Zan Fleming (00:00:12):

Well folks, we are just about to open the formal session and great that everybody is ready to go.

Thomas Seoh (00:00:45):

It's fun to see the people loading up. Hi our friends, Alan and Bernie

Zan Fleming (00:00:51):

Indeed. Sorry we can't be voice to voice, but good to see you

(00:01:32):

Just one minute from Showtime.

Thomas Seoh (00:01:45):

Marianne, you have your coffee now? Ready to go?

Marianne Mann (00:01:52):

Absolutely. Although it's probably going to lose its heat soon, but that's okay. My future possible daughter-in-law bought me this cup that you can, it works through my phone and you can heat it up, which is kind of cool, but it stopped working.

Joy Cavagnaro (00:02:09):

Interesting. Future possible. That's an interesting,

Marianne Mann (00:02:13):

Well they're only 24 and 25 so they're young, but I think so what? We'll see.

Zan Fleming (00:02:39):

Alright, it's top of the hour and welcome to our global audience to the institute session on regulatory nuts and bolts for developing long bio products. Delighted to have you and we've got an all-star panel here to address simple and more complicated questions and we'll do our best to cover a lot of the questions that have been pre-submitted, but we do have a lot of ground to cover. So let's get on with the show and I'll turn you over now to my colleague and chief executive officer, Thomas Seoh, who will give us some housekeeping measures.

Thomas Seoh (00:03:29):

Thanks Zan. A housekeeping reminder to enter any questions in the Zoom webinar q and a function. A link to this recording will be circulated to all registrants and made publicly available within the next business day or so. The chat function has been enabled for audience interaction. So just for warmup, those of you who are willing, please say hi in the chat and your affiliation of desired and from where you are logged in. Many thanks to those of you who have submitted excellent questions. The panelists will try to get to as many of them as there's time for please and then Zan, I'm going to turn the mic over to you to the moderator, Alexander (Zan) Fleming, MD, founder and executive chairman of Kinexum, a regulatory, clinical and product development advisory firm and president and founder of the not-for-profit Kitalys Institute.

Zan Fleming (00:04:21):

Thank you again Thomas, and great to have my friends here to provide what I think will be a very engaging and interesting discussion that will help to provide the various people involved in the development of products that are targeting healthy longevity. First of all, we do have an all star panel and I'm going to introduce introduce 'em in a moment, but I just want to say that the world is coming around to embracing the concept of bending the aging process and we can do so with great advantage with both individual health and public good, improved and benefited. One reflection of this interest are the X rize and ARPA H programs which are intended to catalyze progress in developing solutions. And our session today in part responds to the many questions that we have received from colleagues about the nuts and bolts of getting into the game regulated product development.

(00:05:45):

These nuts and bolts should be of interest to everyone and the general field of neuroscience. We do have my friends who are joining us in this panel, they go back many years, all but one to early FDA days. And let's start by introducing them. First of all, joy Kevin Aro is a icon in the field of what she calls preclinical development. It's more conventionally called nonclinical development. It's everything about not only animal toxicology testing but in vitro and other measures that have to be done before and during the therapeutic development process. And the great thing about joy is that she hits across the entire spectrum of small molecules to advanced therapies and so is a particularly handy resource for this discussion. And then Marianne Mann, Dr. Marianne Mann is a pulmonologist by training and again, a contemporary of mine at FDA back in several decades ago, but she actually was involved in multiple divisions at FDA and since leaving, she has become a preeminent expert and guide the process of developing multiple kinds of drug products and biologics through the FDA process.

(00:07:30):

Then David Fox, who is now a senior partner at Hogan Lovells. When I first met him, he was with me a young man at FDA. He was back in the general counsel's office and was we jokingly say charged with keeping me out of jail by making sure I didn't break the rules. And he since has been an important ally in the development of Kitalys Institute and in particular the authorship of the Thrive Act, which I hope we'll have time to come back to at the end of the presentation. But David is a great thinker in regulatory science and policy and you'll find that he can answer a lot of questions that range across FDA domains of just about all sorts. Then finally, we have the only non FDA alumnus when we dental, but going back years is my relationship with Dr. Keith Watson who was at another premier agency, MHRA, the UK FDA equivalent and for a while part of the EMA and Keith Bringss.

(00:09:11):

Again, fraud broad experience across CMC matters that is making the therapeutic product and having its analytical processes, but not only for small molecules but for biologics. And so we did want to not only expand the coverage from a technical standpoint, but bring in piece of key knowledge about expectations and other regulatory authorities and maybe to provide some contrast of the different regulatory agencies expectations and programs. So let's see if I can advance these slides. I'd like to just begin with sort of the end in mind. This is one way of depicting that a mocked up drug product label that shows an indication for a hypothetical combination drug product and ultimately we are wanting to have this kind of prescribing information for multiple products that could have some role in increasing healthy longevity. It's an awesome and launching project to think of undertaking these programs to develop products that could require longer periods of clinical trials and would require much greater resources.

(00:11:03):

But we'll talk about how we can in various ways crack those nuts at a moment. One thing we did in our last session was to talk about surrogate endpoints and this case a surrogate endpoint that would be predictive of multiple chronic disease risk reduction. Insulin resistance is such a candidate, it is well known for being the biological basis or one mechanism for various forms of cardiometabolic disease, but all chronic diseases and some forms of cancer are driven by insulin resistance. And so we had interesting discussion about this as a particular product that could be used not only in the clinic as it is now being done, you're now looking at the description of a product that you could have done at your local lab and assess your own cardiovascular risk. But this might or something like it might someday become a surrogate endpoint, which would greatly expedite the development of therapies or interventions for improving healthy longevity. So let's just pause there and we'll start with our panel and we'll take our first, we'll get into our first topic, but let me stop sharing and excuse me why I do a technical adjustment. Alright, I'd like to start with Dave who can speak for hours about this different, this particular topic, but Dave, could you talk about the major categories of regulated products and their respective regulatory pathways in the us?

David Fox (00:13:29):

Sure. Zan, thank you for the kind introduction and hello to everybody. So I'm going to give you a extremely high level overview for everything that I say. There are vastly more exceptions, but I'm hoping that this gives you enough grounding to appreciate what we're about to talk about. So first major category is drugs. This is anything that's intended to treat, cure, mitigate or prevent disease or anything that's intended to affect the structure or function of the body within the drug field. The first major distinction that we have is between new drugs and not new drugs.

(00:14:20):

So new drugs sounds like it's new but it's not. So anything is a new drug. If it's a brand new compound that FDA has never approved before, a new chemical entity that's a new drug or a previously approved drug for any new use, a new indication, a new way of dosing it, a new strength. So a new drug is anything that's brand or has been around for as long as you want but is being used in a new way and anything that is a new drug needs to be approved by FDA in advance before it can go on the market. Anything that's a prescription drug or likely would need the intervention of a physician to prescribe it is always going to be a new drug and will need pre-market approval. The only other category, the not new drug are those things that have been around for a very long time for a specific use and are considered generally recognized by experts as safe and effective.

(00:15:29):

And those can be marketed without preapproval by FDA, but those will always be OTC products over the counter. So for purposes of our discussion, I think we're leaning towards prescription drugs, which will always be new drugs and we're talking about brand new compounds as well as existing compounds for new uses. In that case you need pre-approval from FDA and there are multiple ways to do that. On the first side of the line are new drug applications that require the submission of clinical data. We call this five oh five B one and 5 0 5 B two applications under the statutory provision. A B one application includes all original nonclinical and clinical data needed to show that the new drug is safe and effective for its intended use. Generally that's two. For the clinical studies at the human level, it's two adequate and well controlled clinical studies or in exceptional cases one study plus some form of what's called confirmatory evidence and we'll talk about that some more.

(00:16:42):

A B two application requires the same level of data to demonstrate that the drug is safe and effective for its intended use, but at least some of the data is from other sources, either the previous approval of the drug by another sponsor or something in the literature paper. Either way, when you're proving a new use for a new drug, you need to come forward with data, with evidence to show that the drug has an effect, a clinically meaningful effect to characterize its safety and to show that that meaningful effect outweighs any risk associated with the drug there. Also, there's another category for generic drugs. This is the A NDA area. We're not going to talk about that because NDAs are only for existing uses. You can't come up with a new use of a drug under an A NDA and generic if your drug, if your therapeutic consists of a protein, something that's more than 40 amino acids in size or is derived from live cellular material.

(00:17:52):

And there are other categories also vaccines. But generally if you are a protein or you're derived from cellular material, you would have to go under something called a biologics application, a biologics license application, and your approval would be under wholly different statute under what's called the Public Health Service Act. For the most part, the evidentiary standards for new biological products is the same as the evidentiary standards for drugs. Randomized controlled trials to adequate and well controlled clinical trials are one trial plus confirmatory evidence. What's noteworthy about the biologics space for purposes of our discussion is there's no B two equivalent. There's no way to get approval of a biologic at this time based on a hybrid of your own data plus data from other sources. You have to come forward with all of your own data to get a biologics approved by FDA. The next category is dietary supplements and nutritional products.

(00:18:58):

A dietary supplement is essentially a product that's intended to be ingested, so not a topical, not a nasal, but an orally ingested product that includes a dietary ingredient where the intended use of the product is only to affect the structure or function of the body. You cannot make a disease directed claim and still be a dietary supplement. Once you make a disease claim for anything that's orally ingested, you become a drug and you have to go through that triage that I just discussed. And then the last category we'll talk about are medical devices. Medical devices, again, like drugs, anything intended to treat cure, prevent disease or affect the structure or function of the body, but they do it in a way that does not require chemical or metabolic activity. So devices are devices based on using physical modes of action as opposed to pharmacologic modes of action.

(00:20:01):

The device system is basically a three tiered system. It's a risk-based system given the diversity of medical devices, everything from band-aids and toothbrushes to bone fixation devices and implants and pacemakers. So it's an extremely diverse set of products as well as diagnostics. And because it's so diverse to get your arms around it, you have to deal with it by breaking it down into classes. So we have class one, class two and class three devices, class one, low risk, class two, moderate risk, and class three, the highest level of risk. A class three device is very much like a new drug application for a new drug. You need original data to show that there's reasonable assurance of its safety and effectiveness. So it's a safety and effectiveness standard. It's a more complete application called A PMA. So class three devices, high risk devices, PMA, usually what defines a class three device, a high risk device, A PMA device is the way it interacts with the body and the depth of the interaction.

(00:21:17):

So anything that involves interplay with an organ manipulation of the body in a significant way, in a durable way. Class three on the other end of the spectrum, class one, the low risk devices, those get on the market through a notice process and in many instances are even exempt from providing any sort of

notice. Generally class one devices are subject to what's called the five 10 K notification process where if you can show that you are substantially equivalent to a previously marketed device, what's called a predicate device, you get on the market with this notification, which is basically roughly the equivalent of an abbreviated application. So you have class one, low risk, class three, high risk, and then straight down in the middle the moderate risk class two is more of a case by case system for what level of data is needed to get it on the market.

(00:22:18):

And that's usually prescribed through FDA regulations or a de novo process in which you get a bespoke package authorized by FDA. So devices is more initially stratified by level of risk drug. It's much more of a one size fits all system. Pretty much every prescription drug gets rooted through the new drug process and you need substantial evidence of effectiveness and effectiveness outweighing safety risks in order to get to market dietary supplements just to review no pre-market approval as long as linguistically the language you pick can fairly be said to capture only an effect on the structure or function of the body, but not a disease state. And that was a lot in a little time.

Zan Fleming (00:23:08):

Yeah, that was about a week's worth of law. And thank you very much Dave. And we might just ask Keith for a slight difference that you have in Europe and the UK for in effect repurposing biologics. There is sort of a 505B2 equivalent, is there not Keith for biologics?

Keith Watson (00:23:37):

Yeah, I mean, thanks Marianne. Essentially the similar criteria exist in Europe and the uk. I mean up until 2020 the UK was part of the European Union and part of the MEA and effectively, to all intents and purposes, the MHRA, the UK still follows many of the European historical approval systems and recommendations. But again, you are broke into medicines devices and there's also things that are not compliant, not considered medicines. For example, blood components which would be subjected to different regulatory regime in Europe and the uk, but you can have, similar to the US you can have small molecules which are essentially chemically synthesized or you can have biologics, which could be recombinants, plasma derived products, urinary derived products and very advanced therapies are also considered biologics. And again, most products, well they have new products in which case they have to have the full set of data similar to what the FDA would require.

(00:24:58):

You can have what are called follow on biologics or biosimilars if they're biologics where they attempt to copy the biologic, the new biologic, they say the equivalent of a generic in the biological space. There is also something called well-established use which alludes to products that have been on the market for many, many years and have shown to be safe and efficacious and they can be effectively maybe resurrected if you will, or they can be transferred from one member country, say France to Spain. And they're effectively rely pretty much on bibliographic data. So they're using the historical data that's out there to support. So the data requirements I think are virtually identical across all regulatory regimes. It's the interpretation of the data, I think it may be slightly different, but again, to keep approval of a new product, whether it's a small molecule or a biological, would require a significant investment in time and money and studies including some nonclinical, preclinical CMC, which stands for Chemistry, manufacturing and Control, which as we'll come to later, is really a description of how you make the stuff, how you control it, and how you show that it's stable.

(00:26:23):

And obviously clinical data. And similar to the us, often they require two efficacy studies, but depending on the type of drug, depending on the indication, that can be reduced. There is even possibilities in certain cases to have single arm studies, even occasionally open label studies. But there are very few opportunities to do that depending on the indication. But effectively I would say it's broadly the same regime between them, and particularly if you think that the F-D-A-E-M-A and other regulatory agencies have a lot of mutual recognition agreements in place between them. So not only from a manufacturing perspective, but a lot of shared work sharing in certain molecules where they share assessments, they acknowledge share, so often now they support global development, which means that they're very aligned to each other's needs to reduce the need to duplicate studies including clinical and aim to help companies the minimum they need to do to support approval in many regions.

(00:27:27):

Finally, medical devices, again, similar classification system to the US. Class one, class two, class three based on risk. These are approved in Europe. You need something called a conformity assessment CE mark. And these can be approved and support like European approvals. And the MEA doesn't necessarily get involved too much with the conformity assessments. They're done by separate notified bodies, which are around in the European member states and the UK as their own conformity assessment now, which is a UK version. But where the EMA, which is the FDA, if you're aware they get involved, is in the combination products. So for example, particularly with biologics like monoclonal antibodies, a TMPs vaccines where they're almost certainly injectables, you'll often have a prefilled syringe or a pen and that's when the EMA get involved also with their assessment. And that's known as a combination product. But the separate parts are dealt with separately the medicine with the MEA, the medical device with the notified bodies. But it's very similar to the FDA,

Thomas Seoh (00:28:40):

Apologies for the interruption, but Sayief, would you please enable our chat? Thank you. Back to you Zan Sorry.

Zan Fleming (00:28:47):

Right. Well excellent Keith. Very helpful. And it does give us a sense of the global system for evaluating and approving products. Let's bring in Joy and Marianne to the discussion and we're headed towards more and more detail. We've started out very high level and in fact we've actually covered to some extent close to Marianne and Joy. But just again, a high level what is involved in, let's go to Marianne. Substantial evidence that would be sufficient to support a new drug application or a biologic licensing application.

Joy Cavagnaro (00:29:37):

You're on mute.

Marianne Mann (00:29:40):

Sorry, I was muted. I was going to say that's the 64 million question that I get asked all the time. And so does FDA, what is substantial evidence of efficacy and FDA even has an acronym for that. Just so that you all know the C, there's a C guidance and FD refers to CSEE now which stands for substantial evidence of efficacy. And I think they know that that's a key question that everybody has generally per the guidance, it's two randomized, double-blind controlled trials that both replicate efficacy and show a P value of 0.05 or less. And I remember when I was at FDA Z as a new reviewer, I was like, why do we need

two? It seems like one should be pretty good. And a statistician pointed out to me that a p value of 0.05 generally means that one out of 20 times you might be wrong.

(00:30:39):

And then he also said, when you have two trials that replicate efficacy, it's one in 20 times, one in 20 or one in 400 times that you might be wrong. Which do you think FDA prefers for the American public? They like the one in 400. Is that written in stone? Well, no, I think like you've heard from other speakers, nothing is totally written in stone and FDA has a lot of regulatory flexibility and sometimes a single trial is enough, sometimes two trials that are a little bit different. One in pediatrics say, and one in adults can be sufficient. Sometimes two different endpoints, one on one endpoint, one on another endpoint can be enough. Sometimes a drug with a very strong biologic mechanism of action, very strong animal data, mechanism of action, very initial studies that look promising and then a single study to confirm efficacy can be enough. So I just want to say there's a lot of flexibility, but maybe that gives you some idea of what substantial evidence of efficacy is and also why the default answer is two trials, both meeting a P value. Thanks.

Zan Fleming (00:31:49):

Perfect. Marianne and Joy, a tough task here, but just in a few words, what goes into a package for approving an NDA or A BLA? Just a broad strokes

(00:32:03):

With

(00:32:03):

Respect to nonclinical or as you like to say, preclinical data. Okay,

Joy Cavagnaro (00:32:09):

Alright. I'll explain that. I'll explain my definition of preclinical because I look at it as pre the clinical, we're doing things to inform the clinical. To me nonclinical seems very negative. And so I'll say my most frequent question is, what is the least amount you have to do to get into the clinic? To which I say, I'm not going to tell you the least amount, I'm going to tell you the right amount. And then the next question is, do you think the FDA is going to make me do this? So those are my two questions, Marianne, right? So again, I look at it as a continuum. What we like to say in terms of preclinical is the principles are the same. It's the practices that are different. So don't worry about it, it's the practices on how we do it, but we're still asking the same question pre-clinically, it's all about the dose.

(00:33:01):

I'm all about the dose. And so if we knew the dose and we knew the safety and we knew how to inform and inform consent without animal studies, then you don't need them. We have to put something in there. We have to understand what dose do we think is going to be safe initially in subjects. So that's how I look at it. And small molecules to advanced therapy. So the continuous is simple to complex, right? So simple small molecules versus the tissue engineered therapies, IPS derived tissue engineered organs, right? The way we regulate them then it's simple to complex. How we regulate small molecules is very rigid specific guidelines. We talk about checklists to the more complex. We are very flexible in terms of, so I call it digi do. So that's what we do for small molecules, you do the same thing all the time.

(00:34:05):

You don't think about what the clinical is, you don't think about anything, you just do it for larger molecules. We think about the indication in the patient population. The other thing about small

molecules is we generally go into normal volunteers to look at safety and some activity. Sometimes for biologicals, we often go into subjects with the disease as our first introduction into the clinic. And there you see kind of the differences in terms of how we think about safety studies and efficacy studies. And so for small while, both our concern about safety and efficacy for small molecules, it's really all the talks, toxicology, toxicology, that's the key for biologicals and advanced therapies. We look at animal models of disease to try to mimic the clinical disease as best as we can. And then based upon that we may do safety assessment in an animal model of disease. So we get both proof of concept and safety to try to mimic the disease population. I look at it as a pyramid. Those are the differences when we get to the clinical, we all rise to a clinical trial design with what Marianne says. There's less differences in thinking about the clinical as to endpoints based upon the various product modalities as it is on how to get into the clinic. So hopefully that's a

Zan Fleming (00:35:46):

Perfect, that was superb. And then on to Keith, you've already in a sense started us about on the subject of CMC packages, but just in broad stroke, what's involved, what ultimately does it take from the CMC standpoint to have an approved product?

Keith Watson (00:36:11):

Essentially you'll hear the term CMC, which stands for Chemistry, manufacturing and Controls. You may also hear the term module three, which actually is the module of the CTD, which is a common technical document. The way things are submitted now is that there's a format, an ICH format, which allows the data to pre presented in certain sections. And module three is all your CMC data. Module four is traditionally your preclinical nonclinical data. And module five is your clinical. And at the point of an NDA or A BLA that the amount of data that you have to put into each of these sections is quite significant because as you would imagine, it's a new molecule in this case. And you've got to show that not only that your product works, but most importantly from CMC that you can control it. It's about consistency. At the point of you come to A BLA or an NDA, the regulators want to be sure that you understand your manufacturing is controlled, your process is well described, your methods are capable of detecting what you say they are you, your specifications are sufficiently robust that you're going to have a product that maintains its safety and efficacy and that the product can be contained in a defined closure system.

(00:37:42):

Could that be a vial? Could that be a prefilled syringe, et cetera. And that it remains stable. So the data that would be required is quite onerous in some cases. You would have to describe a manufacturing process in quite extensive terms that would be each of the steps, each of the individual controls that you have. The in process controls, you would do that as like a flow diagram, but also a summary narrative discussion of each step. You would also then separately have to break that process down into what are your consider your critical steps, which are the ones that are really critical to ensure consistency and safety. And again, explain and expand upon the control strategy you have there. You'll move into describing your containers, how you store it, are they made, are they plastic? What size are they? Are you sure that they're not interacting with the container closure system so that you're not getting things leaching?

(00:38:46):

And then ultimately you would progress through all the reference standards that you are using to measure your products and make sure that it retains potency through to your stability and stability. Studies are formalized studies, which again at ICH, they have dedicated or defined conditions of

temperature and humidity. You also have to show not only that it's stable under its real time, which is if you claim that you wish to claim that your drug product is stable in the fridge at two to eight for two years, you have to have data to show that it's stable for two to eight two years. You also have to have data that would be classed as accelerated where you elevate the temperature to say 25 and change the humidity. And over a period of six months, you have to show and understand the degradation profile. And also, again, maybe even in use data.

(00:39:44):

So for example, if you were to take that mile and it was say Olly product and you had to reconstitute it and then put it into an infusion bag for example, you would have to show that it remains stable up to a certain point. So there's lots of data that are required. And often CMC is, I would say certainly with biologics, maybe even true with small molecules. It's probably the most substantial section that you would have to put in to get approval. And obviously as you go through the development paradigm, so as you start at the beginning and you're going for early engagement with the agencies and you are perhaps opening INDs or you are coming in with very early data, what will happen is that you will end up with the data requirements would be lower because obviously you've got less data, but they progress through the paradigm.

(00:40:37):

But ultimately the BLA, it's a significant body of work that needs to be done. And all I will say is that there are opportunities for regulatory relief of CMC in Europe. There are certain things called prime, for example, certain regulatory regimes which in theory would allow you to mitigate some often clinical but occasionally some preclinical CMC data for drugs under certain criteria, which effectively means they will accept that you've got only limited data or only few batches of data. And then you can continue to bring that forward later on. But that's usually where there's very unmet need or for life-threatening indications. But there is always opportunities to have some negotiation, but it is a significant body of work.

Zan Fleming (00:41:25):

Very helpful. And Dave, you've already covered the device side and diagnostics to some extent and maybe we'll come back to what's involved. And we should note that certainly devices are in the hunt for healthy longevity and should be considered just as much as drugs and biologics. But Dave, why don't we go on to the beginning. We've started off at the very high level.

David Fox (00:41:55):

Let me, just, sorry, before we go, just put a pin in one thing about the device side, particularly the non PMA lower risk devices. One thing that distinguishes devices for purposes of say advancing healthy longevity programs is that the risk proposition for a device is very different than the risk proposition for a drug. And therefore we find that devices may have a lower threshold for showing a benefit than you would need for a drug because it's a very different risk calculation. And it's just a general principle to keep in mind

Zan Fleming (00:42:41):

Important. And again, we're talking about both devices that treat and devices that are diagnostics and both

David Fox (00:42:51):

Cases

Zan Fleming (00:42:52):

The principle of loss.

David Fox (00:42:53):

But even for treatment, for example, we seen our devices for pain for psychosocial disorders that meet a level of evidence for benefit. That is not a level of evidence that Cedar would accept for a drug. And the reason the way they're able to get there is because the non-interventional nature of the device makes it an easier risk benefit proposition. Now, FDA can't go all the way to the point of having devices that don't do anything that are sham, but the threshold for benefit can be a lot lower because the risk proposition is different,

Zan Fleming (00:43:33):

Right? Well, Tempus, Fuji, and so let's go on to the beginning, to the very earliest stages and maybe Dave, you could talk about what an IND is and when it is required and not

David Fox (00:43:49):

Required. Sure. So remember that category, new drug brand new chemical entity or new use of an existing drug, anything that's a new drug in order for it to move around in interstate commerce, even to a clinical site, needs to be under an investigational new drug application. So you either need an approved new drug application or you need an investigational new drug application, an IND. So that's all it is. It's permission from FDA to move something around the country or import something into the country for further study. Now there are a number of circumstances where you can be exempt from needing an IND and that's a much longer conversation. But generally, if you're taking an already approved substance and you are not changing its risk profile in your proposed use and you don't intend to submit your study for any kind of marketing approval, you may qualify for an IND exemption.

(00:44:57):

But it's rather limited in what you can actually do with that data. And of course you're taking a very big risk anytime you do a study under an IND exemption that you don't have FDA's blessing over the study and you don't have the usual warmup to doing the study where you would meet with FDA A in advance and get them to more or less agree to your proposed study making it much more likely the DA will accept the data for registration or approval down the road. So generally, if you want to do a clinical study assessing the drug, just even for safety only or to a clinical endpoint, you need an IND unless you basically want to use it for more academic or publication purposes. You're not changing the risk profile of the product and you don't intend to ever submit the product, excuse me, the study for regulatory review and then you can be I and D exempt.

(00:45:56):

There's also, I just say there's a range of INDs. There's INDs for the conventional clinical study. There are also circumstances in which an academic, a clinician, anyone can get a single patient IND if they want to use a drug in an experimental way for an individual patient. These sometimes call those emergency INDs. There's also compassionate use INDs, which is a known unapproved use of a drug that's considered compassionate use where there's this predefined protocol that FDA will accept to allow companies to ship the product to individual patients or centers on a compassionate or emergency use

basis. So there's a whole range of IDs, but basically anytime you want to try to put a new drug into commerce and you don't have an approval for it, you need an IND.

Zan Fleming (00:46:54):

Right. And then Joy and Marianne, very quickly, what goes into a typical IND package? In other words, what would the basics seek intense from your different domains? Joy,

Joy Cavagnaro (00:47:09):

You want to start with preclinical, right? So early on you'd have your proof of concept studies in vitro or in vivo like I said, and maybe in an animal model to say, this is what we think the product does. And then you would have safety studies. Again, they're very clear guidances for small molecules, biological drugs and cell and gene therapies, advanced therapeutics. So that one would again be able to follow to be able to design the appropriate studies for the various modalities. And so you would, once you get your proof of concept and your in vitro studies and then you'd start doing your safety studies, safety pharmacology studies, cardiovascular assessments, neurological assessments and respiratory. These are standard again across the various modalities and then your toxicology studies to support. And they would vary based on the indication, the patient population that you're treating, the duration that you would like to treat initially. So the animal studies should support the duration of what you intend to do in the clinic. And that of course differs for small molecules going into normal volunteers too, when you're looking at some of the more complex molecules that will go into patients. Yeah.

Marianne Mann (00:48:49):

Yep.

Zan Fleming (00:48:50):

Perfect. And then Marianne, go right ahead.

Marianne Mann (00:48:54):

And I realize the audience, some of them understand INDs and some don't. So for those who don't, I always break it down into the major categories. So Dave mentioned earlier, CMC, so CMC is chemistry, manufacturing and controls. You got to have a drug, right? You got to have a drug and you got to tell the FDA, what's in it? What's in the drug? Believe it or not, I had an IND when I was at FDA where they had a concept of a drug but not a drug. And then they had all kinds of ideas they wanted to ask and we just said, it's incomplete. You need a drug, you need to tell us what's in the drug, what you're going to be giving to people. And you have to have the CMC information on stability, basic stability, basic information on what's in the drug. It's not a huge package.

(00:49:35):

As Dave mentioned. It grows over time. The more you know you, further you go, the more CMC data you need. But initially you would need some CMC data. The second major category is preclinical as joy just described. And the preclinical data are needed. Basic safety, preclinical data with safety margins established are needed to support giving your drug to humans. Generally these are needed. The only time I've seen them not be needed is if you're giving an already approved drug. And you can sort of segue to the studies done for that already approved drug. So sometimes you don't necessarily need to do those studies, but generally for any new drug, you have to have those with safety margins identified. And then you need a protocol. You need an initial protocol that you're going to be submitting. And the

idea, we want to give this to people in the following way, and you need to kind of tell the FDA as well what your population is, what your safety margins are, preclinically, and how long you're going to give the drug and basically support the safety of that proposed clinical trial.

(00:50:42):

So I'm, I'm going to say you'd like to tell the FDA your eventual indication, but I don't think you have to in an IND. I mean you can start with something and you can change it. So that's flexible. But the CMC, the preclinical and then the clinical section are very important to having a complete IND so that you can do the proposed trial. To be clear, when FDA reviews that IND, they're reviewing only that proposed trial that you have submitted all other studies that you want to do or can do follow under the ID process, but they are reviewing the safety of that particular trial that you propose and other studies follow under the IND process as you make more progress. I hope that explains things at a very basic level. You're muted, I think, Zan. Sorry.

Zan Fleming (00:51:41):

I am indeed. Yes it does. And so let's just keep going. Dave, you might just mention one other requirement that is in effect or related to FDA and that is for institutional review board recall.

David Fox (00:52:00):

Yeah. Yes. So anytime someone proposes to do an experiment on human subjects, they need to conform to very important standards on human subject protection, the ethics of the study and including protecting the safety of the subjects, making sure that the subjects are informed of the study, that they're aware that they're being studied and their rights under the study. And this goes all the way back to international conventions and treaties. But basically what it means is before one can begin a clinical study under an IND one needs to get an institutional review board, an independent body to review the study for its conformity to ethical standards. It's called an institutional reviewboard IRB approval. So it's typically an academic institution if you're doing an academic study. And then there are organizations that will convene institutional review boards to give IRB sign off or feedback. And then the IRB approval works hand in glove with the informed consent that is given to the patients and signed by the patients, making sure that they understand their rights under the study and they understand that they're being studied and how their data will and will not be used. And FDA, as I said, cannot allow a sponsor to move forward with a study unless there's adequate assurance of human subject protection.

Joy Cavagnaro (00:54:00):

Can I add a few sentences?

David Fox (00:54:02):

Yeah, yeah, of course.

Joy Cavagnaro (00:54:03):

Actually participated in an IRB now for 25 years. So it's very Right. An independent IRB, right. And so Exactly right Dave. And again, we don't look at study design per se protocol so that we expect the agency will focus on the study design. We look at compensation of study participants in addition to what the ethics we look at whether or not we think it's appropriate for a legally authorized representative to be allowed for the consent process and in particular, vulnerable people, right? We're very cognizant of that. So that's kind of what we focus on. So we want to make sure that they're sufficiently the margin as

Marianne the safety margin from any animal studies go forward, but it's really those aspects of the ethics of the trial that is the focus of the IRB.

Zan Fleming (00:55:09):

Good. Well, let's go on to the different flavors of IDs. Very quickly in a kind of round, Robin was mentioned that there is such a thing as an investigator IND versus a commercial IND. We have IDs for literally new molecular entities. So IDs for repurposed already approved drugs. So maybe we could talk about the considerations for some of the people in our audience as to whether they should file an investigator driven ID or a commercial ID Marianne, you want to take that?

Marianne Mann (00:55:53):

Got to unmute myself. Sure. I think that the important thing to recognize is that for the FDA, the IND as they review it is the same under the regulations and the requirements are the same. So it can be discouraging to investigators who say, I'm just me and me and my small group, and I just want to study 10 patients. And I'm not AstraZeneca, I'm just me. Unfortunately, the answer is that the FDA looks at your application and the drug and the population and what you intend to do in the same way as they would if it were AstraZeneca wanting to do the same 10 patient studies. So the requirements are still very similar. I mean X, you can, I saw your eyebrows go up so you can clarify. I think the small story I can share, this is just a small story. I had an IND when I was at FDA and a guy wanted to take inhaled potassium iodide, inhaled potassium iodide and give it to patients with cystic fibrosis.

(00:57:00):

And he came in and said, it's just potassium iodide and it's a well-known substance and it's been around for years and years and years and it's a normal occurring ion in the body. And all I want to do is give it via the inhaled route and see if it helps CF with the ion changes. And we had no animal data, no nothing. And we had to inform him that you need the animal data. And he said, I'm not AstraZeneca. I don't have animal data. I can't do that. And we explained that it was a requirement, and we further explained to him that potassium iodide via the inhaled route might be very well absorbed because inhaled drugs are typically absorbed quite well and it could lead to very high potassium levels that could be very dangerous for patients. And he said, well, how dangerous could it be?

(00:57:51):

It's just potassium. And we kind of gently explained that potassium can affect the heart and cause the heart to sort of stop. It's a bad thing to do to patients. And the funny part of the story maybe is that he said at the end, oh, I'm glad you told me that. I've been giving it to my wife who has CF for the past several weeks. And we advised him gently again to please stop doing that. But what I'm sort of saying from that story is that you do need the FDA still looks at what you're doing and says, is this safe? Is this not safe? But maybe you can clarify some differences between the investigator and commercial INDs as well.

Zan Fleming (00:58:37):

Well, I think you're exactly right. Ultimately, FDA has to ask for the same kinds of things. There may be a bit of leniency,

Marianne Mann (00:58:49):

As they say. They call it regulatory flexibility. They have some flexibility. They can sometimes help you along the way a little bit, but they can't change the regulatory standards for safety. Yeah,

Zan Fleming (00:59:01):

Exactly. And the point is, if you're serious, if you're really going towards a commercial use, then you need a commercial IND. Sometimes you see investigator I Ds being done as a way to get started in the clinic. And then the commercial IND is later submitted. But that is a less optimal approach, I think in general,

Joy Cavagnaro (00:59:29):

But interesting. It's what it is. It's a clinical investigation. It's doing research on subject participants versus clinical development. So I think that's what you see with investigative IDs, right? It's not interested in clinical development. They're interested in clinical research.

Zan Fleming (00:59:46):

That's right. That's the intended role for it.

Marianne Mann (00:59:53):

I was just going to say that there's a lot of people, a lot who want to generate initial proof of concept data that will then interest a commercial entity.

Joy Cavagnaro (01:00:02):

Well, no, eventually it's their interest. Of course, that's the ultimate goal. But what I'm saying is, is their precise interests, this is how we advance gene therapy. All academics, okay. They're less risk averse. So sometimes the packages look different from investigator sponsored, even if they do their own preclinical studies versus a large pharmaceutical because they're less risk averse, they may say, well, I don't think we should provide a rationale for not doing a study. Whereas a big pharma might just do everything. And so their package, their IND might look different, but by the pharmaceutical, the agency hasn't mandated that

Zan Fleming (01:00:46):

Yet. They very quickly,

David Fox (01:00:48):

Yeah. So you have the drug company, the sponsor, and they can initiate their own studies. Those are the sponsor initiated studies. And then you have people out there in the community, usually academics who know of a drug and want to use it in an experimental way. Those are the investigator initiated studies. And one of the bright lines historically has been that the drug company cannot have any input into the design of the investigator initiated study, otherwise it will look like the drug company is using the investigator initiated studies to seed the market with regard to off-label uses of their drug. So there's a very important regulatory compliance aspect in the distinction between an investigator initiated trial and a sponsor or commercial trial. Now there's a new flavor, a co-development type IND that's emerging where you're using an academic to co-develop product with a drug company in the proof of concept. And we're sort of trying to work out the rules of the road there where there's some input from the drug company but not enough to cross that compliance line. So just want to point out that there's supposed to be some clear separation between the concept of a commercial IND and an investigator initiated IND, even though as Marion and Joy are saying that the INDs have to fulfill the same regulatory

requirements, but a commercial sponsor needs to stay very tread very carefully when supplying their drug to an academic for an investigator initiated IND.

Zan Fleming (01:02:27):

Very helpful. And just to close out on this discussion, it's worth mentioning though, I think it's obvious that if it's an IND for an already approved product, but seeking a new indication that obviously is not going to require the same kind of nonclinical and CMC requirements as a new molecular entity. Not to say that you might not have to do a nonclinical study, right Joey, or if it's a formulation or a different route of administration, Keith, that you wouldn't have to do some CMC that would support that,

Joy Cavagnaro (01:03:06):

Right. And if you think the same dose would work on the different indication, yes,

Keith Watson (01:03:12):

Yeah's, right? I mean for the new route of administration, you'd have to update because it's the new route you to do some additional CC. But in Europe, I mean just the I term IND doesn't is not a formal term. In Europe or the uk, they use the term CTA clinical trial application, but it's pretty much the same thing. There are some subtle differences. A CTA is probably more protocol driven, whereas an IND is more about the product in terms of as a life cycle, whereas the CTA tends to be an approval reject to the point of submission, although you can make some changes to it. But they have the same thing. They're the review boards, independent review boards with a clinical study. And also in Europe you've heard of the EMA and the MA is sort of akin to the FDA, although technically the MEA doesn't really approve it just administrates across the member states of Europe.

(01:04:12):

So for example, there's 20, I believe 26 now. Now the UK has left 26 member states in Europe. And if you wish to do a clinical study in say France, you have to get approval in France. This is not a European pan approval. Equally, if you wanted to have study sites in France, Spain, Italy, and Germany, for example, you would submit one application, but it would be to each of those four countries who also will review it, a comment on it so that you only would get a pan-European approval should you go to every single member state where you wish to do the study. So I think that's different because of the nature of the way it's set up. But yeah, I mean in terms of investigator and commercial CTAs, they're similar to the F fda. They're the same rules apply. The only exemptions you'll probably get in Europe and in the UKs as if it's essentially a non-interventional study.

(01:05:12):

And there are sort of algorithms that they apply. And you can have a reduced sort of package of CMC. It's called the IMPD in Europe. It's called the investigational medicinal product dossier, which is essentially the module three component of the BLA or an NDA. And if you're using an existing drug, maybe repurposing it or you can then do a reduced package where effectively you just link back to the approved data of that molecule. But essentially they are the same things, INDs and CTAs, they're just slight subtleties. And ultimately if you want to do a study in Europe, you're going to have to do A CTA in whatever countries you're going to. But equally, I think it's important if you wished to get approval of the molecule at the end, like you wish to get an approval in Europe, you don't have to do a study in Europe.

(01:06:07):

You could have a study that was done elsewhere and providing the study was deemed to be robust complying with ICH, and they were happy with the endpoints. The Europeans and the UK are not wedded to studies being done in their own countries. They would accept a US study or maybe a Japanese study or maybe in Indian study for some molecules. It all depends on that, the actual study that's being done and whether is supportive of the endpoint. So you would only need to get the approval if you wish to do the study in that country, but that approval isn't required necessarily to get approval of the product at the end of it.

Zan Fleming (01:06:47):

Terrific. Keith, thank you. We wanted to talk about ways of communicating with FDA and other authorities for that matter. We'll save that for another time. But suffice it to say that FDA and certainly EMA and MHRA are open to having meetings prior to submissions and there are different procedures involved. And in the case of the European meetings, they actually charge for it. That's not the case for FDA, but we'll come back to FDA or regulatory communication. Maybe at another point after having covered some of the nuts and bolts and high level details, let's take some questions that have come up and I think we'll find this fun. We'll try to do this quickly, but why don't we start with the question, does aging need to be a disease for FDA to deal with it? And David, maybe you'd be the one to take that in 30 seconds or less.

David Fox (01:08:06):

So I think that FDA views a disease as some form of a deficiency or a deviation from normal function, and then it's marked by symptoms and such. And I think that FDA would view does view aging as normal biological function. And so I don't see it falling within FDA's mandate to think of aging as a disease endpoint in itself under its existing regulatory authority. So drugs are for the treatment of disease. There are also that you can't have drugs for affecting structure function of the body. But when you get to the approval standards, it has to be clinically meaningful. And I don't think they would say a change from normal biological aging is clinically meaningful or something that is drug worthy. But I think that where we're headed is for FDA to recognize that there are diseases and there are constellations of diseases, recognized diseases. We don't have to go through them that are associated with and more likely to occur as we age. And that if we can show an impact on those diseases, deferring their onset or lessening their severity, and then that's an endpoint that FDA can manage. So I think that's where we're headed. I mean absent a major statutory change to specifically designate aging as a target under the existing regulatory system and anything we've really ever talked about, I don't see it.

Joy Cavagnaro (01:10:17):

So could you align it like the cosmeceuticals, so the cosmeceuticals have biologics and they're used for improving looks of aging people or whatever, but I mean, is there a larger ceuticals or something that we can align where, I mean there are drugs and biologics that are used in these products, growth factors, biological growth factors in cosmeceuticals, is that a class of its own?

David Fox (01:10:47):

Yeah, I mean, I said before there's vastly more exceptions to every rule we talk about. And yes, I mean you're putting your finger on an interesting one, joy, which is there are drugs and biologics that are approved for aesthetic endpoint.

Joy Cavagnaro (01:11:02):

Yes.

David Fox (01:11:05):

And that happened, I'm not sure I know, and it's happening with a lot of debate. It was a bit of regulatory creep and I'm not sure everyone heard about it. And it raises some very interesting kind of risk benefit issues. How much risk are you willing to take for purely aesthetic endpoint? But whether you could broaden that to cover aging more generally, that's a very substantial bridge to build. But inside, along the way to that bridge, yes, I think you can come up with other endpoints that maybe are steps further along the continuum from the aesthetic type endpoint. And this is where we get to the endpoint, like what RPH is looking at an intrinsic function, your overall sort of day-to-day functionality. And I think, yes, I think there is a future in which we would come up with patient reported outcome type, daily function, validated metrics that typically would only be relevant to people as they age but is not aging in itself. So changing the biological clock in a non-natural way I think is a tough one. That's a really interesting nother philosophical conversation. But looking at the signs and symptoms that are associated with aging and coming up with metrics for those that they're functional are they're functional in a clinically meaningful way to the patient and can be measured, I think is attainable under the existing rubric.

Zan Fleming (01:12:59):

Great discussion. Brianne, let me ask you a question that frequently comes up about GLP one agonist, which are being shown to reduce risk of multiple complications of age related disease. Do we have an example last of products that actually be considered to prevent multiple chronic diseases and could have a single kind of unifying indication for doing so?

Marianne Mann (01:13:36):

Well, your made up drug at the beginning of the slide, so it would be the example, but I don't think we're there yet. And I don't know of any drug that has that kind of global indication. And I know that's the interest to see if we can get drugs approved for aging and in doing so, help people do better. And I think it's that latter part in doing so help people do better that FDA would want you to prove and show. And you and I have talked about these surrogate markers and I know there's a great deal of interest from looking at the questions from this group. There was a great deal of interest on surrogate markers and I just want to tell the group that the reason FDA is so speculative about surrogate markers is they have seen them time and time and time again show abberant results when it comes to clinical outcomes that really matter to patients.

(01:14:37):

They have seen drugs that lower HDL and raise, I'm sorry, raise HDL and lower LDL rather dramatically and they have more mortality in the clinical trial. They have seen drugs that have reduced B tac and V-fib and really worked on the arrhythmia, but higher mortality in the clinical trials. There are examples of these in a paper by Tom Fleming on the internet. He's a statistician who raises lots of questions about surrogate markers and in his paper, if anyone's interested, just type in Tom Fleming surrogate markers. There's probably about a dozen examples and for the dozen examples he gives, there's hundreds more at FDA where a seemingly good effect on a surrogate marker did not play out in clinical trials and in fact clinical trials showed harm because of that history. I think FDA is very speculative and really want you to show how the drug works on a clinically relevant outcome.

(01:15:39):

And you might say to me, what's a clinically relevant outcome? Well, it's really how a patient feels functions or survives. That definition was brought up by Dr. Bob Temple. I think it's in all kinds of FDA guidance documents. So how they feel, how they function and how they survive. As an example for functionality, and I think this might be the example you were sort of asking me about for pulmonary artery hypertension. A sponsor came up with an endpoint of the six minute walk just to show that they could walk further and initial drugs for this really pretty devastating condition. What they showed was an improvement in a six minute walk and it was about 40 meters or 50 meters, initial drugs down as low as to even 30 meters of difference between a placebo and a drug. And FDA actually along with supportive evidence that they were showing the effects on the pulmonary artery hypertension, it was getting lower objectively along with that six minute walk, how a patient functions allowed these drugs to be approved.

(01:16:49):

And frankly it was speculative at the time. I'm not sure a 20 or 30 meter change is meaningful, but really in doing so, I think the FDA allowed products on the market that changed the lifespan and really helped people with pulmonary artery hypertension. So they took a bit of a leap of faith on that functionality endpoint. And now we have many drugs approved for PAH and they're even used in combinations and we're really making headway on the disease. So I want to come back to Dave's suggestion that you probably need to for these drugs, couple your endpoints with something about how a patient feels functions or survives some sort of clinically relevant outcome to make any kind of progress for a prescribed drug for this type of condition.

Zan Fleming (01:17:40):

Very helpful, Marianne, and maybe staying on surrogate endpoints. We know that there's a lot of interest in this community about supporting surrogate endpoints and clinical measures for managing age-related disabilities and diseases. One example would be the aging clocks that have been put forward and these are perfectly correlated with survival and other measures, both field and function measures. So what is keeping those from being accepted by FDA as a validated surrogate? Are we going to need to see for those kind of measures to be validated? Surrogates

Marianne Mann (01:18:35):

For me, and I'm not familiar with aging clocks, but I'm guessing it's like parameters that measure various outcomes and you have to look at at those parameters and say bottom line, but is it better for the patient to take this drug? What is the tangible benefit to the patient? And if the answer is well their clocks less, their aging clock is less, they have less evidence of this, this, and this, and those are good things and that's where the FDA comes back and says, prove it. Show us that those are good things with some sort of measurable clinical outcome. Something that really tells us, yes, I know you might say, but they're so highly correlated. They're very highly correlated. And I think that's where the difficulty arises because obviously anyone would think that by affecting that clock you're going to be benefiting the patient. Well, I'll go back to the examples I cited earlier.

(01:19:38):

Everyone thought that raising HDL and lowering LDL would be good for a patient. And guess what? It wasn't. Everyone thought that reducing vtac and V-fib would be good for the patient and guess what wasn't when it came right down to it. So because of those types of examples in the past, any kind of future involvement of surrogate outcomes or a composite of surrogate outcomes, even though it's highly correlated with clinical outcomes, you have to really sort of prove it and show the FDA that it's

truly meaningful to the patient. So I come back to trying to find endpoints about how a patient feels functions or survives,

Zan Fleming (01:20:23):

Right? Well, in this case, they actually are meaningful, including survival. They're very well correlated. But I think what the general objection will be is that it hasn't been shown that the intervention that we know otherwise approved and proves clinical outcomes will affect this measure, the surrogate measure in a way that would be predictive of benefit as a way of validating the predictive value of that surrogate. And so it's kind of a catch 22 that we don't have products approved for this syndication that we could use to infect test. The biomarker actually corresponds and its effect to the clinical benefit that is achieved with the prevention.

David Fox (01:21:31):

What are you achieving by changing the marker?

Zan Fleming (01:21:36):

That's right. That's

David Fox (01:21:37):

Right. And at what cost? I mean that's the part that I think you have to keep your eye on that ball. So you're proposing an intervention that comes with some cost if it's effective, it's also got cost associated with it. I don't mean economic cost, I mean cost to the body.

Zan Fleming (01:21:57):

Correct. Sometimes.

David Fox (01:21:58):

So you can have a perfectly, a solid marker that you can measure and correlate with some form of survival or outcome. But the question is how much are you changing it and what is the cost of changing it and then what's your net overall status after you've done that?

Marianne Mann (01:22:27):

Right. I think that is exactly the kinds of questions the FDA asked Dave as well, you're affecting this surrogate and that's highly correlated I know with things, but is it on the direct causal pathway of the disease and is changing that marker truly going to change the disease? And that's the question.

David Fox (01:22:49):

And what else are you changing by changing that marker? It's a dynamic situation.

Marianne Mann (01:22:54):

Correct. And because FDA has example upon example, upon example of good ideas that went the wrong way, they're going to continue to demand that kind of evidence of efficacy,

Joy Cavagnaro (01:23:06):

But it's likely not one marker. It's going to be some composite.

Marianne Mann (01:23:10):

We're not a composite's fine. You can work with FDA on a composite. Absolutely. Yeah.

Zan Fleming (01:23:17):

Well, gosh, we are running out of time. I'm going to fast forward to lightning round of questions will I think be of adventurous to our audience to have answered. So let's start with Keith and Joy to add ip. This is a question from a attendee to add electric property and improved performance of the product. We want to use a novel. What are the considerations for that? And let's be brief joy first.

Joy Cavagnaro (01:23:57):

Okay, so there's very specific in terms of how you qualify an excipient in terms of the pharmacology and toxicology. So there are guidances for that. So just look at the guidance. I mean that's quick, right? Yeah,

Zan Fleming (01:24:14):

That's quick and sufficient.

Keith Watson (01:24:17):

Yeah. Similar with CMC, if it's a truly novel excipient, you're going to have to provide quite a lot of data to show how that is manufactured controlled. It's almost going to be like its own module three, its own section to show where you are sourcing it, how you control it, what specifications you apply for it. So you can't just sort of add them without any clarification really. There's quite a significant amount of work to justify its use.

Zan Fleming (01:24:49):

Good. And then Marianne, for a product that is aimed at restoring muscle cognitive and immune function, what review division would you go to at FDA? On

Thomas Seoh (01:25:07):

Mute? You're on mute.

Marianne Mann (01:25:11):

My apology. The review division that you go to is really dependent on your endpoint, your primary efficacy endpoint. So you want to look at your cognitive muscle, I forget what survival endpoint and try to think about that endpoint and what background of clinicians might fit it the best. And sometimes it's hard, no doubt. Sometimes there's endpoints that it's hard to know which division to go to. Never fear. You can select perhaps a division that seems logical and if you hear back that it's a different division, so be it the FDA will sometimes figure it out on their own that maybe another division should be reviewing the product. But for muscle cognitive, I would be going into the neuropsych area, but now psych is separate from neuro. So in one of those two areas would probably fit that type of endpoint.

Zan Fleming (01:26:10):

Good. And related to that, Dave or jurisdictional matters, that is what part of FDA would review a product, let's say a combination drug product or device slash drug product. How does FDA handle that?

David Fox (01:26:28):

If it's drug drug, you would know to go to CDER or biologic biologics. So if it's within the same field, you go to that center. But where it gets tricky is if it crosses jurisdictional lines within the same product. So a drug device combination, a device biologic combination. Generally jurisdiction is assigned at FDA based on what's called the primary mode of action, which is essentially the last thing that the product does. So in the quintessential drug device combination where the device is a delivery system to deliver a drug to get it closer to the target, to the site of action, the primary mode of action is going to be that of the drug and the combination would go to CR with some form of consultation with CDRH on the device piece. But in borderline cases, either a combination product where it's not clear what the primary mode of action is or single entity products where it's possible the product straddles the line, blurs the line between say drug and device chemical action versus physical action. There's something called the office of combination products at FDA and you go there for a jurisdictional determination, often you go there and you never leave. It's some people have had all sorts of experiences at the office of combination products, but that's their designated function.

Zan Fleming (01:28:02):

Yep.

(01:28:05):

Okay. Well that's great. I'm going to give Thomas notice that I'm going to turn it over to him in a minute to ask a few questions that have come in or burning. But let me just ask one question about developing a nutraceutical and that will go to again the joy and Keith and Marianne, what's involved there. Do you agree to a drug to start with? I think David said you do and resuming that it then becomes a drug. Keith, can you rely on so-called GMP manufacturing of that dietary supplement?

Keith Watson (01:28:56):

Well, in Europe, I mean it's, in order to be regulated as a medicine, you're going to have to make a medical claim improve nutraceuticals or they'd be more regulated in Europe as a food additive or under food standards. So I think whether or not they're manufactured to a form of GMP, it would be helpful in terms of from that perspective of it. But in terms of getting the proof for some medical claim where you can commercialize them without making a medical claim, you would have to go down the road of showing here's some medicine. So you'd have to show is active, it changes function, form or activity and binds to particular molecules in the body. Just sort of having a vitamin drink for example, isn't a medicine in Europe, the claims are very, they're more controlled by food. So it depends. I mean if you call it a nutraceutical, it's not going to be aphy medicine unless you've got a claim in your,

Zan Fleming (01:30:09):

Okay, enjoy dietary supplements are safe. Right? So they don't need any kind of nonclinical testing if they're going through the IND process. Is that right?

Joy Cavagnaro (01:30:20):

I mean I think really the challenges are most of these kind of piggyback on what Keith was saying and it's all about the safety of the active ingredient. And I would say with nutraceuticals the challenges there is

it's more often the contaminants than the excipients and all of those that you worry about toxicity versus the active ingredient. So if you're not properly looking at the quality of the material that you're making, then the challenges is toxicity related to all of those excipients. So you have to understand the safety of the product, but it's inextricably linked to really the quality of the product. I think that's a difference between, I see with nutraceuticals more concerned about contaminants where we have a process with our pharmaceuticals where we decrease the, or make sure that we don't have those contaminants.

Zan Fleming (01:31:24):

But to be clear, essentially you would need nonclinical data to support the dietary supplement and that's probably not available typically for dietary

Joy Cavagnaro (01:31:39):

Supplements. Right? Yeah. Yes.

Zan Fleming (01:31:42):

Alright, well then Thomas, we're dying to get a few other questions. I wish we had about three more hours, but we are at nearly the end. So Thomas, give us a few questions.

Thomas Seoh (01:31:55):

Yeah, we're in the last minute. I don't want to encroach on people's time here, but there's a couple dozen questions that are among the attendees and then pre-submitted, we've been talking about FDA understandably FDA and our M-H-R-A-E-M-A. But for people who are competing in XPRIZE health span and applying to ARPA H Prosper contracts, they need to generate data and clinical data and to do that, those are not the only jurisdictions. We do obviously for strategic long-term reasons, suggest that you collect data in a way that can be used in filings in the US and in Europe and other places like that. But could you comment, could the panel comment on other jurisdictions, Australia, Japan, Israel, there are also in the longevity field, folks who go to sort of free regions somewhere in Honduras or other locations. Just any comment on going to jurisdictions other than US or Europe or generating data.

Zan Fleming (01:33:08):

We could start by saying that FDA certainly will accept data from other countries and often will allow you to start your IND with a later stage protocol based on data from outside the us. But any other comments

Keith Watson (01:33:30):

That's true of Europe as well then. I mean data and agnostic of where the clinical data particularly generated provided is the right study effectively and the outcomes are correct. I mean the one thing I would say from a general regulatory perspective is if you go to other regions, latam or maybe Middle East Africa, et cetera, and you there may be some regulatory relief there that is not applicable elsewhere. So you may get approval, but it doesn't necessarily mean you'll then be able to leverage and piggyback back to what you would call a stringent or mature regulatory agencies. So often it is best to make sure that you are, I think aligned at least in the principles with the Europeans, the Health Canadas the European and UK regulatory agencies because that will often allow you then to get faster approvals in other regions through expedited and collaborative pathways. So effectively and approval in the UK or

the F-D-D-M-A may open up half of Middle East and Africa and Laan because you've already got that data. So it's possible to, they will allow data to be used to support the study, but it's going to have to meet their criteria to get approval. So I would couch be careful getting full approval elsewhere without some buy-in from the mature agencies because you would end up having to repeat studies.

Zan Fleming (01:34:55):

Good. Well that's great. Very helpful. And darn, we are out of our regular time. We will have a period where we'll have more informal discussion and maybe we can continue with a few of these questions that Thomas will throw out. I did want to mention that looking to the future, we've been working on something called the Thrive Act. Essentially you can see the very broad strokes of what it's about here, but everyone should be of interest. This is a way of facilitating the development of products aimed at healthspan and we believe could be the way that we could get products to people sooner based on solid scientific evidence, but doing it in a stunt wise fashion, you'll find data on our website, the CATA Institute. Please do check it out. But Thomas, I'm going to turn it over to you for our terminal housekeeping message.

(01:36:05):

Thank

(01:36:06):

You. Lemme just thank our panelists ly for our wonderful participation. I wish we could keep going a couple hours.

Thomas Seoh (01:36:15):

So all registrants will receive the link to the recording within a business day or so as well as announcements to future targeting healthy longevity 2025 sessions, future sessions and planning include one on sarcopenia and frailty and we hope a fireside chat with the new FDA Commissioner Marty McCarey. So with that, the formal portion of this event is closed with thanks to the panelists and to you the audience for your attendance. We will be leaving this Zoom webinar open for some minutes, maybe up until one o'clock for those speakers and audience who are available to Terry and chat. So many thanks Zan, back to you.

Zan Fleming (01:36:53):

Thank you Thomas. And again, thank you panelists for staying on. We know you may have to drop off shortly, but we're glad to continue to take a few questions and Thomas, you could maybe go to the next one and see if we have some takers among our panelists.

Thomas Seoh (01:37:13):

Well, one of the questions that I pre-submitted was the FDA tends to deal with treatment of diseases. There are some exceptions for prevention like vaccines or statin or contraceptives, but there was a question about commentary on lessons we can learn in the health span field from the development of vaccines for the prevention of diseases like cancer or Alzheimer's. What can we say about that?

Joy Cavagnaro (01:37:48):

Well, I have some experience with HIV where one wanted to vaccinate to prevent needlestick injury for healthcare workers in high risk situations. And the way the agency thought about it again years ago

when I was there is really to understand that you at least had to show some therapeutic benefits that it worked in a therapeutic way before you went into prevention. So you had to show that it modified exactly what you thought it was going to do and prevention. And then of course with vaccines, we have the option of challenge studies in normal volunteers to show that they prevent against disease by doing challenge models. I don't know what we have in that respect in drugs, but

David Fox (01:38:48):

Maybe one step closer, Tom, it would be vaccine for cervical cancer, right? So it's a vaccine specifically to

Joy Cavagnaro (01:39:08):

Prevent HPV vaccine

David Fox (01:39:09):

Prevent cancer, but it is based on the human papilloma virus. It's the virus that makes the patient susceptible, I don't know the whole biology, but makes the patient

Joy Cavagnaro (01:39:20):

And that's also also used as a treatment vaccine as well, a therapeutic

David Fox (01:39:23):

Vaccine. But yeah, as opposed there are now cancer vaccines that are more like immunotherapies, that's a different issue, but more conventional vaccine specifically for cancer endpoint is Gardasil for HPV related cervical cancer. But in terms of learning there, my recollections goes back a long way is there were tens of thousands of patients studied over years, like 50 50 randomization of 20,000 some odd,

Joy Cavagnaro (01:39:54):

Right, to show that it works exactly

David Fox (01:39:57):

Patients over four years and looking at incidents of cervical cancer. There were some other indications probably for vaginal cancer, anal cancer, but it was, it's more or less a traditional vaccine study of exposing a very large population over a long enough period of time to have some difference in the two groups in terms of events. And I think it'd be interesting to look back and see what they consider it to be an event because full cervical cancer or survival had been probably a 20 year study or a 15 year study, but I think they may have looked at adenoma and evidence of emerging cancer as the endpoint as a surrogate. It'd be interesting to go back and take a look at a program like that, but I'm sure they looked at something short of survival endpoint because it would've been a very, very, very long study. I don't know if they ever did a full confirmatory study, but they would've looked at emergence of tissue pre-cancer or I don't know, we precancer but neoplastic tissue over a certain amount of time, however many years, I think it was like four or five years, and then looked at the two groups for a difference in events.

Zan Fleming (01:41:25):

Right. Well again, it comes down to the endpoint would reflect a benefit related to some aspect of multiple chronic diseases of age related disabilities and a lot of devil in those details.

Thomas Seoh (01:41:47):

Thomas, I do think that the thesis of for trying to understand George Denberg, our friend who's been on MEI and targeting healthy longevity before is very paying, very careful attention to the development of Alzheimer's vaccines. And I am not, haven't thought through all of the implications of what you need to do to, actually, this is a great panel to ask if you are the FDA and faced with the claim of a vaccine that what delays or reduces the risk of Alzheimer's. I think that's an interesting model for other chronic diseases and aging health span

Zan Fleming (01:42:27):

Commerce. That's the real important distinction because we have a long tradition from FDA of proving products for averting serious disease. The first product I approved, statin has been shown to prove, prevent or reduce the risk of cardiovascular disease. So that's one disease, but what we're talking about is multiple chronic diseases and so the Alzheimer's vaccine may or may not work for other chronic diseases. And it's not to say that that isn't a vitally important program, but it's not really in the long bio domain that is not.

Thomas Seoh (01:43:12):

But I mean in the tain trial, as you well know, there can be baskets of chronic diseases and conditions that people are trying to delay or there's a lot of chat discussion about rapamycin and metformin combinations in clinical development. So folks are certainly trying to do that for not just one disease like Alzheimer's, but multiple chronic diseases.

Zan Fleming (01:43:39):

Well, that's the distinction that our audience aspires to reduce the risk of multiple chronic diseases and not just one. If it's one, then we have a model, we have a prevention model based on measuring clinical outcomes, whether it be cancer or effects on dementia.

Marianne Mann (01:44:03):

Just a few words about that too, I wanted to add in, I thought somebody asked about fields function survives as a question on the chat group. I saw that and they wanted to know do you have to affect all three of them how you feel? And the answer is no. You can select some of those for fields. It's often these patient reported outcomes and or some sort of significant set of patient symptoms that you're going to modulate for functions. It can be like the six minute walk that I mentioned or some sort of outcome that captures what a patient can do and maybe fewer hospitalizations could also, that's certainly not a function endpoint, I guess that's more of a health outcome. But survives includes morbidity and mortality outcomes like clinical outcomes that are really relevant. What I see happening with these drugs that are going to potentially help with longevity increase healthy longevity is that you're going to try to select a composite of outcomes that result from aging and that are bad outcomes that you're trying to avert.

(01:45:12):

And when you pick a composite Zan, you know this, you want every component of the composite to be similarly significant and severe. If you pick something that's not as severe as another and one goes in the

right direction, but another goes in the other direction, FDA has great difficulty with it. So an example that's often brought up is the MACE outcome where the endpoints are myocardial infarction and stroke and death and all three of those being very, very significant and very, very comparable. Perhaps death being the strongest, but they're all very serious clinical outcomes. What you wouldn't want to do in such a trial is to also include peripheral blood clots or something superficial venous thrombi or something which is not nearly as relevant as heart attack, stroke and death. So you want to think about your drug, you want to think about what it's doing for longevity, you want to think about what clinical outcome that might therefore modulate logically and select that outcome along with maybe just a few others as a composite to then show that you really are benefiting patients over time with the drug. And it's challenging, very challenging to do all that work, but I think that's the kind of work you need to start thinking about doing because simply moving a surrogate marker, like I said is just the beginning of the process with the FDA. It's not the end.

Thomas Seoh (01:46:48):

Can I actually be provocative, but on the field function or survival question, if it's feel like patient reported outcomes, it's not just patients going, yeah, I feel better or I feel stronger today. The FDA A is going to have a higher bar or a rigor for that. But I was a little bit surprised. I guess that your anecdote about the six minute walk being an avatar if you will for a patient or it would be non-patient or a long bio, CEO here. If someone is able to walk a material 3% longer maybe is not that big deal, but a significant percentage farther, why is the FD say, well, we're not sure that's not a particularly significant enough gain of function grip strength or a lot of things are out there for measuring sarcopenia and frailty and so forth. So this is very relevant to what sort of endpoints applicants and competitors may be shooting for when they design their clinical trial protocol. Why wouldn't some combination of feel and function if the patient thinks, no, no, I'm a Parkinson's patient, if I can put button my shirt, that's a big deal. Why wouldn't the FDA kind of take that slight gain of function, whatever that is, of being able to button and feeling really it's very important to the patient. Why wouldn't they be sort of bending over backwards to say, if we can find safe interventions that affect that result, why not get it to the patients?

Marianne Mann (01:48:22):

Yeah, I think the agency is open to a combination, if you will, of how a patient feels and functions because you raised the six minute walk along with maybe feeling better. Something like that could be discussed with the agency. It all comes down to the ultimate package, the drug's risk, risk and then the benefit that you show and whether it's acceptable. You asked Thomas about the six minute walk and why the FDA was questioning it. I think I questioned it myself. Actually. A lot of the drugs that were approved were based on a 20 or 30 meter difference in the six minute walk for the group, the two groups, the placebo group and the patient group. And I looked across

Thomas Seoh (01:49:04):

What percentage was that about?

Marianne Mann (01:49:05):

Well, I mean look at 20 meters, it doesn't even matter what percentage. They began low and they improved by 20 or 30 meters. And if I look across the bedroom that I'm in right now, I've got 10 meters to the wall and then I think about, okay, they can walk across my bedroom, but that's on it. That's the part where I think people are like, I'm not sure what that really really means to a patient. But when you couple that with perhaps a dyspnea score that trends in a good direction and also the basic

pathophysiology of the disease, the pulmonary artery hypertension is lower. The measurements of the PA pressures fall, which is the direction you want to go. And you couple all of it together and say they're having less symptoms, they're able to only walk 30 meters, but that's okay. You can look at that data and say maybe, and then look at the safety profile of the drug and sometimes find your way towards an approval.

(01:50:07):

So I don't want to make the FDA sound like they never talk to you unless you show survival. That's not true. They will look at combinations of various outcomes sometimes to support the approval of a product. And I think the PAH drugs are a good example to get familiar with if you're wanting to know how far the FDA will go. And I think they went pretty far in that example. Nowadays the FDA is generally requiring more clinical outcomes to look at progression of PAH, evidence of progression. And they are more clinical outcomes that suggest that the patient's really progressing with their pulmonary artery hypertension. So they're more clinical based and the good old days of six minute walk alone being enough for FDA approval are probably passed and now they're moving on to more clinical outcomes. So

Joy Cavagnaro (01:50:57):

In terms of who's the age range of what we're talking about, because when we talk to me, that's the biggest question. Okay, we're talking about prevention at what age, I mean these composite endpoints are going to matter based upon age. It's almost like if we created as a disease, it would be disease severity. The older you are, the more severe the disease. So when you're treating the severe disease, the age, this is a vulnerable population. So I would look at it similar to we look at juveniles prospect of direct benefit, what are we going to give them? But in effect, when you're actually not, it's actually a treatment as well as a prevention, it becomes a prevention where you can move it down to 40 year olds and 50 year olds. But initially for proof of concept to understand we are talking about my age,

Marianne Mann (01:51:59):

I'm sure it's a struggle because some of these therapies may need to be given early in order to have their impact downstream. Yeah,

Joy Cavagnaro (01:52:09):

That's what we do with gene therapy. We

Marianne Mann (01:52:10):

Treat how do we wait 10 years to prove that? Yeah,

Joy Cavagnaro (01:52:13):

We treat infants. Yeah, yeah.

Zan Fleming (01:52:16):

Well, it's such an important point, joy and the point has been made many times in different ways that it does come down to benefit and risk. And so when you go further and further into healthy populations, then clearly the product has to have more and more safety, so to speak. Right. Exactly way of putting it. But it goes back to the question about GLP one agonists, which for sure are doing amazing things to even affect reverse type two diabetes, prevent cardiovascular risk, but these are in people with obesity and or diabetes.

(01:53:03):

Now,

(01:53:04):

When you move into the normal population, the first question is will they work for them? Clearly, if you don't have as much abnormality or any abnormality as far as the mechanism of the drug life be concerned, then there's less effect size that you're going to see. But there's an even greater consideration about what the safety profile should be. And these agents, of course do have adversity. They have effects on bone mass, muscle function, and so they may not be appropriate even if they work, then younger people who do not have these diseases.

Joy Cavagnaro (01:53:48):

I mean the higher bar is for a preventative vaccine than a therapeutic vaccine.

Zan Fleming (01:53:54):

Yeah, yeah, exactly.

Thomas Seoh (01:53:58):

I just noticed the comment by an anonymous questioner, but it may be Alan, I think, but oops, let me see if I can find it again. Apologies. He says, we don't want a six minute walk or a 30 meter test. We want to measure the patient on a 24 times seven basis. And digital wearable technology enables that. So I'm just throwing out a question to the former regulators, what do you think the agency should do today and going in the future in thinking about these kinds of real world evidence? Of course, a percentage point gain may not mean a lot, but you're going to have a lot more confidence in the data than you're going to get with a patient who comes into a clinic to get tested once discussion thoughts.

Zan Fleming (01:54:52):

Yeah. Marianne, what about an endpoint based on a cell phone, celler and other airplanes that would allow this so-called real world evidence?

Marianne Mann (01:55:04):

Sure. I mean, I think I like that idea a lot. Anything new? I will say that six minute walk comes up because it's tried and true and tested at FD and at least has the precedence of being used as a primary outcome. But if you're like, we want to go beyond that, we want something far, far better maybe and better is good. One of the problems with something like what you just sort of suggested, like a 24 hour monitoring of what a patient does is I'm not sure, but with so much data, very small differences could be shown between arms that are not all that relevant maybe and just by chance. So I think that, gosh, when you have a whole lot of data coming in and supporting that you're doing something for the patient, the question is always going to come up at the fda. Okay, you showed us that difference, but is it meaningful? And that's the issue. I've seen it myself in the pulmonary field with forced vital capacity and FEV one still comes up. Is that actually meaningful to the patients? You always have to defend that. So

Thomas Seoh (01:56:23):

Marianne, I'm sorry to interrupt, but let me turn it around a little bit differently. Again, as an avatar for a long bio CEOI am asking this panel, there's a litany somewhere AI can come up with it of all the different

endpoints that the FDA has used to approve stuff, but digital technology is enabling us to measure all kinds of things that we were never able to collect before.

Marianne Mann (01:56:49):

So

Thomas Seoh (01:56:49):

I want to go to the agency with an endpoint that's never been used before for approval because it's never been able to be measured, but I've come up with a creative way to measure it. How do I go and maximize the chances of not having to spend 10 years trying to convince the agency that is a candidate for being a validated endpoint, but in fact use it? And I think this happens a lot more on the device side than on the therapeutic side. But how about on the therapeutic side?

Marianne Mann (01:57:21):

Yeah, I'm all for it. And I think FDA would be all for using AI and these technologies, but the bottom line is that the question will still come up, but what are you really doing for the patient? And I'm sorry to keep saying it that way because sometimes with such large data sets you can show relatively modest changes with huge P values, P oh oh one,

Thomas Seoh (01:57:43):

I'll ignore the ones that have marginal, that's no different than failing a trial, a conventional trial by 0.001 or whatever it is.

Marianne Mann (01:57:50):

No, I'm saying it wins by 0.001. I'm saying you win, and yet the difference you're showing is relatively possibly modest. I think you have to look, I'll come back to F FDA A will look at the data and if you're able to sort of show that patients, nobody's going to ignore a possible product that shows that patients who are very, very limited and not able to live their lives are now truly able to do so much more and they're much, much more active, 10 times more active than they were before or five times more active than they were before. That could be very much carefully looked at by FDA. I think the problem when these various AI methods come into being and to showing them is they have so many, many data points that very, very small differences between arms can be presented with a P value but not be very clinically relevant. And that's the problem. So we want to always go back to the clinical relevance in defending that and defending that usually requires clinical outcomes studies or at the very least supportive trends on those various clinical outcomes. So I'll come back to the composite outcomes that might be some significant outcomes that you can actually measure to show the benefit of the drug to the patient. I'm not trying to reign on the parade of AI measures. I think they're very useful, but approving a drug solely based on those will still be challenging.

Zan Fleming (01:59:27):

We're up for it.

Marianne Mann (01:59:30):

No, I mean I love the idea and I've seen patient reported outcomes similarly proposed and they face the same issue. I had a drug for hereditary angio neurotic edema and they cut patient's symptoms in half.

And I told them, normally I'm very worried about pros and how to validate them. But I think what we just say to the agency and to advisory panel meetings and for our label is that we took the symptoms that patients experience and reduce them all by 50%. And that way nobody was sitting there scratching their head saying, is it really relevant? Cutting symptoms in half was very convincing. So that was a drug that got approved by the pulmonary division and they're one of the most conservative divisions out there and they approved the drug based on cutting patient symptoms by half. That's pretty compelling. So Thomas, back to your AI question, cutting things in half, doubling times, tripling times, those are worth looking at.

Thomas Seoh (02:00:35):

Go ahead, Jerry.

Joy Cavagnaro (02:00:36):

So we have to, I mean everything keeps changing so fast, but somehow we start to have to embrace some of these and start collecting data even before starting some historical control or some type of case study.

Marianne Mann (02:00:55):

Let's see how much we do impact them.

Zan Fleming (02:00:57):

And this comes down to having ways that will incent the development or the acquiring of these data.

(02:01:11):

And

(02:01:11):

To do that, we have to have a way of getting products out there either approved or under some kind of status that's going to allow them to be used and preferably reimbursed. So it's a chicken and egg thing. We need to get this products out there. We need to get the technologies going, we need to be collecting the data, but that doesn't happen in a vacuum. It's going to take changes in the way we in effect incent biomedical research and it comes back to the Thrive Act, which I hope people will take a look at as the way of maybe in different ways speeding the development of these solutions.

Thomas Seoh (02:02:03):

ZI see like a one minute left for the half hour after party. I wanted to just mention my favorite example for share it with the panel. I guess that there's a company that has a device that has very precise accelerometer that measures perturbations in the stability of the head as a proxy for vestibular balance. And they have very nice clustering, which predicts the number of fractured hips from falls within six months. So that gets you the actual AI data, big data conclusion together with clinical outcome. Now, if you have something that closely related when you have both ends of it, it seems like it's a pretty good case to make to the FDA, but to your point, Marianne, those CEOs who come forward with AI data that just shows even if highly significant, just marginal gains, that's kind of silly to me, but I think there's something between a 1% or a 2% gain in function and 50%. I think I'd want to ask the patients, well, maybe 5% isn't a lot and we the FDA don't think that it's enough for you. But if it's 20%, I mean their drugs are approved. Well,

Joy Cavagnaro (02:03:29):

If one, the first phase three clinical trial showed a 20% difference, you wouldn't need to do your second confirmatory trial, right? When you have

Zan Fleming (02:03:42):

In general, I mean that's a very persuasive result. So to your point, effect size does matter.

(02:03:52):

If

(02:03:52):

It's a questionable effect, then sure, that makes it hard. But Josh, we have gotten to the end and we are going to take all the questions that have appeared in the chat and have been previously submitted and provide answers as best we can. We'll post them on our website along with the video recording and perhaps a transcript of our conversation and we'll continue the conversation. In effect, we do want to hear from you. We'd love to hear your suggestions for how we can improve other topics you'd like to hear presented. And so do be in close touch. And again, to our panelist, I can't thank you enough. You guys are amazing. So glad to have you as my friends.

Joy Cavagnaro (02:04:49):

Thank you. Thanks.

Marianne Mann (02:04:51):

Bye-bye everyone. Have a great weekend.