Thomas Seoh (00:05:46):

Welcome everyone. I'm Thomas. Sir, I'm the CEO of Conexion. We are delighted to have you join the 2024 edition of our annual Wow or Yao, I should say, wow or Yow expert panel discussion on FDA last year in review and this coming year in preview jointly organized by Conex some a regulatory, clinical and product development strategic advisory firm. Hogan levels an international law firm with a large food and drug law practice, and Hyman Phelps and McNamara, a specialist law firm with the largest dedicated FDA practice in the United States. We have a chaka block set of topics to cover. So I will just remind you to enter any questions you may have in the chat column and the panel. We'll try to get to them as well as questions posed by registrants on their registration form to the extent time allows in the last segment of this webinar, just to warm up the chat function, those of you who are willing, please say hi in the chat and state where you're logging in from a recording of this webcast will be posted over the weekend and a transcript will follow.

(00:06:51):

And I'll now turn the mic over to our moderator, Dr. Z Fleming connects some founder and executive chairman and FDA alumnus Z.

Alexander Fleming (00:07:01):

Well, thank you Thomas. And I apologize for being somewhat under the technological weather here out in West Virginia. I will hope to correct that in a moment. But we do have a great program lined up and no need for me to go on except to get us started. And we'll do that as usual with David Fox, who is one of my highly respected legal minds and the food and drug arena, and he will give us his FDA and review top hits. David, go right ahead.

Dave Fox (00:07:46):

Thank you z respect level may go down after this. Give my usual apologies in advance for everything you're about to hear. These are my own views, not the views my firm. And for better or worse, I take responsibility for what you're about to hear. So for 2023, let me start with the usual scorecard and then a few observations along the way. As you might've read, CR approved 55 new molecular entities in 2023. It's the largest single year total in five years, and it's the second most in the user fee era dating back to the early 1990s. If you take 2023 and 2022 together because 2022 was a bit of a down year, that averages out to about 46 approvals per year. And that's right in line with what we've seen over almost the last decade since 2015. So while it was a banner year 2023, it's sort of part of a very consistent trend.

(00:09:04):

And then just in terms of overall efficiency, I know people are really keenly interested in this. It was a remarkable year for first cycle approvals. North of 80% of all of the new molecular entities were approved on a first cycle. So we'll call that our first wow of today. Now, digging a little bit deeper, and I know frankowski be covering this in detail, so I defer to him, but on the rare disease side, about half the approvals were for orphan diseases, which is about in line with historical numbers. But what's I think is interesting within that group is five of the new approvals included companion diagnostics, which is the numbers are small, but interestingly we see 'em only about two, sometimes two or three companion diagnostic drug approvals per year. So five is maybe the start of a trend. And what's going to be really interesting, and kellyann might touch on this as well, is we're now entering an era where CDRH has asserted authority to approve all laboratory diagnostic tests. And it's going to be interesting to see what

effect that has on the ability of CDRH to keep up with parallel drug approvals when the drug approval is dependent on the approval of companion diagnostic. So just something big picture to look out for.

(00:10:43):

On the Seber side, the latest numbers, originally it was reported as 14 approvals, now it's up to 17 approvals in 2023, which if that 17 number is correct, that's the highest number for siber in modern times and really shows the cell and gene therapy sector just taking off. But overall, so with those large numbers, the headline, the chatter and the trade press has been quantity over innovation, lots of new approvals, but very few new targets and very few first ones through the wall type innovations. So roughly only one in three approvals this year were for first in class and the number has generally been closer to one in two approvals. Now, maybe that's just a product of having so many approval, the denominator being so great, but I think some people are expressing concern that there is now an effort more towards me toos and best in class rather than first in class and more approach.

(00:11:56):

But my own gloss on that I have to say is when one of those approvals was for a CRISPR Cass nine based gene editing system, it's really hard to argue that we're at a low point in innovation. So I mean the CRISPR Cass nine project Vertex is casca for sickle cell anemia. I just took a moment just to sort of step back and think about for all US FDA nerds what it means to have a package insert for true gene editing. I mean, it's kind of amazing and I went back and read the package insert, it could have been written by Walter Isaacson and I want to take a moment just to read from it. I think it's really remarkable. So this is right out of the package insert cas is prepared from the patient's own stem cells. The cells are genome edited by introducing the CRISPR Cass nine RNP complex.

(00:12:56):

The guide RNA in the complex enables CRISPR Cass nine to make a precise DNA double strand break at a critical transcription factor binding site in a specific enhancer region of the target gene. As a result of the gene edit, red blood cells are prevented from sickling addressing the underlying cause of the disease, thereby eliminating vaso-occlusive crisis. So that's a wow. I mean, I just think it's really remarkable to see that in an FDA package insert. So you have to love our friends at F FDA A, you're approved to change the code of all life. Just be sure it's truthful and not misleading. So really great stuff. Back to the numbers, about 20% of the approvals were for cancer indications, which is actually down from prior years. And relatedly, I think we aren't seeing as many headlines about accelerated approval. Those numbers are continuing to go down as well, particularly in oncology.

(00:14:07):

They're down to about half of what they were just in 2020 and 2021. So only about 16% or nine out of 55 of the CR approvals when accelerated approval, that's that's low. Another interesting number also nine out of 55 or 16% is the number of breakthrough designation approvals. So we're also at a low all the way down from about 40% in approvals. Under breakthrough designation, again, is that less innovation or perhaps it's just cedar being stingier about handing out breakthroughs and reallocating their use of resources. For those who are interested in the nine out of 55 for accelerated approval and breakthrough designation, is that the same cohort of products? Actually, it's not. There's only three that overlap. All three are monoclonal antibodies. One is chebe for Alzheimer's, the other two are for multiple myeloma.

(00:15:11):

So that's for really getting underneath the numbers overall beyond oncology. Hematology and autoimmune was white hot in 2023. And if you are back at the white Oak campus, the, I will tell you, the

metabolic division is coming for your excess office space. They're hot too. But we used to talk about eradicating polio as a goal, and now the talk is about eradicating obesity. And I would say that's a y careful about that immunology and inflammation is the new buzz in replacing oncology and rare disease as the focus of our approval numbers. Switching gears to the generic front, if you think 55 approvals on the new drug side is a lot, the generic drug office is the well-oiled machine at the agency cranking out about 50 approvals a month. So things are cranking. There is a little bit of shatter though that the outflow, the number of approvals at OGD is exceeding the inflow, the number of new applications coming in.

(00:16:28):

And that's an interesting possible trend about the generic drug industry. The thing to watch for though on the generic side I'll tell you is there's been a tremendous amount of agency funded research, but coming out of gdufa generic drug user fee funds on innovative ways to approve complex generics. And we're starting to see the fruits of that with generic drug approvals in the topical space, relying on in vitro release methods rather than comparative clinical trials to show bioequivalents. So there's a lot more coming in that area. And I just wanted to flag that transitioning to biosimilars, we had five new approvals in the biosimilars area of the five they were against three new reference biologics, three biologics that have not previously gone biosimilar. So we're now up to an overall total of 45 approved biosimilars in the United States against 14 different reference products. The big news in the biosimilar space at FDA this year was FDA, putting out a guidance, removing the need for a statement on biosimilar labeling, stating that the biosimilar, if this is the case, has not been shown to be interchangeable with reference products.

(00:17:55):

So removing the interchangeability statement or lack thereof from biosimilar labeling, and that is part of a larger conversation that was started by a group of officials at FDA who published a journal article in which they did a meta-analysis of all of the biosimilars approved to date finding that based on the original biosimilar package, no new information was gleaned from subsequent interchangeability studies. And this has set off a debate about whether eventually there will be a legislative effort to remove the separate interchangeability standard. I'm quite cautious about that because I would point out that the meta-analysis that agency did was against a very limited set of biosimilars that had been approved as of now, but it doesn't really take into account the true diversity of biosimilar products. And so I don't know that all of the risks associated with interchangeability have really been surfaced yet. So something to watch for.

(00:19:05):

Speaking of guidance documents, three other standout guidance documents in 2023. First we got another guidance document on what it means to have a single study plus confirmatory evidence. Another frankowski topic near and dear, so I won't say much more about that. But the other two guidance documents also gave rise to two new acronyms. There's SIUU, which is scientific information on unapproved uses. So this is not my area of expertise, but this is a milestone epic guidance that is part of a multi-decade saga about loosening up restrictions on off-label communications. What's interesting about the guidance among many other things is it was jointly issued by CVM cber, CDRH and Cedar. So all of the therapeutic centers combined issued the guidance and essentially about how to disseminate information that's consistent with your labeling but not necessarily expressed on your labeling. The other guidance and the other acronym is gas.

(00:20:22):

We have a new, this is yet another new acronym for generally accepted scientific knowledge. And if you haven't paid attention to this guidance, I strongly recommend that you do. It's an effort to find ways to alleviate the need for nonclinical studies or certain types of nonclinical studies if the information can be gleaned from what's known in the aggregate as generally accepted scientific knowledge. So not necessarily referring to a specific study like a paper NDA type approach, but invoking aggregate general scientific knowledge as a basis for not having to do a nonclinical study. I think there's a number of reasons for why FDA is focusing on this now. I think one is the encouragement from Congress through Rand Paul and Corey Booker to look for ways to avoid having to sacrifice animals and do unnecessary animal studies. I think the other reason is I think that the agency is looking for ways to fill in the gap in the biologics approval system where we don't have an equivalent to 5 0 5 B two under the biologic statute.

(00:21:35):

So you're either a true biosimilar or you're a full standalone under the biologics law. And if you're a full standalone, you may find yourself having to reprove, particularly at the nonclinical stage, things that we already know or believe we are well known. I think the gas guidance is an effort to try to throw a lifeline to applicants who can't be a true biosimilar, have to be a standalone applicant, but don't want to reprove, for example, the toxicology of insulin. So that gas guy is tremendously important. And then let me close here with two other noteworthy approval type events. So first, and this is really for Thomas. So Thomas, I think you always expect that I'm going to come up with some approval off the radar that tickles your funny bone. So like the time when FDA approved air and gave it new chemical entity exclusivity as a drug.

(00:22:45):

So this year there's so many great approvals for just, I mean, and again, Frank covers this beautifully, so I wouldn't take his time up in the rare disease space and urgent need and unmet medical need. But this one is again, for the regulatory nerds that FDA approved birch bark, birch triterpenes as the third true full botanical products. So we love botanical approvals. They raise so many interesting issues, they're few and far between. I wish there were many more. There should be many more. This is fil, it's a topical gel for treating really, really difficult to treat wounds in patients with a rare genetic disorder in which they get really heated, blistering lesions for what we would ordinarily consider to be a minor cutter scrape. So fantastic approval again in a really, really important niche area of FDA approvals. And then the last one I want to call out, this is not an approval yet and it's not in Cedar, it's not in Seabert, it's in CBM, but we're all tracking it closely.

(00:24:01):

It's loyal, loyal dog and their major step towards conditional approval of the first Drug for life extension. And this would be for life extension in dogs over 40 pounds. And if we have time, we could talk about it some more, but Z Thomas, a number of us on this are fascinated with the area of health span, the study of drugs and interventions that will allow us to lead a healthier disease free life for as long as our natural lifespans would take us. And the Loyal Dog program really is the first major, I think FDA overseeing program that can open and unlock the door to much more focus and study in the area of preemptive and preventive medicine. So I'm all for it. And with that, thanks as always. It's always a pleasure to do this annual event.

Alexander Fleming (00:25:07):

Well, it's a pleasure to have that rundown, Dave. That was terrific and I'm glad that you ended with the loyal story. We actually wanted to feature that with an expert who would introduce us to the fourth

therapeutic division in Cedar. We rarely talk about, if ever, the Center for Veterinary Medicine. And as you mentioned, there is this novel pending approval of a product that could increase the lifespan of large dogs, not just any dog that need to be large. And there's a mechanistic side to why large dogs would be responsive to this particular therapy. But let's stay on that because Ann Donahue, who we were hoping to bring in as a veterinarian and a real expert in CVM matters is nearing the north or the Arctic Circle. She's on a cruise and we were hoping against hope that she'd be able to come in, but that is just not going to work out.

(00:26:17):

So let's speak a little more about the significance of this particular action at CVM. Now, it differs from the accelerated approval that we are certainly familiar with on the human side and what its potential impact could be for human medicine. So bringing in Dave, staying with us, and Thomas, you can chime in here even who knows CVM to some extent. Let's talk about this particular instance of FDA, putting the product on the market for a, what you can call a healthy longevity indication and one that could even serve as a model for CR or CB or CDRH for that matter. David, any additional reactions from the legal standpoint or the regulatory standpoint?

Dave Fox (00:27:27):

Sure. So under the statute governing veterinary medicines, there is a specific statute for conditional approval, not to be confused with what we have on the drug side for accelerated approval. So specific legislation that essentially allows for the approval of veterinary medicine in certain types of animals based on safety only. So it's essentially you make an overwhelming showing of safety and then you have five years to demonstrate efficacy. And so it's like a true conditional approval and it's more open-ended than accelerated approval is limited to only serious life-threatening diseases where you're substantially better than what's already available and approved and you still have to show an effect on a surrogate that's reasonably likely to predict clinical benefit. Those constraints are not built into the CBM system. So if you can demonstrate to a high degree of confidence the safety of the agent in the specific animal that's recognized under the statute, you can get on the market. And then while on the market you have five years to prove up efficacy.

(00:28:58):

And in the case of loyal, I think they're still going through the safety review, but they have shown a reasonable expectation that their effect on a certain biomarker having to do with the IGF one pathway, which is over expressed in large dogs, gives CVM the confidence that it's reasonable to approve this under conditional approval. So I think large dogs are bred to overexpress IGF one. That's what makes them, it's insulin-like growth factor. That's what makes them large, but it's also what accelerates their demise and shortens their lifespan sometimes eight or nine years. So loyal has a good mechanistic hypothesis. They're using agents that they are confident they can show me the safety threshold and then they would have five years post-market post initial market to prove up their thesis. We are very interested in that model on the human side because we think it could be a very viable model for health span products where you would use older, well-known agents that we think have a mechanistic reason as to why they would potentially get to some of the root causes of the onset of major chronic disease and X.

(00:30:19):

You can speak to that, but the practical reality is it's really difficult to run a clinical study to prove overall reduction in risk for major chronic disease over a long period of time. You'd need very large studies over a very long period of time unless you have a really, really strong biomarker. And so from a feasibility

perspective, we're kind of locked out of doing really good advanced clinical studies for health span products. So we're looking at models like the CBM model with a safety first approach for older compounds that have been around for a long time with a really well characterized safety profile, really well understood dosing and risks and patient selection. Then incrementally good scientific research on a plausible biomarker and plausible mechanism enough to get you onto the market during a trial period over which you would have an obligation, whether it's three years, five years, seven years, to progressively either prove efficacy or pull back from the marketplace.

Alexander Fleming (00:31:29):

Well, that's such a great summary. There's not much to add, David. It just goes without saying that this is such a daunting project to not only identify which we can do easily, but actually to complete satisfaction that it were agents that are designed at decreasing the risk of multiple chronic diseases and slowing the aging process. We need a way of doing that practically that investors are willing to support and could bring solutions to people sooner. That would take if we rely on the conventional large clinical trials over literally a decade or more to show a survival benefit. So maybe we should move on, but we might come back to related discussions if time allows. Thank you again, David. Let's now go to kellyann, our expert on the CDRA side who always is able to keep us informed about developments there. kellyann?

Kelliann Payne (00:32:40):

Yeah, right ahead. Thank you. Yeah, thank you. Thanks for having me again. Happy 2024, although we're almost through January, al, that's possible. I'm not quite sure. Yeah, so on the device side, as Dave mentioned, laboratory developed tests. FDA is proposing greater oversight to those based on a modifications to the definition of in vitro diagnostics. So a lot of hype about that. We'll have to see how that plays out and the resources, I mean, that's the same group that just came off of all the covid tests and everything. So we'll have to see what their bandwidth is. I will say on the companion diagnostic side of things, just on a day-to-day interaction with sponsors, we do see more and more discussions on the device side of companion diagnostics and interactions with the agency. Even outside the traditional companion diagnostics, we see a lot of software-based development of diagnostics in the machine learning space. To that end, FDA to date has cleared or approved over 700 artificial intelligence devices to date from a software perspective. And this year, oh, can you guys cutting out are

(00:34:00):

(00:34:00):

Yeah, I see that. Sorry, I don't know whether it's hardware. Do you want to jump to someone else quickly while I try to fix this or can you hear me? Sam, you're on mute.

Alexander Fleming (00:34:23):

Kellyann, why don't we come back to you as the next panelist, but let's go to Frank Sosnowski who needs no introduction. You could say he's the father of orphan drugs, or at least some senior status along that line, but no better person to talk about or drugs than frankowski.

Frank Sasinowski (00:34:53):

Thank you Suzanne, for that kind introduction. And just like Dave says, I'm not speaking for anybody else. I'm chairman of the board of the Every Life Foundation for rare diseases. I'm not speaking for the every life. I'm not speaking for Hyman Phelps. I'm not speaking, I'm an adjunct professor of neurology at

the University of Rochester Med School. I'm not speaking to that, I'm just speaking for myself. So just in terms of rare diseases, it's a little bit of a Yao and a wow combined. I mean it is a Yao because we know with biotech financing the way it's been the last three years and we know then with the IRA, which also has erected another barrier, we know it's been difficult, a very difficult year to get financing many companies that were biotech innovators who have acquired by big pharma companies. So that's not necessarily a Yao for, oh wow, it's not a Yao not painful for that company, but it's taking a player who is doing a lot of innovation and moving it into big pharma.

(00:35:54):

So that's a little different, but there's a lot that's very positive. I mean, Dave, with his great introduction, always his great introduction highlighted some of this. So let me expand a little bit and give you two things that I think are major YOWs wows to watch for. One of them is that Dave already mentioned it, that this phenomena one 15, that is the 1997 law that says as an alternative to having two adequate well controlled studies or the FDA May, 1998 guidance that says as an alternative to that, you can have one highly statistically persuasive, but only for very limited cases like when you're looking at irreversible morbidity to mortality and you couldn't ethically do another trial. So those are really the background. And then in 1997, we had an alternative which said, you can have one adequate and well-controlled positive study that's positive at just the nominal statistical success criteria of less than 0.05 in your primary endpoint and confirmatory evidence.

(00:36:54):

But the concept of confirmatory evidence was never elucidated by the FDA until December, 2019. Actually, Peter Stein kind of let us get a look inside the tent when he appeared at an Every Life Foundation scientific workshop at the Willard Hotel in September, 2019, and he showed a slide, he knew that the guidance was being reviewed at OMB, and so he knew he could share what was going to be in that guidance that came out later that year in December, 2019. So we have seen the movement, especially in rare diseases, to an uptake of therapies that wouldn't have been approved before. And for instance, I talked last year about a drug called relieve reno, a drug for a LS that if you look at the press releases that came out of Aly, you would've seen that the FDA threatened a refusal to file. They weren't even going to look at it.

(00:37:48):

It was only one trial with a P value of less than 0.05, but not less than 0.01 P value about 0.03. And they said, look, that's not enough. You didn't do two studies. It's not one that's highly statistically persuasive, but the drug ended up getting approved and Dave and I will both involve them. So that's an example. Now, if you look at the beginning of the year 20 23, 1 of the first drugs that was approved in 2023 rare disease was for Sky ADA's drug first drug for ataxia. That drug had almost the same kind of quantum of evidence that is, it was only one adequate well controlled study, again with a P value of about 0.03 in the primary, which was modified FARs.

(00:38:34):

And we on behalf of reta that it had confirmatory evidence, part articulated what that was, and the drug ended up getting approved on rare disease day of 2023. I don't think the FDA timed it that way, but it was great news for the rare disease community. And at the end of this year, I mean the last rare disease that was approved in 2023 was the drug that Dave mentioned, ubic, which is for epiderm Veloso. That's the condition that is diagnosed at birth because the nurse taking the newborn from the mother to clean the newborn up, the skin is falling off the newborn, horrible disease, horrible disease. And yet this birch bark, as Dave said, it's the third botanical approved, was approved, and it was approved on the basis of,

again, one single quent and well-controlled study. They don't give in the December, 2023 guidance. The FDA does not list a P-value for that study.

(00:39:40):

It lists the study and it just shows the confidence interval that went from 0.8 to 25.6, meaning it excluded zero. So you knew by statistical principles it would've had a P value less than 0.05, but because it came so close to zero, 0.8 that it probably wouldn't be big number that is wouldn't be very, very small. It'd probably be slightly less than 0.05. And so the FDA didn't give a P value, but it's sort of like the AMEX example for a LS, sort of like sky claris, the RIA example, previous ataxia, again, one adequate and well control study, not highly statistically persuasive, but there was confirmatory evidence. So this is the way that rare diseases are going to get approved in the future. And I would submit to say that although the FDA never articulated it, it's the way that most rare disease therapies have been approved in the past.

(00:40:39):

But now we in the community, the patient community, the sponsor community, the investment community, we can all look and as well the FDA reviewers can look to a pathway that's legitimate, that's recognized, that gives the statutory authority and has guidance with it. So there's more certainty it de-risks popular word. So it de-risks the regulatory pathway for developing rare diseases. So that's one great big wow. We're really launching this process, which remember is a 1997 long. So things take time, t, t, t. And the second wow that I'm going to talk about is just like that. In September, 2018, Janet Woodcock was at this every life scientific workshop at the Willard Hotel. And I called for two things, one for Janet and the FDA to establish a rare disease center of excellence and also to establish a standing rare disease advisory committee. Janet asked me to join her in her conference room later that fall with Peter Stein and Patricia Cone.

(00:41:54):

I brought James Valentine with me and the five of us talked about those topics. What you just saw in December was the FDA announced the creation of a genetic metabolic advisory committee nicknamed Gen back, and I just love it. Dave was talking about gas, so I had to say something fancy too. So it is called GEM dac, and this GEM D is for inborn areas of metabolism, but really it's going to be used. Watch for this. Watch for this. I think it's really going to be used anytime there is a rare disease. These are going to be experts in the science of small trials. So whether it's the peripheral and central nervous system committee meeting about a rare psychiatric or neurological condition or the cardiorenal advisory committee, if it's a rare cardiology or nephrology therapy, they're probably going to have a joint meeting that would have the gen back with it.

(00:42:52):

And right now, here's your early canary in the mine. This is fun for all of you to watch. Watch the FDA A is trying to stand up this committee, right? That means right now they're going through the process of screening people, seeing if they can get them through conflicts so they can be a special government employee. They don't have enough yet to announce the standing up of this GEM D, but as they get people that are special government employees who understand the science of small trials, watch for the first advisory committees that happen in 2024 that are going to be for rare diseases and see if the FDA doesn't add to them ad hoc members who understand rare diseases. And I'd be willing to bet that those people are probably going to be the people who are going to constitute the gem D when it's put into place.

(00:43:41):

So this is kind of a fun thing for us all to watch on the outside and see what happens. But I did mention that at that time in September, 2018 when I called for these two things and now we see one of them basically has taken flesh. The other one that I called for is a rare disease center of excellence. Well, it turns out Rachel Sherman and Rob Kiff during the Obama administration when Rob was commissioner and Rachel was the principal deputy commissioner, created a rare disease council. Well, Rachel's now retired from the FDA. Rob's still there. Rachel and I are working with ideas like resurrecting a rare disease council so that you can have better coordination between centers. I hear almost weekly, usually a sponsor in the center for drugs say that, look, I have a competitor who's over in Siber and OTP and Rachel Anal and Nicole Verdun are doing a great job and they have much more flexibility over there and that's not fair.

(00:44:47):

And so this idea of having better in-center coordination to have better consistency and the consistency could also apply within a center. So I think that we're moving towards, at least Rachel Sherman and I are trying to see what we can do to achieve either a rare disease center of excellence or if it's not called that something that would give a home for patients with rare disease to go to as a single locus within inside the FDA. So I think there's, although I started with a Yao because of financing and because of the IRA with respect to rare diseases, I want to say there's a great big wow. And I'll say one more. Wow. My friend John Crowley has been named the new executive director of Bio. John is obviously a great fan, a great advocate hero for rare disease therapies. And with John starting March 4th as being executive director of bio, I'm looking to John to provide the kind of enlightened leadership he always has. So help to advance the field of rare diseases. So I think there's a lot to be very positive about as we embark on 2024 back to using,

Alexander Fleming (00:46:03):

Well, Frank, it was not only packed with amazing information but eloquently delivered and just very memorable. Well, by hearing your words ringing in our ears as we looked for the first meeting of that advisory committee, thanks for all that you do for the ortho drug community. Well, let's go on to RT Van Luck, who is a partner of Frank's at HBM and an expert on foods and cosmetics, and we look forward to your update agreement.

Riette van Laack (00:46:47):

Yeah, well thank you. I'm sort of the odd doc out. I'm with the center that doesn't do much pre-marketing stuff. It's all post-marketing. So very briefly, I actually asked some people around me that I work with and say, so is there any wow in 2023? They didn't come up with very much, but for me, the main thing is in 2022, there was a lot of stuff going on in SIFs and center food safety and nutrition, which now we like to call the human food program because of the infant formula, let's call it the disaster, the supply chain issues. And so the Reagan Oodle report basically identifying miscommunications, lack of transparency conflicts within the agency. So since January, basically FDA has been working on figuring out a way to restructure, rather than losing the F in FDA, we still have the F in FDA, and we're trying to restructure.

(00:48:03):

So in December, 2023, December 13, I believe it was, they actually a proposal for reorganization restructuring of the human food program was published. As anybody that has heard about this, no, it was not limited to just a reorganization within csun. And there's also the Office of Regulatory Affairs, some measures, proposed measures to avoid the application and get better and communication and

chain of command. In September, 2023, there was a deputy commissioner appointed. And so at least we have that now. That is a direct line with the commissioner, and that's also the decision maker if there's any conflicts within. So that's a new development, will it help? We hope. And as last week I attended a discussion about the reorganization, and at this time it's just a proposal. It's going to, they basically move to boxes on the diagram how FDA is going to be structured, hopefully FDA hopes that they can start implementing this in 2024.

(00:49:42):

The big issue on the SIFAN side though on the food program is the continuing struggle for resources, and this is budget neutral. So we will see, I heard somebody say they weren't very optimistic and they thought this was like moving the chairs on the deck of the Titanic. Let's hope that is not the case and we will have a positive year 2024. Some other things that I think are note worthy that FDA has since and the food program has been working on greatly is the nutritional aspect, the program to get consumers to make more healthy nutrition dietary choices. So there's a focus on added sugars. How can we get people, I mean, I know that there's drugs being developed that presumably help against obesity D, but there's a lot of diseases associated, chronic diseases associated with the diet, and there's a big push. So the FDA in 2022 had proposed a regulation for healthy.

(00:50:59):

They're still continuing to work on that. Hopefully there will be a final rule in 2024 from a nutritional point of view. It's a good regulation in my opinion, a proposed regulation. But will it work for getting the message across to the consumer and educational? Also, Willow worked for actually development of the food products. A big issue that had been industry had been waiting for plant-based meat alternatives, animal product alternatives, FDA published drought guidance, which was not as positively welcomed by both parties. The animal industry has been pushing back against these plant-based products that use terms that are used for milk from animal products. How can you use something that's make out of almonds? How can you label it as milk and milk or the plant-based industry was not happy about FDA's suggestion to have more disclosure about the nutritional differences between the plant-based product and animal-based product.

(00:52:23):

So there's a lot going on within the food program. Hopefully it will become more structured. The continuing struggle with resources will remain an issue. As you mentioned, I also do some cosmetic work. Last year, the big thing was in 2022, 29th of December, we had a law passed the modernization of Cosmetic Regulation Act. A lot of task for FDA, they got funding for that too. Needless to say, that takes some time before the program gets up and running because you can give them money, but you don't have the personnel and you have to figure it out. So the main thing that so far has been accomplished is that we have registration and listing FDA has developed the platform, but this registration and listing was supposed to become mandatory by the 29th of December, 2023. Well, they didn't get it up and running in time and some guidances had to be issued.

(00:53:36):

So now we will, the deadline is now the 1st of July in 2024, I think in 2024, we will see a lot of development in the cosmetic because the modernization of Cosmetic Regulation Act did include quite a few changes. Adverse event reporting, they're still on clarity about the adverse events because it's much broader defined than in the drug or in the dietary supplement world. So FDA has to get going on developing good manufacturing practice regulations. And so there's a lot of stuff going on. Switching back to the food program, I was going to mention something on dietary supplements. There's not many, I guess noteworthy WOW developments. The reorganization is not very positive for the dietary

supplement industry because they sort of lose a little bit of their standing. So we will see where that goes. But one of the things that was mentioned, new diet ingredients and FDA's process on that not much process, actually, I think FDA continues to not only struggle, but making inconsistent determinations.

(00:55:05):

For anybody who doesn't know new diet ingredient notifications are required for an ingredient that has not been present in the food supply yet. That's a very rough statement. And so then you have to do a notification to FDA, but if you have a new dietary ingredient that is before it was used as a food, a dietary supplement, as a food has been studied as a drug, then it can never become a dietary ingredient unless FDA and issues of regulation that it can. And so the interpretation of this provision remains on the FDA side, in my opinion, inconsistent. And so FDA actually did, so you do a notification to FDA and then FDA can object and say, Hey, no, you can't do this. Or if they don't object, then you basically after a certain time can start marketing your ingredient in it basically would be legal.

(00:56:13):

And they actually did that with an ingredient. And then the second party that also did the dietary ingredient notification for the same ingredient got to hear, oh, no, no, no, it's excluded because there is a drug in development. And so now the company that did the first notification then also got told you can't do this. And so this whole timing FDA's interpretation, they get challenged on it anyway, for years, we now have had issues with this and it doesn't seem to get better. And FDA is supposed to at some time issue a guidance and every time they issue an updated draft guidance, and then So that's a little bit of a, yeah, quite a bit. So anyway, that's a very short discussion about what is going on in the food side and the cosmetic side,

Alexander Fleming (00:57:10):

But very valuable. Thank you very much. I hope we can come back to a couple of the items you mentioned, but let's go on to Dr. Tim Franon, who is both a master drug developer and master humorist. It's an extremely synergistic combination and he returns after excused absence last year. But by popular acclaim, we are bringing Tim back. So Tim, please go.

Speaker 5 (00:57:48):

Thanks Ann and welcome all some very interesting discussions here. And my goal will not to be providing a humorous spin as much as some reflections on FDA's overarching role as the critical bridge between r and d and patient care and practice. So some of those things involve two major themes, and I'll do my best to be brief. Those themes are on misinformation and microbes, which may be the most threatening elements in our current climate today. So we're certainly all aware that as confidence of the public is confounded by misinformation or misunderstandings that impacts the receptivity of patients as well as practitioners to new innovations or practices. So our great science and great progress essentially can be blunted for lack of the proper messaging and understanding. So this includes preventive medicine developments as with vaccines. And this is not a rant on vaccine deniers or anything, but it is an important recognition that when misinformation occurs, there's a cascade of unwelcome collateral complications that leads to a blunting innovation.

(00:59:14):

Of course, the FDA commissioner Dr. K has called misinformation one of our greatest public threats. And as a result, commissioned work by the Reagan Udall Foundation of the FDA. And thanks to Susan Winkler and her colleagues there, they put together a very learned summary of issues of

misinformation, how one detects, how one begins to address that. And I think that's important for all of our industry and related endeavors as we try to move forward, if you will. One of the most compelling things that came out of that report that I'll share is that misinformation untruths travel six times faster than the truth on internet. So that means we're putting a race of truth and lies where lies gets to wear. Nike Jordans and the truth has tomato over shoes not a good situation for the public to be in. So if you will, these lead to breakdowns of breakthroughs, which is tragic. And when you see that public faith in science as well as FDA is eroded by confusing messages and outlier events, which are amplified by the press and social media taking covid as an example, that leads to some very unfortunate complications. To put it somewhat whimsically, more people now believe that Elvis is alive and well and performing on flat earth cruises than they believe in vaccines. That's a distressing way to characterize this, and I wish I was kidding entirely about.

(01:01:06):

So misinformation is the enemy of our family members and others if it discourages them from adopting new and exciting practices that enrich their health. The second topic is microbes. We are at war. I'm not talking about with each other, but with the microbes. The bugs outnumber us by many, many log scales. They're inside and outside of it, and they have very evasive tactics that they use to blunt the effect of our current therapeutics. So to combat these kinds of things is a holy cow, and that would be something of great enrichment in our environment. So let's add that to what else is going on that may be threats to our public wellbeing From the microbial side, and whether you believe in climate change or not, there's really no debate about the fact that mosquitoes and other vectors have adapted to changing temperatures. And those which now inhabit our southern states used to be limited to the Caribbean.

(01:02:20):

And furthermore, tropically, and for those of us who follow CDC and other similar authoritative sources of surveillance information, you may have noticed words that you're not used to like dengue chicken, gya virus, the fact that malaria cases plus those two viral diseases have been reported with increasing frequency in Florida, that is not something that's comforting. And it brings back the memory how COVID-19 began with only a case or two. And should we worry, I'm not attempting to be an alarmist, but just to observe that the more we can rapidly react to evolving resistance, the better we are able to protect our population. So all those things which used to be only important to we ID doctors on our board examinations are now practical in a clinical sense, and we need to be thinking more about that. So it strikes me that the most dangerous immigrants we have are of the winged variety, and we need to concentrate more on that.

(01:03:30):

So as we think about that, add to it, you may have read the stories about the recent melting of permafrost in the Arctic and the fact that this has released what some have called zombie viruses, whether they truly are a threat or not, remains to be seen, but clearly microbes, which we thought were long gone or never even knew about, are now appearing in our environment. And the juxtaposition for that is if you follow the antimicrobial development landscape, you know that very few companies in that area have survived, probably for very practical reasons. If you have an antimicrobial that works and works well, then in 10 days, two weeks, even six weeks, the therapy is done. That does not compete economically with drug developments that require lifelong utilization. So something needs to be done that we refocused on incentives in those kinds of areas, and we need to do both incentives and development and also reversal of misinformation.

(01:04:43):

When the lay public hears that as they did from the Florida State Department of Health and their governor, that mRNA vaccines are dangerous and lead to incorporation and DNA without any credible scientific evidence, and you're a lay person without a scientific background, you become very confused. So who do you believe you probably stand back and do nothing. That is a bit of human nature when we see confounding information. So how do we work to support FDA's concern about misinformation? Well, we need to collaborate more on very clear communications, what we know and also what we don't know, which perhaps we did not do very well during the covid outbreak and continue, we need to consider leveraging better benefit risk assessments as with the new guidance that had been registered over this past year. How do we accentuate the importance of some of these public health concerns and do it in a benefit risk type fashion? And also what we need to do to identify what key targets are going forward with resistant fungi like candida orus with other antimicrobial breakthroughs that could be fostered for the things that endanger, especially those who are in a hospitalized setting. So I'd close that with the holy cows in, and I know we have more things to discuss. I'm especially excited about the longevity issues, as I'm sure many of our listeners are, because it's clear that in lifelong survival, the dogs have a leg up on us.

Alexander Fleming (01:06:28):

Oh yes. Well, we knew that we'd get some of the humor. Tim, I love that we really need to get you before Congress and on 60 minutes and into the mainstream media. That was terrific. And I do want to come back to a few issues including the provenance, the holy cow add to our epithet. So we will hopefully have some time for that. But no, let's try Kellyann Payne, who was having some technical challenges just as I was and see if they've been solved. Ann,

Kelliann Payne (01:07:08):

I'm going to try this again. Can you all hear me okay?

Alexander Fleming (01:07:11):

Hear you fine.

Kelliann Payne (01:07:12):

Okay. Apologies for that. Okay. So just to pick up where I left off, we started with LDTs, the definition of that from an IVD perspective, expanding to include potential oversight of LDTs by FDA and seeing what that phase out of enforcement discretion looks like will be seen. I'd mentioned there are in my day-to-Day practice. Lots of discussions, furthering companion diagnostics, even outside the traditional companion diagnostics, including AI-based development of companion diagnostic devices. And so that's an exciting area. FDA has cleared or approved over 700 AI devices, machine learning based software products or products within traditional medical devices to date last year for de Novo's of the over 120 marketing authorizations in CDRH 47 of those were denovos. So quite a number of Denovo products, which are more novel technologies, were given marketing authorization at FDA.

(01:08:16):

That's always kind of good to see from a novel development standpoint. But also in the same year, FDA issued some guidances and one of them was around picking an appropriate predicate device, for example, for your five 10 K pathway. So it seems like they're drilling down on what are appropriate predicate devices, looking closer to intended uses and how predicates fit into the five 10 K paradigm versus going through the Denovo process for some devices that are coming to market less, but at least

though denovos, there is a much larger user too of those compared to five 10 Ks, while FD doesn't always want to go through the work. Now that the user fee, I mean for traditional fees over a hundred thousand dollars close to one 40 at this point, there may be some incentive for having more and more de Novos go through the agency.

(01:09:04):

But with regard to things that we saw this year as well, I think they're pretty similar to 2022 maybe in different phases. FDA came out with the final guidance document for predetermined change control plans, which was long awaited. There were predetermined change control plans that got through the agency, a handful of them prior to that guidance document. But there was a lot of negotiation and no one really knew what FDA wanted leading up to try to put in a predetermined change control plan. So that guidance gave us some clarity as to what FDA expects to see in those plans. I caution people, they're not buying checks for making modifications to AI based or other devices. It's not just AI based in the field. FDA wants to see a really robust protocol around what those proposed modifications would be. There's a lot of negotiations still that goes into them.

(01:09:54):

I wouldn't just put one in front of the FDA without some pre-submission interactions. So there's a lot to be seen as to how that guidance plays out and what a final version looks like for that predetermined change control plan process. In addition, I'm still answering and filling a lot of questions on the 2022 guidance for clinical decision support software. I will say CDS has a pretty broad meaning. It gets used pretty regularly and I think when people use it, they mean that they're exempt from FDA regulation. A lot of times that's not in fact the case. There are regulated CDS products to be a on-device, CDS product. You have to meet the requirements in the guidance document. And some of those key requirements that people need to be aware of are, it can't come from an image source or another signal from another device that's being analyzed.

(01:10:45):

That's not a clinical decision support tool. It has to be transparent. So when you talk about machine learning or AI and you talk about on-device CDS clinical decision support. They don't go together most of the times because one of the requirements is that transparency to the healthcare provider, to how that result came about from the software. So that's a key aspect of it. And then one of the other key aspects that came out in the 2022 guidance, which people are still struggling with a bit, is the time criticality. So if it's giving a time critical finding, it's less likely to be on-device CDS. And one of the examples FDA gave were sepsis risk scores in that device, CDS guidance. And so what people may have thought was a non on-device in the past is likely now device regulated by the agency. And so you see a lot of people just coming to the agency, talking to them, figuring out how these are going to be validated.

(01:11:37):

A lot of these come from large EHR databases and how do we get our hands around that and validate them and even how does FDA want to see the validation take place? So a lot of those conversations with the agency as to how that enforcement is going to take place. It's to be seen if there'll be warning letters in the future, in the future if people do not start to comply with that CDS guidance. If you are regulated, FDA always gives a bit of time to get up to speed, but now that we're going into 2024, there are a ton of these CDS software products within EHRs and other products. So it'll be interesting to see how FDA goes about enforcement discretion or enforcement action with those products. So I'll make it quick. I know we only have probably 20 minutes or so for questions. The one other thing I'll mention is the Total Lifecycle advisory program with FDA was launched in 2023 out of cardiovascular neurology. So that's for breakthrough devices to help get those products to market quicker, more interaction, total lifecycle

approach to looking at those products through the agency. So I think there are about 13 or so that are in that program right now that started this past year. And so we'll see what happens there. But sorry for the problems and thanks for having me.

Alexander Fleming (01:12:59):

Well that was terrific. Very good KELLYANN Pistol clear as well. We'll come back I'm sure to some of those issues as well. But we do have a lot of great questions that were pre-submitted and I'd like to go down a list, we'll take them, take as many as we can. I'd like to turn to Frank to talk about the FDA pilot program to provide work or operation work speed type of regulatory interactions and what can we expect to happen this initiative?

Frank Sasinowski (01:13:46):

Yeah, the Operation Warp speed is a great concept and I applaud the FDA, obviously for initiating this program. It's based upon the name the Operation Warp Speed was of course for the Covid vaccines that Dr. Peter Marks created that really cut down, I think the estimate is by nine months, six to nine months, the time it took to get Covid vaccines. It was having a very interactive process that is that it wasn't quite 24 7, not seven days a week, 24 hours a day. But the FDA was pretty much open and they were open to getting questions and trying to give answers to the covid vaccine manufacturers within a day or two. So it's not like going through the normal process of asking for a type C guidance meeting and then going through this process that can take six months by the time you ask for it, you get it, you get the minutes, you digest it, maybe have a follow up.

(01:14:40):

So instead it's very interactive. And so this Operation Warp speed gave rise through the Center for Biologics for Peter Marks to come up with the idea. And then when Patricia Cone and Peter Stein heard about it, they said, us too. We want to do this in Cedars. So they called it, instead of Operation Warfare speed, they called it the start pilot program so that it wouldn't be, it'd be disentangled from being solely a seabird program about both the Cedars program. But Peter Marks called me this morning, we've had plenty of times we've been on programs together. I've talked to him a lot about it. Dr. Verdun too, what she said to me earlier this month was, look, we expect more than a hundred applications in CBRA for three slots. And what we're really looking for is we're looking for therapies that are going to treat children who are going to be fatally affected by that condition by the age of 10. So I told the CEO of a gene therapy company whose product did not meet that description to not take the time, don't distract their team from the work they're doing. You ought to be kind of exercise some discretion before you overburden our colleagues at Seaburn and Cedar if you really don't have a shot of this. And you should be very careful about how you articulate the communication plan if you do want to improve your prospects for being selective. So that I think covers that topic, Sam.

Alexander Fleming (01:16:11):

Excellent. Frank. I want to turn now to Tim to perhaps give some insight into terminology that I referred to. Jim is our master punster and wordsmith holy cow is of his making. And our colleague Tom Va asked a question that goes as is holy cow in the webinar name a reference to the anticipated market size and medical impact of semaglutide and Tirzepatide. And he goes on to ask, what do you think the opportunity is for side effect free administration of similar agents? I won't go into the enumeration, but that's a good advertisement for Tom's platform and good for you, Tom. But yeah, that is a holy cow when you consider the Tim's former company, Lily and Nova are now last I checked the top one and two

market cap, big pharma companies on the globe. This is taking the air out of the room. Holy cow. Maybe you had that in mind, Tim, but what are your thoughts about this feeding frenzy or weight loss product?

Speaker 5 (01:17:48):

Well, it's a weighty matter and I think it's important to look at it cautiously. I would say I did not originate the term holy cow, that goes to Harry Carey, the now late baseball commentator who wins something that was truly remarkable and moving would say, holy cow. And I think that that relates well to here as well. The obesity market is clearly huge, but we ought to look beyond the market at what the secondary complications of excessive weight are. And Xan, as an endocrinologist, you could describe that better than me, but with the concerns for cardiovascular complications and so forth, those kinds of interventions can be very valuable societally as well as for individual patients. So I don't know how this will all play out, and I presume as broader uses occur, there will be signals that we need to look at and understand an evolving benefit risk relationship.

(01:18:55):

But the trials that we've seen to date have certainly been highly encouraging. And while it looks like it would require long-term therapy, just a quick brief therapeutic window that we do that for other chronic diseases. So I think we're probably needing to approach it in that way. But I welcome the comments from others and I would just close with, I think one of the things we can do much more efficiently is data share. And I'll put in a plug for the Critical Path Institute in Tucson, which is funded by FDA and EMA and actually the co-founder of that was Janet Woodcock with a sentinel paper some 18 years ago. None of us is as smart as all of us as the satchel page goes. And the more we can share information about new observations of benefits and risks with these new drugs, obesity or otherwise, I think it will benefit all and especially public health.

Alexander Fleming (01:19:59):

That's great, Tim. And this is a subject of great interest to a number of us, particularly related to healthy longevity because ultimately it is obesity that drives multiple chronic diseases and answer itself. The supra peptides are not the long-term answer. They have their own downsides including reducing muscle mass. So there is a need for a new generation of products that will have a more sustainable overhaul bus effect on I just weight, but on middle body function and quality of life. But a great opportunity to say holy cow. Indeed. I hope that you've still got some lily options that if you can use, you mentioned FDA and EMA and their collaboration. There's a question about the joint scientific advice process, Wayne, FDA and EMA. Anyone want to comment on experience or your views of that? How much is that being used?

Frank Sasinowski (01:21:30):

I asked Ellis Unger and Julie Bytes who are now with my firm about what was their experience when they were at the F fda. They didn't have a lot of experience. I think Julie had one case, Ellis had none, so it was just not being invoked. So we don't have a lot of precedent, at least not aware of a lot of precedent for this. There's some collaboration like in December, the FDA and the EMA announced a joint question and answer on quality and GMP aspects for prime or breakthrough. The prime is the EMA equivalent of breakthrough. And so there are these kinds of collaborations that the FDA and the EMA are involved with beyond ICH. But these direct collaborations, when you actually, and I have sponsors regularly ask me this, like maybe once a month I'll get somebody saying, look, can't we save timeframe if what we do is we invoke going both to the FDA and the EMA together? And it just doesn't happen, at

least not my experience. I don't know if others, Dave, I don't know if you had experience with that or Tim in

Speaker 5 (01:22:38):

Yeah, Dave, do you want to go first? Go? So my experience has been limited as well, but I think the important thing to recognize is therapeutic class that there are certain areas where the fundamental perspectives, QTC prolongation, obesity and so forth tend to be quite divergent between the US and Europe. So those areas would be challenging to harmonize. Conversely, in other areas where there's a lot of dialogue, my understanding is some of the review divisions have a working relationship and if I recall correctly, there's a memorandum of understanding between the EMA and FDA to be able to capitalize where those things are operational would be good.

Dave Fox (01:23:30):

Yeah, I was going to, I think there's progress being made on getting input from different regulatory authorities into clinical development in order to consolidate your development program. But I think we're a long way away from having one regulatory body rely on the assessment or judgment of the other. And I'm still seeing, and sure Frank, you're alluding to this too, EMA and FDA, looking at the same dataset and reaching different conclusions. And I mean some of that is you can sign pejorative tags to it, but some of it is also fact that there are just different standards, different precedents, different treatment settings within the countries. So I mean, especially on the heart, the hard decisions, there's enormous amount of judgment that needs to be exercised. And I don't think we're prepared to have one body exercise that judgment for all.

Alexander Fleming (01:24:30):

But there is increasing collaboration. We have for example, the joint FDA Health Canada MHRA workshop on pharmaco vigilance coming up next month as just a small example. But we do see increasing collaboration and communication among the major regulatory authorities. Dave, a question for you and that relates to in Tesia and what is the status of that case, which is the rather long story, but in the short of it, what can you tell us?

Dave Fox (01:25:12):

So briefly, it involves a GLP one ra and speaking of which, I'm following up on Tim's comments as well. So we had at one of our fall conferences, a very senior official from one of the previously named top two pharma companies say that they have as a goal in working with UK health authorities, the goal of eliminating obesity in the uk.

Alexander Fleming (01:25:46):

That's right. That was the CEO of Lilly. And he did say that on her webinar.

Dave Fox (01:25:53):

So that's part of the holy cow. On the other program you mentioned, so it involves exenatide, which was the first approved GLP one RA for type two diabetes. It's currently available in a once a day or once a week injectable. And the product ICA six 50 would put exenatide in a implant. It's a matchstick size implant that's been used in other products like viader based on an old ALSA delivery systems, very unintrusive implant that would allow for the delivery of exenatide over a six month period. Once

patient's is maintained on the product, which is a game changer, it's well known that more than 50%, more than half of people diagnosed with type two diabetes don't continue to fill their prescriptions after about six months. It's an asymptomatic condition, so they believe it's under control or they forget about it, or for whatever reason, people are not following through on their type two diabetes medication leading to just a cascade of just disabling and eventually fatal sequelae. So it's a terrific idea.

(01:27:23):

It's been the subject of a lot of regulatory back and forth that I really won't get into. It went before an advisory committee in September. It was a special purpose advisory committee, not a traditional committee for a review of an application, but this was an appeal advisory committee remained I think, cautious and concern about the safety data and did not give a positive endorsement of the product. And the appeal itself I think is still pending at the office of the commissioner, but we're seeing more of this. And I think that the concept is extremely important and that is taking our existing products and finding better ways to deliver them to enhance compliance and compliance is really so much a part of the game that we forget about. So we have all these wonderful drugs that we're talking about, but if the patients don't take them, don't abide by a schedule, they do them no good.

(01:28:31):

And I think one of the fundamental issues that remains unexplored is how much additional risk or different risk are willing to accept for taking existing products and putting them into alternative dosage forms. And I think in some instances you'll see review divisions say, well, we already have that drug, so any additional risk is not worth it. And they aren't really giving, in my view, at least adequate value to offering options to patients therapeutic options. And I think if you take a no incremental risk perspective, you're going to shut down a lot of really important innovation. And I think that's in the swirl of issues around six 50 product and others that we see. I think that's unexplored territory. I think that's something that's very subjective on a reviewer by reviewer basis, and I think it's one of the areas where we need more policy and more consistency within the agency.

Alexander Fleming (01:29:36):

Thanks, Dave. And let's go back to Frank for the question of great interest to me. What about the status of the pediatric voucher? Will Congress renew it?

Frank Sasinowski (01:29:51):

I have to say now I will put on my hat as chairman of the board of the EveryLife Foundation for rare diseases, we're strongly in favor of having it renewed. I know that other patient advocacy groups are also similarly aligned and are doing work up on the hill. I know that a lot in the biotech industry are mobilized as well. So all of that movement that I see up on the hill makes me very sanguine about the prospects for getting that because it's bipartisan. You've got the patient voice, which often is listened to by one party more, and you have the biotech industry, which is often listened to by the other party more. And so you have a bipartisan kind of support for this. And so if people are interested, I'm pretty optimistic about prospects.

Alexander Fleming (01:30:44):

Great. Thank you. Frank, what about the Chevron case before the Supreme Court? Let's have a food fight here or hand wringing or a holy cow or maybe a Yeah, but Frank Dave,

Frank Sasinowski (01:31:00):

I'll let Dave go on that one.

Dave Fox (01:31:02):

That's a pow. Trying to address it in two minutes or less. Yeah, I mean, things do not look good given the current composition of the court and the view of the particular justices with regard to administrative agencies. This is a longstanding effort by Justice Gorsuch to undo the Chevron case. Kind an interesting backstory, I think his mother was the administrator of the EPA,

(01:31:32):

So I don't know what went on there that now he wants to dismantle the administrative state. But very, very long story short, the idea would be that this relates to statutory interpretation only. We're a statute is ambiguous, unclear. It doesn't on its face resolve a problem that is presented in a case. Then there's room interpretation. And under Chevron deference, the shorthand is that if the agency offers a reasonable interpretation that's within the scope of the ambiguity of the statute, that the court is required to defer to the agency and can't second guess the agency. If we undo Chevron deference, it potentially allows any federal court judge to substitute their judgment for the agency's judgment as to what is a reasonable interpretation of the statute. So the conventional wisdom, which is probably right, is that that would have an enormous destabilized effect on federal administrative law.

(01:32:36):

You can go around the country and reopen the agency's interpretation of statute. So we have one federal agency, let's say FDA, who gives an interpretation that applies across the board. Now we'll have federal court judges in every district who will be given the discretion to relook at the agency's interpretation and potentially reach their own decision. The other side of the story, the way to look at it is in the long run, what it will really do if the doctrine goes away is it will cause federal agencies like FDA just to have to work a lot harder. They'll just have to do a much better job and use their technical expertise, which is the underlying basis for Chevron difference. Use their technical expertise to be more persuasive as to why the decision that they made in interpreting the statute is the best decision. Yes, there are always multiple ways you can read it, but the one that's the most reasonable, the one that could be implemented and sustainable is this and here's why.

(01:33:38):

And then the agency really has to use its expertise. So it could be that this just makes for more work for the agencies. And I think for any reasonable federal court judge, if they're presented with a very persuasive argument from the agency that's backed up with their technical expertise and data, et cetera, it's very hard for them to come in and then play commissioner of FDA or play doctor and second guess it. But of course, we also know that there are going to be judges here and there who are just of a different stripe, and they're going to want to impose their own will. And this new development in the law, as esoteric as it may be, may actually give license to some judges to really insert themselves and become commissioner of FDA A for a day.

Frank Sasinowski (01:34:23):

Let me, Dave, just as a note, say you have a controversial drug. You can just imagine what this will do.

Dave Fox (01:34:32):

Well, you don't have to imagine it.

Frank Sasinowski (01:34:33):

Yeah, I mean, and look, I can illustrate the other side. When in 2023, the FDA approved the drug ferin for SOD one A LS, the primary endpoint of the pivotal registration trial hit a P value of 0.9. I'm not misspeaking. It wasn't 0.09, it was 0.9 about as bad result as anyone could ever imagine. Yet the FDA gave it accelerated approval. Why am I saying that? I'm saying the opposite occurs all the time. That is, we don't know about it because the drugs are rejected, but they're close. They're close. And so you can just imagine a sponsor of a drug who's invested a great deal. There's a huge unmet medical need. It's a serious drug, might even be rare. And you can see mobilizing the patient community and getting them mobilized, make it very appealing case. You bring the anecdotes because there always are anecdotes in every case and you bring those people before a court. So I think, I don't want to say instead of Wow and Yao, and you said PI think this is chaos.

Dave Fox (01:35:44):

Well just maybe level set for a second. I don't think the current debate for the Supreme Court is really going to impact individual cases that involve the exercise of scientific judgment around a certain data set where the interpretation of the statute is really not central. So that remains, I think that's still fairly solid. But I think we are going to see more cases like the 11th circuit case decision changing, the FDA's longstanding interpretation of the Orphan Drug Act, where the judges are going to look at the statute and say, no, no, no, fda. And they didn't even look at the FDA's regulation to say that no, it says disease. And so when you have an orphan approval, you own that disease for seven years, not just the indication that you got approval for. I think those types of situations are going to become more prevalent. I think the individual judgment of how you interpret a data set, I think we're a ways away from saying that that's going to devolve into chaos. But of course, obviously

Frank Sasinowski (01:36:46):

It is

Dave Fox (01:36:46):

Political environment and we often all say, we'll see everything is up, is down, is up.

Frank Sasinowski (01:36:50):

I hope Dave's right on this, but what I have to say is that case you cited, I mean I wrote the implementing regulations of the Orphan Drug Act that the court ignored me circuit. So I have a great deal of feeling about pride of authorship, but it is an interpretation of the statute. It's what is substantial evidence of effectiveness and was the agency decision arbitrary for purchase. And so I think if Chevron two goes away, I am hoping Dave's right. I'm hoping I'm wrong.

Dave Fox (01:37:27):

Sosnowski definitely has been blown up by the 11th circuit. Yes.

Alexander Fleming (01:37:32):

So

Dave Fox (01:37:32):

Chevron to follow.

Alexander Fleming (01:37:35):

Wow, that was a great discussion. We could go on for quite a while. We are in over time, however, we will take a few more questions, but I'm going to give kellyann one more question that came in be submitted. And that is what is the product standard for a medical device and what is the property that makes a medical device classified as a drug or cosmetic?

Kelliann Payne (01:38:06):

Yeah, sure. So FDA has the regulatory definition of a medical device, which is to treat, diagnose, cure a medical condition or disease state. But it comes down to how it performs its primary mode of action. So medical devices do not perform that primary mode of action through a chemical process. So you have to look at how does it perform that primary mode of action with cosmetics and devices. So that's a drug. So if it's chemical, you may well be a drug or a biologic. With cosmetics, it's a little different. What are your indications for use? What are you claiming it does? Are you saying it treats fine lines and wrinkles? Are you saying it helps with the appearance of fine lines and wrinkles? Where is this line and what are you saying about the product? So I think you start with the indications for use, the intended use and what are you saying about it? And then you move on to the technological aspects and how does it perform its primary to function, is it more of a physical application software, things like that. That would be more on the medical device side that don't know. Dave, if there's anything on you from the drug side that I missed there for that definition,

Alexander Fleming (01:39:13):

I think that was terrific. And we'll then leave that as settled. Why don't we go to Thomas to pick up a few questions that have come in during the call during our discussion. You're on mute.

Thomas Seoh (01:39:32):

Unmuted. I'm on mute.

Alexander Fleming (01:39:34):

You're val.

Thomas Seoh (01:39:36):

Well, I listed some in the, I brought over from the q and a, some of the questions that folks posted into the everyday chat. I know we talked about rare pediatric vouchers. Claude was asking, what are we going to do about well, sugar and other processed foods? I asked that question I think earlier. We have a question on the current IP landscape by dough margin. It's, it's a favorite that comes up every few years. Trips, waivers 1 0 1, et cetera. The potential effect on incremental innovation for effect on innovation ZI guess I'm throwing these out. We're in our last minute or minutes. What do we want to end our 2024? Wow. Or yeah, one. I should also ask the question. There's so many questions that popped up we don't have time to address here. Certainly don't want to commit the panelists to answering them, but I think the interactivity is useful. So there may be opportunities to write up some couple sentence answers or something and post them somewhere. I think that is a service for the people who come and listen to our webinars.

Alexander Fleming (01:40:55):

Yeah, we will do that. We'll actually answer the questions that have been posed and provide a transcript session, and we hope that there'll be many more people who will do the webinar with their leisure. So gosh, it's frustrating to have to come to a close, but we will not take your time any further. We do intend to stay in close touch with the transcript and feel free to talk back with other comments and questions and stay tuned for other webinars that will be coming up, either from Conex or our not for profit or Alice Institute on express for healthy longevity. So Thomas, please, I

Frank Sasinowski (01:41:52):

Just wanted to thank you and Thomas Fromum for inviting us. We enjoy this annually, and I can't speak for Dave and Kellyann at Hogan levels, but we, RT and I at Hyman Phelps, we just are truly grateful to you and honored that you would have us as part of this annual panel. So thank you very much.

Alexander Fleming (01:42:15):

Well, Frank, that was high praise from you indeed. And what an honor to have all of you panelists, distinguished in your own right, join us every year. This is just a great privilege for us to be able to host this important discussion and we'll do more. We'll take advantage of our dear friends. So Thomas, I think you should close us out and we will, we'll say not goodbye, but until we get together again,

Thomas Seoh (01:42:50):

Meet again. Well, this closes the formal part of the proceedings. Thanks everyone, certainly to the panelists and to you, the attendees. And we, as I mentioned, a recording will be made available within the next couple of days and the transcript probably within the next couple of days to a week or so, maybe we can get it out earlier. If it's just the artificial intelligence rough copy, it takes time to try to clean those transcripts up. So with that, I want to wish everybody a great afternoon and a great weekend. Thank you for coming. Thank you so much

Alexander Fleming (01:43:22):

Question. Well, to your health,

Thomas Seoh (01:43:25):

We are keeping the room open for just a couple minutes for those who can stay on to if you'd like, but it's not mandatory, but terrific. Thank you very much. That was a great addition. And as you said, there's so many things you could fill another couple hours of discussion. So there's that frustration. It's a good frustration.

Dave Fox (01:43:47):

Hey, can I just ask a question? So Tim, on the microbe issue, sure. When you testify in front of Congress at Z's invitation, yes, please, to me, there actually is a very accessible solution to the incentive problem, and that's a tradable exclusivity. So if the developer of a course of therapy, an antibiotic course of therapy gets approval, they would get exclusivity and they could sell that exclusivity to somebody who has one of those drugs that is for a chronic condition is a much better economic proposition than a short course antibiotic therapy. And to me, it seems so obvious that if we have this societal issue, we're all in the same boat here, given the fundamental problem that the goal of an antibiotic is never to use it. Once you start using it, the bugs get together and figure out how to beat it. So the more sparing we can be, the better off we can be to save it for when we really need it.

(01:45:02):

And that's antithetical to drug that privately financed drug development. And that's why we are in the situation where we are. No major drug company, not Lillian Novo. They're not racing antibiotic programs, they're racing for obesity programs. So we don't want a lot of trim people who can't outrun a microbe. So the answer is you get exclusivity for the antibiotic and then you attach that exclusivity, somebody who's willing to pay for it, and we see what the priority review vouchers, people are paying a hundred million dollars to get prior review voucher just so they can jump the line for two months. So imagine if you give somebody your exclusivity, you give them some form of exclusivity, new antibiotic exclusivity, three years attached to all your patents and all your exclusivity. I mean that would sell for a large amount of money and would really subsidize the development of antibiotic. That's a great idea. That would solve the incentive problem.

Speaker 5 (01:46:10):

I think

Dave Fox (01:46:11):

We do it for rare pediatric diseases. Why aren't we doing it for something that could turn all of us? Well, we have it for tropical medicine, tropical medicine, tropical diseases. I just don't understand. We had the GAIN act and the GAIN act was an absolute fool's errand because the gain act gives you five more years of exclusivity, which I mean, it was like, okay, so we're willing to give out exclusivity. It wasn't like we're anti exclusivity, but what's five years attached to something that has no value to begin with? Oh, you get another five years of not being able to sell your drug.

Speaker 5 (01:46:43):

Yeah, I couldn't agree more. I think there have been several initiatives, one by the antimicrobial working group that I'm familiar with, that 16 or were approximately that number of small antimicrobial developers. And the concern is that there wasn't a lot of traction when that was proposed. And what's been worse, I think when you look at the broader climate, the exclusivity from best pharmaceuticals for Children's Act for that extension has been deemphasized by FDA. And there was a trial balloon about discontinuing priority review vouchers overall. So I don't know that we're in a climate that

Dave Fox (01:47:26):

You, there's a climate issue, but this is a big problem. You got to get over that issue. And like I said, with the GAIN act, they were willing to give out exclusivity. The BBCA is a perfect example. I mean, FDA and Xan knows this. We could not get sponsors to do studies in children. They didn't want to jeopardize their database. We could not get them to do it. Then the BPCA passed and you get six months and people can't do pediatric studies fast enough. We are awash in pediatric data and yeah, we're so awash in it that FDA is like, okay, at this point, okay, enough, alright, we got to calm down or we got to make it harder to get the six months. You're going to have to do more work for it. So there's some moderation going on, but it's a perfect example of something that nobody wanted to touch. And then you just offer six months, six months time and everybody is doing it. And I mean, what bigger problem do we have than being overtaken by a resistant bug? To me that's the next pandemic may not be, well,

Speaker 5 (01:48:33):

I'm not sure I'd agree that I agree with the majority of your points. I'm not sure agree that there's a sufficient number of pediatric studies that have been done. I still think there are huge gap areas,

Dave Fox (01:48:47):

Right? Right. But what I'm saying is a six month inducement has mobilized the industry. It's a regular part of everything they do. Every timeline I get on lifecycle management has a placeholder for getting the six months. I mean it is integrated into it. It shows you this is an industry that responds to those kinds of incentives. And yes, I mean the dog side is people will say, well, it's just more monopoly that's all the industry wants is more monopolies. To me it's a cost shifting. You're shifting the cost of the development of antibiotics to other patients and other payers.

Speaker 5 (01:49:26):

It makes sense

Dave Fox (01:49:27):

Sometimes. Again, we're all in this together. Well Dave,

Speaker 5 (01:49:30):

We need to put you

Dave Fox (01:49:31):

In front of Congress for this. That's the last thing you want to do. But anyway, anyway. Well, Tim, if you get plugged in on that issue and people talk about it, I was the antibiotic counselor at FDAI was part of a task force to try to incentivize development of antibiotics that I believe failed. And yeah, I'm really interested, but I'm interested in solving that issue, not think it's an incentives issue. And I think we don't need to break any new ground in order to solve it.

Speaker 5 (01:50:07):

Yeah. Well that's near and dear to my heart. Steven Spielberg and I were the folks, people for pharma when the BPCA actually came forward and very familiar with that success and very frustrated with the antimicrobials environment. So I think it's a great

Dave Fox (01:50:31):

Suggestion. People would be falling all over themselves to develop an antibiotic if they knew that they could sell off their exclusivity to Lillian Novo to block generic versions of GLP one RAs for another six, six days. Six months, six years. I mean you would get such an injection of cash into the development of antimicrobials. Yeah. Yeah. I

Speaker 5 (01:50:56):

Think that's a great idea. Great point.

Dave Fox (01:51:04):

You can call it Kardashian exclusivity. All the Kardashians in California will pay for the development of our anti pipe pandemic medications.

Speaker 5 (01:51:18):

Well, that would be a cosmetic,

Dave Fox (01:51:20):

That's a reasonable trade.

Thomas Seoh (01:51:22):

Dave, is this an initiative talked about at all or is it sort of springing from your mind or you see it in the back waters, but it's not really seriously discussed?

Dave Fox (01:51:34):

No. The idea of what we call, I was on this task force with Jesse. Good. Was it, what's his name? I'm sorry. Yeah,

Speaker 5 (01:51:44):

Jesse Goodman's the ID guy and was at FDA.

Dave Fox (01:51:48):

Yeah, yeah, on his task force. And we called it wildcard exclusivity. That's a great term. Yeah, that was a major part. So it's this idea. This has been kicking around for a long time and I don't know how I was checked out on it. I was doing other things. I don't know how we got the gain act and who came up with the bright idea of an inducement being you get five more years of exclusivity on something that we don't want you to sell it. It did zero. It was a complete bust and we ought to recognize it and just amend that legislation. The gain act, you get five more years of exclusivity, but you can sell it.

Speaker 5 (01:52:33):

Well, I have a couple colleagues on antimicrobial working group that I will be sure that resurfaces with them.

Thomas Seoh (01:52:41):

Sam, do you see a question in the chat from Gary? This was harking back to our health span discussion and the fact that GLP ones are at least the first generation, are not respectful of preserving muscle mass, lean muscle mass. And I guess this one functional way to think about losing muscle mass is aging and he's asking for a further discussion. I mean, I know it's a topic that we keep coming back to because we're quite obsessed with it, but it is very relevant and there's a hundred billion sucking motion of the incretins that's lifting the entire field and creating an ecosystem with a lot of people funding money.

Alexander Fleming (01:53:25):

Well, certainly this is such an important area and one of great public health significance that deserves yet a full webinar in itself. There are downsides to these agents and yet they may help to reduce risk of other chronic diseases, not just diabetes and cardiovascular disease, but neurodegenerative disease as well as cancer. So it's a very tantalizing prospect. We have these powerful agents and yet they are a bit of a two-edged sword. And they certainly are an economic hit to our healthcare system. It just can't be made available to everybody who might benefit from it

Thomas Seoh (01:54:13):

Or their entire lives.

Alexander Fleming (01:54:16):

And that may be a good thing That is rationing the use of these products, which should not be used exuberant as they currently are. So very interesting set of public policy, scientific, clinical and ethical issues wrapped up in our field. And then we have options to throw in as a bargain. Lily options that is,

Speaker 5 (01:54:52):

I lost all those when I took the USP role. Oh,

Alexander Fleming (01:54:56):

Okay. Well,

Speaker 5 (01:54:56):

Conflict of interest.

Alexander Fleming (01:54:59):

Wow.

Speaker 5 (01:55:00):

But I can dream

Thomas Seoh (01:55:03):

Somewhere in the multiverse, Tim. There's a wealthy Tim France and at least wealthy on lily options because you took a different life course.

Speaker 5 (01:55:12):

Well, I'm thrilled for them for all my old Lily for doing so well and no regrets.

Alexander Fleming (01:55:20):

Yeah. Well Indianapolis is now the center of the universe in some ways, so maybe that's a good thing.

Speaker 5 (01:55:29):

Yeah. Well holy cow applies there given the bovine surroundings.

Thomas Seoh (01:55:35):

Just the point of order, Tim, before we wrap it up, I guess, but this holy cow, as you envisioned, it was based generally positive or I kind of thought it was generally negative, but I suppose it can swing either way.

Speaker 5 (01:55:51):

Actually, if I recall correctly, Harry Carey used to use that whenever there was something unexpected.

Alexander Fleming (01:56:00):

It could go either way.

Thomas Seoh (01:56:02):

Okay.

Alexander Fleming (01:56:04):

But holy cow is a good ad, Tim. We appreciate that. We're always looking to buff up our terminology. Technical language,

Speaker 5 (01:56:18):

Happy to help. No charge.

Alexander Fleming (01:56:21):

And T, thank you so much for hanging on and for bringing important information about,

Riette van Laack (01:56:28):

Well, it is all very interesting. I find this whole thing with these new weight loss drugs and the interaction with the potential nutrition programs, we going to, as you said, there's only part of the population that is going to be even access to that. And so we already have the poor people having poor nutrition and having more chronic diseases. So how is this going to ultimately work? But then this morning I also read an article very interesting that the development of these drugs and the availability of these drugs has made people think more about glucose levels in their blood and how to manipulate those with the diet. And then now they have devices that can help you see what basically your glycemic responses to food. And so it is, but Sifan is struggling and we have been struggling in every country. We are struggling to make people eat better because we always said there's no such thing as a quick fix. And now we have a drug that supposedly is going to help us lose weight without too much effort. Is that then going to make us healthier? Because yes, I know that the weight is so associated with diabetes and with cardiovascular disease and all that stuff, but there's still certain things we have to eat. And we should not just eat bad things and say, oh, we take a pill. Problem solved.

Thomas Seoh (01:58:09):

Said the similar thing when he said, you're addressing a specific symptom, but you're not doing much about the underlying problem of junk food or sugars or whatever. You mentioned several things that we could be working on that are higher up the pathway, shall we say, than at the end.

Alexander Fleming (01:58:28):

Or we could say the fundamentals and it's what we eat, how we are, the kind of social relationships we have. All of these are so important and we know they're safe and effective. It's just they're underutilized,

Thomas Seoh (01:58:47):

Inexpensive, relatively inexpensive.

Riette van Laack (01:58:51):

You can't also make money off it, not as easily off it.

Alexander Fleming (01:58:55):

That's a minor detail that we need to,

Thomas Seoh (01:58:58):

I think that's a driver. We need to find innovation in new business models where people can make money in helping people stay healthy well and prevent diseases. Right now, the system has grown up to provide a lot of money for people who are helping people once they get there. That's going to be fascinated to read the last chapter of the book when that's written. It's going to happen. But I don't know what central, well,

Alexander Fleming (01:59:24):

This is a topic Dave and Thomas and I have been talking about how, and we incent the development of evidence to support certain dietary supplements that make otherwise exorbitant claims with very sound or no, not to say that we're going to abolish decay, but can we add a new enough way to get proprietary health indication that would go with a particular product that is supported by kind of evidence that we would expect for a drug. So we're wondering would this ever happen? Clearly it's not available through the regulations and administrative order as it stands.

Riette van Laack (02:00:29):

Yeah. Well I mean that is actually for the new dietary ingredients. Many people think that if you do a new dietary ingredient notification, you should have a period of exclusivity or it should be proprietary. But that because dietary supplements are food and to say that you have a food ingredient, that you have exclusivity that just sort of counterintuitive. And if you start doing this for dietary supplements, you start basically making them some kind of a category of drugs.

Alexander Fleming (02:01:08):

But you have to say that many dietary ES supplements art, drug light, and in fact some have crossed over to become drugs. And so there is this kind of gray area of agents that not, they don't provide calories or vitamin light properties, but they do have biologic activity that could be considered drug like though.

Riette van Laack (02:01:41):

Yeah, but so is fiber. Fiber doesn't provide calories. And would we consider that now a drug?

Alexander Fleming (02:01:47):

Well it could be a medical device. In fact there are some agents It could creates a moving experience.

Riette van Laack (02:01:57):

Yes. Yes it

Alexander Fleming (02:02:01):

Is. Oh my gosh. Well, speaking of moving, I guess we should probably move along. Got one class I got to go to. Yeah, this is great. Thanks to all for hanging on in. Great to work with you all. Alright, take it easy. Bye. Thanks everybody. Well.