the house side, I think FDA is probably less likely to be in the hot seat there on healthcare issues. **The Republicans are much more likely to press on the drug pricing provisions in the Inflation Reduction Act.** Since the IRA, as you recall was passed without any Republican support, the GOP can use their new chair post on energy and commerce and that's Washington's Cathy McMorris Rodgers for aggressive oversight on certain provisions including Medicare's new prescription drug negotiating authority. So, a repeal of the IRA is not possible without Republican control of the Senate and the White House, but GOP oversight during most of the key implementation periods will be extremely important for innovator companies.

The only thing I'll just mention is that I live in Maryland and the sole Republican among the Maryland representatives is Andy Harris and it's been announced that he will share the Appropriations Committee in the house that oversees FDA. He's a little bit of a wild card as seen in some of his comments and actions during the height of the COVID pandemic. So, he could come down hard on FDA and Commissioner Califf during appropriation hearings. Couple of FDA-related issues that I just want to mention that could get attention from a GOP-led house access to RU-486, that's Mifepristone, the medical abortion drug, that had already been an issue for Commissioner Califf during his most recent confirmation. And then in a similar vein, FDA's review of a potential OTC switch for oral contraceptives could become a flashpoint.

On that issue, FDA has scheduled an advisory committee review. **This is a Perrigo switch application for an oral contraceptive, Opill, in November. That's one of the big OTC switches that we may see this year.** That meeting has been postponed. If FDA reschedules it as promised, it could be held while Republicans have control in the house. So just something to mention as a potential flashpoint and maybe some hearings on the hill or at least some chatter there. **I want to pivot just a little bit and talk about Commissioner Califf and what his priorities will be for the next couple of years. It's important to note, I think the good news is that he has announced that he will stay on until the end of President Biden's first term. So, there will be stability at the helm of FDA, at least until the end of 2024.**

And given the vacancies that we've had in the last really 10 years, I think that'll be good news for everyone compared to where we were a year ago when we were all together. I think the commissioner is much freer now to pursue his chosen priorities now that the emergency phase of the pandemic is over and there will always be an infant formula crisis or a food safety issue, but I think it gives him a little bit more room to talk about what he wants to focus on. **And those are really two big meta issues. One is transforming evidence generation and the other is combating misinformation.** So combating misinformation, I'll tackle that one first. That's something Califf knows quite a bit about from his time at Alphabet, the Google parent. **He's talked about the fact that government cannot solve this issue alone given that there's already so much mistrust in science in general that we've seen over the last couple of years and certainly in regulatory and scientific agencies.** And he's talked about **the need for a network of people that are committed to the promulgation of reliable and truthful information.** But he's also admitted that he really doesn't have a very good solution to this problem and that he's talked to anyone he can talk to about how to address misinformation and is coming up short. So, one idea, and I'd be interested to hear what our attorneys on the panel think about this, but he said that he's working on some **sort of limited safe harbor for sponsors to defend their products without complying with the normal restrictions on advertising and promotion.** That's something that he says he is actively pursuing. I'm not sure how that would play out in practice. So would love to hear what others think about that. So

the other meta issue that Califf sees facing FDA and industry is a need to improve the clinical trial enterprise. And this seems to be where he really wants to make his mark for the remainder of his time at FDA. **So, this includes increased diversity of clinical trial participants, expanded use of real-world data to support regulatory decisions and the creation of data sharing systems.** As we know, he's a former clinical trialist at Duke. And so, **finding better mechanisms for evidence generation is really one of his long standing areas of interest.** He came back into the commissionership position under the Biden administration with really a heightened interest in expanding the agency's use of new rigorous sources of data. And I think here, **the emphasis on clinical trial demographics and methods in the FDA Omnibus Reform Act or what we're calling FDORA, may serve as a jumping off point for Califf to really advance a broader trial modernization initiative as a legacy project in his second term as head of the agency.**

So just to recall, Congress passed a clean authorization of the Prescription Drug User Fee Act at the 11th hour last year. But when they did that, they left a lot of provisions on the table and some of which they knew needed to be reauthorized like best pharmaceuticals for children, Orphan Drug Grants. And then there were also some other provisions in there that have been discussed over the years but kind of fell off of the clean PDUFA, like regulation of laboratory developed tests, which is the VALID Act, accelerated approval provisions to give that program some more regulatory teeth. Cosmetics regulations for example. So FDORA, which ended up getting wrapped up in the omnibus package and pass during the lame-duck session did include some of those provisions like AA and cosmetics, but it also incorporated a series of provisions under the heading Clinical Trial Diversity and Modernization.

So, while the primary motivation at the political level for these measures is really concerned and well placed and necessary concern about increasing clinical trial diversity and representation in previously underserved populations, **the provisions really will fit well with Califf's long-standing interest in reinventing the clinical trial enterprise. And there's a lot packed in there, but the provisions relate to decentralized trials, digital tools, innovative trial designs**, those are the parts that are most likely to be the most significant for FDA and Califf to advance ideas for transforming the conduct of clinical trial research in the near term. So there are going to be a lot of public meetings and guidances on all of these topics in the months to come. And the last thing I'll say about this is that we've already started to see movement on this.

This is something that the Oncology Center of Excellence had already put forward with its Project Equity program. And now there was a guidance issued, I mean almost a year ago now, maybe nine months ago that says, "**That all IND holders should plan to submit a race and ethnicity diversity plan by the time they reach the end of phase two meeting stage at the latest**." So we're already seeing a lot of interest and movement on this and the FDORA provisions will only continue to push this forward. Lastly, I'm just going to look ahead really quickly. **As far as Califf's priorities are concerned, he is going to continue to focus on the response to the opioid crisis. FDA released an opioid prevention framework in August and a key part of that and a priority of Califf's, is enabling an OT switch of naloxone.** That's the other big switch this year besides Opill, the contraception.

And he also needs to support the reauthorization of the Pandemic and All-Hazards Preparedness Act, which could be used as a potential vehicle for the VALID Act and maybe we'll see if our dietary supplement friends think there could be some that could also serve as a rider for some of those regulations that fell off the FDORA bus. **And then most recently, and I'll end on this, he's expressed an**

interest in developing frameworks and strategies to address common chronic diseases and mental health. And has made an argument recently that industry really isn't focusing enough on still those big primary care, big market products. **And he really seems to pit that a bit against industry's interest in developing targeted products for smaller markets.** And I know later maybe we can get into some of the IRA provisions and the incentives there and how that kind of works against small market or at least small molecule drug products. But maybe I'll end there in the interest of time.

Alexander Fleming:

Okay, you fully delivered on my vaulted description of your profile, so thank you. Let's now go on to Kelliann, another Sterling expert on our panel. Kelliann Payne is a partner at Hogan and she expertly dwells in the device world supporting strategic development of medical devices and diagnostics as well as submissions of pre-market applications for those products. And she served previously as an in-house corporate council for QVC. So Kelliann has great experience and Kelly, so much going on at CDRH. Take it away.

Kelliann Payne:

Yeah, a lot going on at CDRH. I would say kind of similar to the drug side of things, **it seemed a little quieter this year I would say for De Novo applications for example, we were down by about 10 De Novos.** So we went from about 30 to 20 in the De Novo space as far as De Novo requests being granted this year. Which just gives you an example kind of what we're seeing, and I would say **what's missing from the De Novos that were granted this year are largely machine learning or AI-based devices, which we saw quite a bit of last year.** It seems that people are filing 510K's on top of already cleared devices for those types of technologies. So there's a good number out there that are serving as predicate devices for the 510K pathway. That said**, I think we'll see more De Novos this coming year. I think we'll see them in the mental health space for a lot of AI or digital health based devices.**

An example of that is the publicly available **breakthrough designation given to Oxford VR for their anxious avoidance CBT cognitive behavioral therapy digital device. And so, I think we'll see others in that space following on the heels of Akili, which has the ADHD device.** So I do think we'll see more there. FDA also came out with the Clinical Decision Support final guidance document this year, so I think that'll change some things. They added a time criticality function to that guidance and they noted things such as sepsis calculators in EHR systems that will be required to be regulated by the agency likely. So I think that's a switch as well, where we may start to see more De Novos come in for devices such as that. Also in the omnibus there was what we call the provision for predetermined change control plans with FDA, PCCPs. And I think these were mentioned last year, but there's been a bit of a switch.

We were being told in the past that we needed a De Novo to develop special controls to enforce those change control plans in the field for AI-based devices. The omnibus would now allow those to go through a 510K. They did note that any changes in the field made through a PCCP, could not stand in as a predicate for future devices. So they put that limitation on. And with PCCPs, FDA expects usually the changes in the field to be superior, not substantially equivalent. So there has to be a performance increase. So that is an interesting development and something a lot of people were looking forward to. And we're also still looking forward to a guidance document from FDA on the types of changes that could be incorporated into those predetermined change controlled plans. They will give sponsors some flexibility who have AI-based devices to not have to come back to FDA for every modification made to those devices in the field.

This year we go another year without seeing any device indicated for Alzheimer's from CDRH. So that is a missing element I think people are still looking forward to. So I think that's largely the year end. There was a PMA this year that came out in the orthopedic space. The traditional devices are still getting PMA approval. **One was CartiHeal for their calcium carbonate insert for knee lesions. And so that went pretty smoothly through FDA on the PMA side. And again, a lot of 510K notices were seeing iterations of AI algorithms.** FDAs being somewhat flexible in allowing one indication to serve as a predicate for say another similar indication. So taking a fracture clearance and allowing it to be a predicate for a mammography device because they're both identifying something on an image. And so some flexibility on the 510K side. But that's largely what I'm seeing on CDRH's side and I know there's others behind me, so I'll let them talk and I'm happy to answer questions during the discussion period.

Alexander Fleming:

Well, terrific. We'll be coming back very shortly. Riette van Laack is quite an amazing story in her career and changes thereof. She worked as a food scientist with a PhD before she went back to law school and then on to Hyman, Phelps & McNamara for many years. She's provided counsel on over-the-counter products including food and dietary supplements, cosmetics and animal feed and drugs. And all this across a very wide range of FDA, USDA, FTC and Consumer Product Safety Commission issues. So we're delighted to have for the first time, Riette van Laack join us. Riette, tell us about the F in FDA.

Riette van Laack:

Yeah, well thank you for the introduction. The F in FDA has been silent for a long time, but the last year became noticeable because F does not only stand for the grade that the F in the FDA got, but there were a lot of food issues that came on the forefront. Of course, I'm pretty much sure that everybody on this call has heard **about the infant formula mess that the was created and then the F in FDA became more visible to everybody. There was a report by political, which basically said it's a gigantic mess, FDA. Then the food group, the Center for Food Safety and Nutrition, many people did not know about CFSAN, but now more people know about that. There's in this organization, structural issues, decisions are not made. There is infighting, there's all kind of issues.** There are many regulations that are implementations of laws that the regulations are there, but FDA doesn't seem to make progress on these issues or in the system, in the agriculture water for produce.

There's a rule that the law has been passed. Food safety organization actually passed in 2011 and now we are in 2023 and we're still dealing with the issue. What is going on? There is infant formula issues, there is heavy metal issues, there's nutrition issues that USDA publishes diet guidance every five years. Nutrition teams do not make progress. We get more and more issues because people are not on healthy food. So, the infant formula crisis resulted in an FDA internal investigation. There was a report published and then there were questions, more and more questions, and then we got the Reagan-Udall report, which was published, what was it? In October, November last year? Basically, came to the same conclusion as the political report was that there is... What did they say? It looks like a football field. Anyway, it's a chaos theory.

There is chaos. Different people don't know who to report to. There are not really completely silos, but there's just no communication and there's no ultimate decision maker or there's not a line of command. So, the report suggested some corrections and one of them, basically **new restructuring of the organization in CFSAN. And this all resulted in, as has been happening before, a call for a single food**

safety agency or single food agency or some form that maybe not be part of FDA, so that you would get maybe DA, which some people think that the F stands for federal not for food so that they could still have an FDA, just changed the meaning of the abbreviation and then have a different agency on the food, so that it's more clear and gets higher priorities so that the F is not so silent anymore.

This call for single food safety agency or single food agency is nothing new. Has happened more than the 17 years that I have been doing this kind of work. And so, I don't know if it's going to happen. I think it was two days ago, there was an article in the paper about this and one of the things that was repeatedly mentioned in the comments is because there is also a funding issue, it's not a priority. I mean **drugs and devices and even tobacco, they get much higher priorities than food. We all eat, and the foodborne diseases are a big issue. All the outbreaks are very costly, but also our general health. We have still mortality because diabetes, we have heart diseases, all that stuff, and it's all related to nutrition, which is food. Anyway, so will we see a single food safety agency in the future?**

I predict that I will be retired by the time that might happen if ever, but hopefully at least there will be restructuring in the way that the chain of command gets easier and that there's no more infighting and that things become more effective because it is very frustrating for the industry too. Many products are FDA, the food side is much post-market enforcement and not pre-market approval, but certain things that we need to get done from FDA, don't get done. So that was a major negative last year. I think that **the positive for last year is that FDA issued a proposal for the healthy definition. It's what they call a nutrient content claim. And foods that meet certain requirements can be called healthy.**

There has been, since FDA issued the proposed regulations or the final regulations, amended regulations for nutrition labeling, added sugar has become a big issue. The healthy definition did not consider added sugar. There has been a lot of private litigation in that aspect. And FDA's new definition is a big change from what we did in the past. **In the past it was very nutrient-oriented, and you could just add nutrients to a product in many cases and make it healthy. Now it is much more food oriented and diet oriented, which is more consistent with the dietary guidance, which the diet guidance presumably will lead to healthier people, better nutrition for us. And so that is a big change.** That said, we will have to see where it goes. I think it is very consistent with the nutrition science and that's what FDA claims too, but it's still very hard to see how that will be implemented in practice. So that was a positive.

And another negative, talked about food and single food agency, one of the things that people tend to forget is dietary supplements are foods. And all these reports, it was **the focus on food, and food safety and nutrition, not so much on dietary supplements, because dietary supplements are sort of in between. But FDA, also, in the opinion of many people, has not been so favorable looking at dietary supplement.** And one of the main things that they have been doing the last couple of years and last year, again, is, there is a provision in the Food Drug and Cosmetic Act that says if you have a new diet ingredient, if it is marketed before the product is investigated as a drug, or approved as a drug, and it is valid and otherwise, it's a race to market. Market it first as a dietary ingredient, then you're safe.

If it's first marketed or investigated as a drug, then you can't market it as a dietary supplement. FDA has interpreted that provision in such a way, and that came very clear last year, that a company can be marketing a product because it has determined that the exclusionary clause does not apply. And then a couple of years later, FDA said, "Oh, wait a minute, there was an investigative new drug approval for this ingredient, so you can no longer market it." The way that FDA has interpreted that provision seems, it's

in my mind inconsistent with the law, and it seems also unworkable. And FDA has been very inconsistent with that. So hopefully, that will be addressed in the future by litigation, or by statutory amendment, or something. But it relates in great uncertainty in the industry about if an ingredient is legal or not.

And then the last thing that I want to mention, which I think is exciting and a positive thing, in the last year FDA basically finished its first consultation for animal cell culture product. And so, **this is very briefly, instead of growing animals, having farm animals and killing them and all that, so we now are working, there's a big development and interest in growing cells in culture, and making meat or animal products out of that.** And so, we are optimistic that in the foreseeable future, really the foreseeable future, there may be actually that type of product on the market, not necessarily in the meat and the poultry, but more on possibly the seafood and even milk products, whatever, that are not from animals, but are animal similarities. **They are animal cells, but they're not from animals, except for the original cells. So that's very exciting and that's something that we are like a wow.** Hopefully, this will come to happen in the near future. That's all for now.

Alexander Fleming:

Thank you so much. Great to get coverage of the FDA. And we'll maybe come back to a few issues in a moment.

Riette van Laack:

Sorry, I forgot my whole cosmetic part. Kate already had mentioned that there is in FDORA the Cosmetic Regulation Act. And so that's an exciting event. But basically, there's now the Food Talk and Cosmetic Act. The SEA has gotten attention and there's provisions that require FDA to issue regulations for good manufacturing practice. **There are some other safety regulations, industry will have to register facilities. There will be listing of the products, mostly the ingredients, focuses very much on safety, so not so much on labeling. It will help with getting a bit more certainty and uniformity and regulation of cosmetics. And it will get them somewhat more credibility since now, people always say, "oh, cosmetics are not regulated." Well, we will get more regulations.**

And so that's an exciting development, and we will see what happens the next year. Most provisions become effective after a year, after the enactment, so the end of 2023. And then some regulations will have to be developed in the next two to three years. And actually, FDA got money for that work that they have to do. How, if they can do it, if they have enough resources as far as personnel, remains to be seen. But that's a new and exciting development in the cosmetic world.

Alexander Fleming:

All right, well, thanks again, Riette. And now, last but not least, Frank Sasinowski, the director at Hyman, Phelps & McNamara, and a singularity having helped secure over a hundred approvals for more than, or across a range of new molecular entities and cell and gene therapies. Many of these are for cell, are for serious and rare conditions, his trademark, specialty. Frank joined FDA in 1983 as regulatory council, where he was key to implementing, not only the Orphan Drug Act, but the very important 1984 Hatch-Waxman law. So Frank, take it away.

Frank Sasinowski:

Thank you very much, and I appreciate it. Always, this is what our sixth or seventh year, it's a wonderful program that connection puts on. Let me say this, that I just celebrated the 45th anniversary of my 25th birthday last Saturday. So, with that perspective of time, I'm going to talk about three topics from the perspective of time. **One is something that happened 25 years ago with the FDA Modernization Act, phenomenal 115, I think that's a huge wow. And then talk something about 35 years ago, when the FDA out of its creative genius came up with the accelerated approval pathway to deal with the AIDS crisis. And then lastly, talk about this month is the 40th anniversary of the Orphan Drug Act. And I think all three of them are wow.** I'm going to start with the one that's 25 years ago, the FDA Modernization Act.

Why am I bringing up a law that's 25 years old as though it's a wow? How can that be new? Well, let me just briefly explain. Carl Peck, when he left the FDA, the Senator head of the Center for Drugs, he came up with this idea that we should have an alternative pathway to approval at that time to show substantial evidence of effectiveness, **the only path was by adequate and well controlled studies, which the FDA had always interpreted to be at least two. So that had two positive, adequate, and well controlled studies. So, he pioneered coming up with an alternative, which would be one adequate and well controlled positive study, plus confirmatory evidence.**

Now, in the meantime, FDA knew that this was happening, **so the FDA came up with a guidance document on substantial clinical evidence of effectiveness, which said, "By the way, there is another way. We will accept one highly statistically persuasive study if it's likely on something like irreversible morbidity and mortality, where it'd be unethical to do another trial. So, we do have a pathway for one study, but remember, that's a very narrow pathway.**" What Carl was talking about, what got created in the law, was a very broad pathway, because it said, you can have confirmatory evidence. So, the question was, what constitutes confirmatory evidence?

There was one workshop that Carl convened on that, and the key breakout session was, what does confirmatory evidence mean? And he asked Janet Woodcock and I to co-chair that. And so that's been published and stuff. So, this has lane fallow for a long, long time. What do I mean by that? I tried to persuade my good friends, Janet Woodcock and Bob Temple, who co-authored that May 1998, Clinical Evidence Effectiveness Guidance document, to revise it. And it took some time. Peter Stein, the head of the office of the new drugs at an Every Life Foundation for Rare Diseases, made a monumental breakthrough announcement, in which at that Willard Hotel Conference in September 2019, he said, "I'm going to speak to what constitutes confirmatory evidence." First time publicly, FDA had done that. He showed a slide that showed four different ways you can have confirmatory evidence as illustrations.

Now, he could do that because he knew OMB was already reviewing the draft guidance document that was going to be released in December 2019. So the guidance document came out using those same four examples that Peter Stein announced at the Every Life Foundation Program. And so that was a groundbreaking sea change. How do I say that? Because, as Zan said, I've had a finger in the world of rare diseases since 40 years ago. And it turns out my view is that most rare disease therapies are approved under that 1997 law. It might not be acknowledged by the FDA, because they didn't have any guidance on it until December 2019. And I didn't even start to see FDA revision speak about it until spring of 2021.

But now I can cite to examples. And for instance, Dave Fox brilliantly gave an overview of all what happened in 2022, he always does. And in that he talked about Relyvrio, a drug for ALS. And he talked about how the Spring 2022 advisory committee said, does this meet the standard that May 1998 standard of one highly statistically persuasive study? And the advisory committee said no, because it only had a P value of 0.03, it wasn't highly statistically persuasive. But the question was changed in September 7th by advisory committee. It was like, does it meet the confirmatory evidence, this 1997 law? And it did. You remember Dave talked about it, that there were two things, an open label extension, as well as some natural history. Natural history was one of the four things Peter Stein talked about, one of the four things that's in the December 2019 guidance.

What's a little unusual about the use of natural history in this context is, natural history, one of the things that the FDA is interested in looking at is, how does natural history compare to the placebo arm? **Because remember, one of the ways that you can see it between group difference if you do a study is, what if by chance, especially in a rare disease, by chance, those who get randomized the placebo arm actually deteriorate faster than what you would expect. So, you might see that would be a false positive. You would see a drug trial that was positive, but it was driven by something that had nothing to do with the pharmacological benefit of the intervention.** So anyways, Relyvrio is a good example of one of those types of ways you can have confirmatory evidence. Livmarli, a product for rare liver disease, Alagille, its primary hallmark symptom is pruritus, itchiness. But what it did is it also showed it had a big effect on serum bile acids, which are mechanistically predictive of the clinical outcome. How it affects, how patients feel or function.

And so the FDA said, yes, you had a positive study, only one, wasn't highly statistically persuasive, but you know what you had, you had mechanistic information. And over the time we've always talked about biomarkers as being important. **Biomarkers can be important for proof of concept, they can be very important for dose selection. But now biomarkers are important because they can be the second basis for the approval. Biomarkers as mechanistic information can be a type of confirmatory evidence that can complement your single adequate and well controlled study, so now biomarkers take on a whole new level of significance in the drug trial armamentarium. So I think that it's a big wow** to talk, and I could talk for days about this topic, but that's enough for that.

Second topic: accelerated approval. Again, you heard Dave and Kate both talk about that. I think that my view of it, and it could be a little bit different, is that I view what happened in 2022 as a big wow for accelerated approval. And how can you say that? I mean, really, Frank, obviously your 70 years are showing you're getting senile, because how can it be a wow? Here's how I think it's a wow. I think it's a wow because I expected that when Frank Pallone first start came out with ways to ratchet back on accelerated approval, they were pretty draconian. Senator Burst stood up to that and said, "I won't take that in PDUFA VII." So, what came out, and what Kate was referring to in the omnibus, the FDORA provisions, are not really that significant. So I thought that the attack on accelerated approval would've had much sharper knives, and it would've been eviscerated. It was not. In fact, it's largely intact the way it is. In fact, they could stand to have some improvement in terms of accelerating the path that the FDA can have to remove an approval. I think that can still be looked at. But the point is that they very kindly referred back to something I said last year about Aduhelm, that the story of amyloid hasn't been written yet. And what I was saying is that **accelerated approvals outside of cancer have been very important. Look what they did, when I was at the FDA and I had a very small part in helping to create the accelerated approval, look what it did for a death sentence. HIV was a death sentence back then. It's**

now a chronic condition because you know what? They have been something like 26 drugs approved on accelerated approval, which have changed that condition dramatically. The very first non-cancer, non-infectious disease accelerated approval is one I helped with Betaseron for multiple sclerosis.

I don't think Betaseron is that much prescribed, I have no idea, it didn't look at IMS America. But there's something like 19 other MS drugs. So, the first drug that gets approved by accelerator approval like AZT for AIDS, doesn't have to be the best. Betaseron, doesn't have to be but it opens up the floodgates to more research, it encourages people to come in. Same thing happened with other accelerated approvals. I'm thinking about Eteplirsen, I had a hand with Sarepta's Eteplirsen, first drug for Duchenne muscular dystrophy. I think we have nine drugs now approved for Duchenne muscular dystrophy. And so that's why I was saying with Aduhelm, that the amyloid story is not over. So, I think accelerator approval, what happened in 2022 is actually, a wow, because we dodged, in my view, we dodged a bullet.

We had people like Ellis Hunger, former FDA who's now at my law firm, he said something at a congressional caucus on rare diseases that I chaired a panel on in February, in which he said when he was at FDA, he interpreted being reasonably likely to predict as meaning 70% of the time that therapy would actually convert into showing benefit. Now, that's not 90 or 95% of the time, which I think sometimes I get the feeling that some people believe it has to be that prognostic to be able to have an approval, but it's certainly not 50-50. So I think that we're moving forward. Now, the last thing I want to talk about was 40 years ago, the Orphan Drug Act. **And the Orphan Drug Act, I think it's a wow. I mean, look what's happened. I mean, everybody cites that in the decade before the Orphan Drug Act, there were something like only 10 drugs approved for rare diseases. Now we have 500 or something for 350 different diseases.** So it's remarkable what's happened in the 40 years since. But there's a lot more that needs to be done. And how can we get a lot more done? Because to get to the 10,000 rare diseases at the rate at which we're doing it, it would probably take something to the year 2,350, and most people with a rare disease aren't going to live that long. So, we need to accelerate the path of getting new therapies out for rare diseases.

So flexibility, global statistical test and the randomized control trial. I'm going to touch on each one in about a minute, just to give you a heads-up. Flexibility is a concept many say I helped to start, but I won't go into the history of that. But what I now see with time, and the reason why I mentioned I had a hand, because with time I now see that maybe it's a concept that needs to be rethought, because flexibility when we tell FDA, as Billy Dunn said in his opening remarks at the September 7th Relyvrio, the ALS Drugs Advisory Committee, when he cited FDA has a mandate, and he cited the FDA regulations at three 12.8 in other places, where it **says FDA is mandated to apply flexibility where there's a serious or life-threatening disease with unmet medical need, people understand they have greater risk, they'll accept more risk, they'll accept less certainty of benefit.**

He said, "We have an obligation." Here's my problem with that, Billy Dunn is exactly right, that's something I've been saying for decades. **But what I feel bad about is the pressure it puts on FDA officials, because they have no guidance as to how far, I call it coloring outside the lines.** They're told we have an obligation to color outside the lines. That is, don't stick just to what a trialist would require you to do, because this is a rare serious disease with an unmet medical need. Okay, that's fine in concept. But how far outside the lines can you color? What colors are you allowed to? When have you gone beyond that? So, I think it puts an enormous personal pressure on FDA officials that is unfair**. So**

maybe we have to think about coming up with something that will give them a bright line test, that will be more quantitative. Something like the Emergency Use Authorization authority, which says, the known and potential benefits should outweigh the known and potential risks. Then you can have some sort of quantification. That's one topic.

Second topic is global statistical test. One thing that I see emerging, there was an FDA official, Dr. Wang, spoke at an FDA mitochondrial disease workshop in 2019. And she said, **for rare diseases, what you should do is not look at one primary endpoint but combine them. Because what you want to do is with a rare disease there probably it's going to be heterogeneously expressed among different symptoms, and how it affects people's function. And so, you want to combine them.** And so that way, because for any individual, they might be affected on one symptom more than another, and so you won't have a chance to be able to show a benefit, and if you only have those people, it would dilute out your ability to see between group difference, especially in a small trial. So, she said, an example she gave was Pompe. She says, you should not look at just six-minute walk, or pulmonary function tests like forced vital capacity, but combine the two. And she showed the power statistically to see a lot more. And when I've talked to FDA officials about this, the way you convert that, because it's almost like a Z score, so how do you convert that to section 14, your clinical trial section labeling, so that it's meaningful to physicians? It's time. **What you're doing with the relentlessly progressive disease is that when you combine these different things, you're looking at how much you're slowing the progression. So, the common metric is time that you're measuring. So, you're actually getting more to a disease modifying therapy, which we would all want as a society rather than merely symptomatic benefit by looking at one endpoint.**

And the last thing I wanted to say was RCTs. Whenever anybody comes up with a hierarchy of evidence, strength of evidence, RCTs are the gold standard. And it's true for common diseases. But for rare diseases, especially ultra-rare diseases, I think we shouldn't incense at the altar of RCTs. I had an FDA review division tell a client of mine who has a very rare disease, I'll say less than 300 people known in the world. They said, "Look, why don't you do an RCT? Do six versus three. Put six on drug, three on placebo." And I went to my friend Bob Temple and said, "What are you going to learn?" So, I think then doing a run in where you run people in for a year or two years on the same instrument, sure you're going to have some expectation bias when they have an intervention, you can kind of factor that in, or a natural history control, which is an external control to, you have the same expectation bias things. But you might be able to have more confidence, or at least as much confidence in an ultra-rare disease with that kind of analysis than you would with an RCT.

So, three things. I think they're all wows. The phenomena 1-15 is the way that I see almost all rare disease therapies as getting approved in the future. So that means when you start going in with your pre-IND meeting, you should be showing FDA how smart you are. I'm not only talking about what is your clinical trial design for a pivotal study, the one pivotal trial, but talk to the FDA about how you're going to provide confirmatory evidence. Second thing, accelerated approval, I think we dodged a bullet. I think we're in good shape. I think we're going to continue to see accelerated approval, do good work for the American public. And the third is the Orphan Truck Act. And my God, it's been a wonderful creature. Maybe we have to think about the ODA 2.0. Think about kind of refining it a little bit along some of the things I talked about. But I think overall, I think 2022 was a great big wow. So, thank you.

Alexander Fleming:

Well, Frank, that was just an amazing extra Jesus, wow. So much to talk about there. And we have come to the end of our presentations, but we now have time for some questions. And I see some questions have been asked and answered. There may be some others coming in, or have Thomas put out some questions in a moment. But let's go back to that Reagan Udall report, which was actually requested by Commissioner Califf. And they did present a model of taking the FDA. It was not a recommendation. It was one of five different options that they described. But in all of those options, they had this little black box, or gray box, for dietary supplements. They did not say a word about dietary supplements and how they should be managed. And coming back to Kate's comment about Rob Taylor's interest and evidence, what can we hope for in terms of how we apply evidence to the package around dietary supplements and helping consumers to choose wisely when they look at the hype often that is associated with marketing dietary supplements? So, who would like to take that up? Riette, you have a thought?

Riette van Laack:

Well, to start with, I can say that the evidence, dietary supplements, that has been, it's an issue in the current FDA or in a future food agency, if dietary supplements were to go there. But the thing is that in the past, I mean FDA has authority over substantiation in one, **if you make claims for dietary supplements, then the structure function claims you'll have to notify FDA. FDA has in all the years, focused on if it is a valid structure function claim, which is permitted for dietary supplements, or if it is a drug claim, which is of course, not permitted because that makes it a drug.** The substantiation it has left to basically the Federal Food Commission. So that wouldn't need to change if you were to move it into another agency or in another part of the agency. So, I don't think that this is the biggest issue that we would have to deal with if we were to create a new or different structure in the FDA.

Now, if you just go completely to the basic and say it's not so much the claims but evidence that we even need certain nutrients to remain healthy because some people say supplements, we don't need them. **You just have a good diet, no supplements needed. Then that's a nutrition science issue. Some people, and we have some evidence, but we also have of course counter evidence, claim that only nutrients when they're in the food matrix and not outside the food matrix in the capsule, are beneficial.** And so that would be a whole different ball game.

Alexander Fleming:

I hear you and I didn't want to hijack the discussion, but I guess my concern is that with the present structure, **there is no incentive for dietary supplement manufacturers to get evidence to support even structure function claims, much less some kind of clinically meaningful claim.** But I wonder, Kate, if you think that this is just a structural political problem that's never going to change? Or do you see that there could be some kind of congressional action that would help us to modify our approach to dietary supplements?

Kate Rawson:

Yeah, this is a little bit outside of my bandwidth. So, I mean Riette's probably better to comment on this. But I mean my one thought was, when those cosmetics regulations were passed and now, we have this OTC safe use pathway that's going to be coming down the pike, which is interesting. Then I think you must then turn your focus to other areas that aren't as regulated, like dietary supplements. So, I think it's just a matter of time and there has to be a champion sort of behind that. Like we've seen with cosmetics. So, I think that the fact that there have been some other, there's been attention to some of

these other kind of unfortunately, tertiary parts of FDA, that means that it's only a matter of time before dietary supplements get their time to shine.

Alexander Fleming:

Well, that's great. Why don't we go to Thomas and Thomas, you might pass on any questions that have come in.

Thomas Seoh:

We may need to go into a sort of lightning round mode. And the chat function worked well. People, there were questions that were asked and answered. Dean Calcagney asked, there's a lot of talk with Congress urging FDA to cooperate more with the Department of Defense. Does the panel know anything about is this just lip service or is it something substantive going on there? And then John Wood asked about whether there's any movement to get cross division consultation in rare diseases, to make sure that there's consistency in the flexibility that's applied in rare diseases. So maybe we can address first Dean's question about FDA DoD relations.

Kelliann Payne:

I can say from the device side, I haven't seen it move things along any quicker with any DoD involvement. I mean, I've done battlefield use devices and things like that and while it's helpful to have the support and the labs and the testing and all of that available from DoD, I haven't seen it make FDA move quicker.

Thomas Seoh:

So, the absence of vigorous comment, Dean, I think means, no, not yet. How about John Woods's question? Frank, maybe you might want to take that?

Frank Sasinowski:

What I'm hopeful for is still someday seeing a Center for Excellence for rare diseases, so we have more consistency across centers as well as across review divisions. But until that day comes, I haven't seen... The FDA announced major programs like the ARC program last May, in June, the rare neurodegenerative disease including ALS program. And yet I haven't seen much output from those to give me confidence that there is actually something afoot that's going to try to get the consistency that John Wood was looking for.

Kate Rawson:

Yeah, I know there was some legislation, I think it was called the STAT Act a few years ago, that would've created a Rare Disease Center for Excellence. And I think the issue there is just the will at the top. So, we have a couple of centers of excellence so far. They take a lot to stand up and a lot of resources. And I think, until you have a commissioner that really is focused on that, you're just not going to see it.

David Fox:

Let me offer just a lawyer's perspective on that and Frank, on your point about coloring outside the lines and do we need a more formulaic approach to guide the agency? My own view is the way you can solve the consistency issue, is to force FDA or encourage FDA to explain its decisions in comparison to other decisions that it's made. So, the agency, the reviewers, the review teams, always take the position that

each application is a thing unto itself, and they cannot keep track of how their principles that drive their decisions line up with how they've made other decisions.

And I think it's completely out of hand. And it's what I think, puts the F in FDA, frustration. When you can't walk any kind of semblance of a line through the various decisions they make. And as we get more and more approvals, it gets harder and harder to see consistency. And so what you get is a lot of approvals that seem to be the expression of the proclivities of individuals. Somebody really likes your program and so you get the benefit of the doubt at every turn. Somebody doesn't like your program and you're spinning your wheels for years. And so until they start explaining how they're thinking on one approval, lines up with their thinking on the last three approvals that are reasonably analogous, we'll never get there.

Frank Sasinowski:

And Dave, I think you're very, I'm going to give you an example you cited at the very top of the program, which was with RELYVRIO. I think that's one of the things that Billy Dunn did in his opening statement on September 7th at the advisory committee said, hey look, with respect to this flexibility that I say we're mandated to provide and implement, let's look at what we've done with our other two ALS approved products. Let's look at Rilutek, let's look at Radicava. And he looked at those and he held them up and he said, this is the type, the quantum of flexibility that we should be applying to a therapy for ALS. Now the problem with that is that almost every therapy I'm working on is the first one for that disease.

And so, I like the way you just said it because you said those that are reasonably similar. So, if you look for others that, if you're talking about Pompe, where you look at other inborn errors of metabolism, your allergy, when I talked about a rare liver disease, you might look at what's been done for other rare liver conditions. So, I think that would be a great step forward if the FDA would announce that.

David Fox:

You did that a second time, the first time through he didn't. And the advisory committee was completely at sea. Once he anchored the advisory committee in some analogous decisions, they were able to navigate. I mean, I totally agree.

Frank Sasinowski:

And that's why I think that somebody, and that's why I'd like a Center for Excellence for Rare Diseases, I'd like somebody who has authority over all of it to say, this is what we should be doing as an agency with respect to these approvals. Because otherwise you just get, as you said, the proclivities of the individual. This was Billy Dunn having a great insight and applying it, but is it just going to be a one-off? Because we'll never see anybody else ever pick up on that sentiment that he expressed.

David Fox:

I think that's where the commissioner could have a great influence. Commissioner not supposed to get involved in approval decisions. But I think that commissioner.

Frank Sasinowski:

Yes.

David Fox:

And I think given Dr. Kalif's expressed concerns, for example, about the lack of development for chronic diseases, I mean a lot of that is driven by a really tough regulatory system for broad-based conditions for large populations. And I think if he could come in and say, I'm not going to get involved in individual approval decisions, but I want the divisions to explain their thinking more and why are they exercising flexibility here? How much flexibility? How does that compare with how they treated other products? I think adding that layer of discipline to the review process would solve a lot of these issues. Now it'll create a lot of work, it's going to be intellectually challenging to do it, but I think it would pay off in the long run.

Thomas Seoh:

Isn't the question of consistency across a number of issues, decisions for sure, but within rare disease, flexibility, accelerated approval. I'm interested in if anyone on the panel has any observations on trends and breakthrough therapy designation? I'm struck by the difference between the centers. The device center seems to be very innovative and progressive in handing out breakthrough designations, while the drugs that CDER and SIBA seem more rigorous, shall we say?

Kate Rawson:

Well, except for oncology. I mean.

Thomas Seoh:

Except for oncology, yeah.

Kate Rawson:

Right. And I feel like whenever we talk about FDA regulatory policy, it's always, except for oncology, because that's where Breakthrough really started. So, I think it's, I hear what everybody is saying. I mean, FDA, we say it all the time, is an agency of individuals. And so, somebody like Billy Dunn is going to get on board with your program, then that's where they're going to, you're going to be in a better place. But Breakthrough can also go away. I feel like breakthrough was, it felt like, at least from maybe the Wall Street investors, as soon as Breakthrough was issued, it felt like, well, this is definitely going to get approved. And we've certainly seen that that hasn't been the case. So, I feel like it's not as a wow as it was a number of years ago.

Kelliann Payne:

I would even say on the device side, group by group, it differs. You know, don't see a lot of breakthroughs coming out of radiology, but you will see them out of neurology, for example. So, it's very different depending, some divisions we don't even try because we know it's not worth our effort.

Alexander Fleming:

By the way, Kelly, we noticed that CDRH has added a criterion for their breakthrough status consideration, and that is for addressing inequities in healthcare delivery. Haven't seen that for on the drug side.

Kelliann Payne:

And that's still in draft and we haven't really seen how that's going to play out on the device side yet either. So still question about that.

Alexander Fleming:

Has anybody seen? Well, good to know. And we're watching that carefully. But what about on the drug and biologic side, Frank and Dave, have you seen any evidence that that's coming for breakthrough, as a criterion?

David Fox:

Yeah, I've not.

Frank Sasinowski:

Neither have I, no.

David Fox:

It's a great idea.

Alexander Fleming:

All right, Thomas, back to you.

Thomas Seoh:

Well, we're kind of fresh out of questions or we're current I guess, is what I should say. So, unless people want to go back to topics that we discussed, we could maybe open it up to the town hall part because we're at the 12:30 mark, so we're done with the actual time that we sent, we advertised. But maybe we could invite folks to turn on your cameras, those of you who are willing and raise hands and try to answer any quick questions.

Alexander Fleming:

Well, just as an observation, it's great to see a diversity of people on the call. And a lot of my friends are long standing. I see Bill Kitchings going way back to my days in Atlanta when I was in medical school. So quite a remarkable assembly of people.

Thomas Seoh:

Just maybe in the chat, if people say, based on this discussion and your personal observations, do you see 2023 for the FDA as a wow or a yow? Just put W or Y into the chat. We'll see what the sense of the audience is, please.

Alexander Fleming:

That is quite a composite endpoint.

Thomas Seoh:

Tom says wow, Beth, Jewel, goodnight to Germany.

Alexander Fleming:

Frank, I'd love to debate the salience of that sort of composite approach. Having the summary statistic of multiple endpoints. The problem, as you know, is defining what is clinically meaningful with a number that is a composite of multiple endpoints. So, something to come back to.

Frank Sasinowski:

It's the thing that I think I helped on a product called Mepsevii for MPS VII for Ultragenyx which many people I think, misread as having been approved on a multi-domain responder index. Because in the FDA review documents, it speaks of an MDRI analysis. Whereas you'd look at each individual, there are so few individuals with the condition, you look at each individual and see if, along several different instruments, they had a positive response. And you kind of try to get a sense of that. So many people try to come up with setting up a cup point, a responder cup point for each one of several different instruments and then come up with that. But that's much more difficult to do in terms of statistics, unless then you do some sort of ranking analysis.

So, the global statistics gives you an ability to come up with a Z-score to come up with a number. And then the question is, what does the number relate to? And I've had discussions with Billy Dunn, for instance, about different products where the disease is a unilaterally progressive disease and what the Z-score represents is actually an effect on, maybe the disease is progressing 30% slower in the group that had the intervention than in the control arm. And so that's what it represents. So, you're able to translate it into something meaningful, because you used the word meaningful. So, there are other ways to interpret clinical meaningfulness. FDA and labeling often uses a cumulative distribution histogram to try to display meaningfulness. So yeah, this is a big topic, but I don't think this is a topic for this big group.

Alexander Fleming:

No, I'm sorry.

Frank Sasinowski:

Yeah, yeah, yeah. Sorry. Because you know, it's too easy to distract me, as soon as you start mentioning something, I'm going to go down the rabbit hole, so I'll stop.

Alexander Fleming:

Well, your words are invaluable.

Thomas Seoh:

Can I take this opportunity to ask this expert panel just a question that's bugging me, I guess. With all of this innovation, we're seeing new ways to address new parts, interventions and diseases, and it's always a challenge to get the FDA to accept a registrable endpoint or surrogate endpoints, and they want evidence for that. I'm struck again, by a little bit of the difference between the device side and the drug side, but are there comments on the panel, with respect to any movement, with respect to ways to get clarity on endpoints, field function, survival, confirmatory evidence? There's a totality of evidence. There are different ways to get FDA to approve something, but when you have an innovative approach to a disease, particularly disease modifying approaches, sometimes you're doing things you couldn't do before and now you have to establish standards for. And it clearly seems to be doing good for the patient, but you must validate the scale as well as the actual efficacy and safety of the approach. Is that

a meaningful question or not really? Because that's always been something there for the last half century.

Kelliann Payne:

I would say on my experience in the device side that the scale must be validated. We try novel scales, but we need quite a bit of evidence to show it's validated. I think **in the De Novo space, there's some flexibility because the regulatory standard is the benefit outweighs the risk. So, we get a little bit of flexibility in how we present that our benefit outweighs our risk, versus having to improve safety and efficacy. So maybe you see a little more creativity in those De Novo submissions.**

Thomas Seoh:

Right. There's a question. Any updates from the digital therapeutics area? That was quite the talk in the Biofuture conference, Biotech Showcase and JP Morgan, in the past couple of months. Kelliann, I suppose that would be addressed to you mostly.

Kelliann Payne:

Yeah. So again, I think in the digital therapeutic space, we see it in a lot of the De Novo, kind of like the ADHD treatments. Like I mentioned, Oxford VR has the anxious avoidance for agoraphobia, CBT breakthrough designation from FDA. So, I think we're starting to see a lot more in the digital therapeutics area. Rehabilitation devices, virtual reality devices. A lot, I think in the new coming year or two.

Thomas Seoh:

What do you think? Should we formally close the proceedings?

Alexander Fleming:

I guess we should. With great thanks to our panelists. It was just outstanding. Can't thank you enough. And for everybody who joined in the audience, we're so glad you did. Hope you'll come back. Also be looking for the Healthy Longevity Conference, which is going to be coming up in a different format. So, stay tuned about that. We'll be telling you more very soon. So, thanks to all and Thomas, we'll let you close it out.

Thomas Seoh:

Well, just to remind everyone that if you registered on Eventbrite, you will automatically get a link to the recording of this, hopefully within a couple of days. I would say thanks to the panel and the audience for your attendance and wish you all a good day and a great weekend. I guess I'd invite you to the post event reception. We won't close the room for a couple minutes, so feel free if you want to again, turn on your camera and get something off your chest. But don't feel obligated to stay on.