THERAPEUTIC HEALTHSPAN RESEARCH, INNOVATION, AND VALIDATION ENHANCEMENT ("THRIVE") ACT OF 2025
Targeting Healthy Longevity 2025 Conference Session 1

February 2828, 2025

Transcript

https://youtu.be/QLNRof6zLs4..

The following is a transcript of the above webinar, in which the panel discussed proposed legislation that sets out a regulatory pathway, evidentiary standards and incentives for healthspan drugs, devices and dietary supplements that target, prevent and/or delay multiple chronic diseases and extend healthspan (that period of life free from debilitating diseases and conditions).

A recording of the webinar can be found at: https://youtu.be/QLNRof6zLs4.

The draft Act, and a summary, can be found at: www.kitalys.org.

Zan Fleming (00:12:40):
We are at the top of the hour, 11:00 AM, in and around Washington DC. Welcome all. We are delighted to have you joined us live. Or maybe you're now looking at this recording of this session. We are here today as a first step in developing landmark legislation for encouraging the development of drugs and other regulated products that can slow the aging process and prevent chronic diseases instead of simply

just treating these diseases after they appear. The THRIVE Act is unprecedented in its scope and provisions for the US Food and Drug Administration and for other regulatory authorities around the world. Indeed, we hope that similar laws will be enacted in other countries. The THRIVE Act responds to the immense opportunity provided by amazing science to substantially improve the public health. But today is but a first step. This bill is not ready for Congress. It needs to be worked through a cauldron of deep thinking and consensus building. Only then will it be ready for lawmakers. So let's now take this first step of the thousand mile journey. Over to you Thomas Seoh. Kinexum, CEO, who will moderate our discussion.

Thomas Seoh (00:14:46):
Thank you Zan. This is a housekeeping reminder to enter any questions in the Zoom webinar Q&A function. A link to this recording will be circulated to all registrants and made publicly available within a day or two. 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, your affiliation if desired, and from where you're logged in.

I want to introduce the panelists: Zan [Fleming is] Founder and Executive Chairman of Kinexum, a regulatory, clinical and product development strategic advisory firm and President and founding Board member of the not-for-profit Kitalys Institute, whose mission is to catalyze science into solutions for preventing chronic diseases and extending healthy longevity for all.

David Fox is a global regulatory partner at Hogan Lovells, an international law firm with one of the largest food and drug law practices in the world. Dave is a former Associate Chief counsel at the FDA and a founding Kitalys Board member. He authored the first drafts of the THRIVE Act and has acted as chief scribe over various collaborative revisions.

Eve Herold is an award-winning science writer whose work has appeared in Time, the Wall Street Journal, the Washington Post, the Boston Globe, and other major publications. She's Director of Policy Research and Education for the Healthspan Action Coalition, a coalition of over 200 organizations dedicated to healthy longevity.

Steven Grossman, President of HPS Group is a co-founder and a longtime past Executive Director of the Alliance for a Stronger FDA and was previously Deputy Assistant Secretary for Health at HHS and Counsel and Health Staff Director on the Senate HELP Committee, where he was one of the Chief Senate negotiators of the Orphan Drug Act and the Hatch Waxman Act, and 2024 recipient of the Reagan Udall Foundation FDA's Innovations in Regulatory Science Award.

I'm Thomas Seoh, CEO of Kinexum and EVP and a founding Board member of Kitalys. We will start with a fireside chat with Zan and David, then bring in Eve and Steven and then we'll work in audience Q&A. So please again put your questions in the Question function. If you've not yet seen a draft of the THRIVE Act, the text of the ACT and a summary can be found at kitalys.org. I begin with a question to David. Why do we need a THRIVE healthspan law?

David Fox (00:17:26):
Well, thank you Thomas and thank you Zan. I really am so appreciative that you've brought me into this and the short answer to that question is because Zan asked for one and Zan deserves a THRIVE act, but more expansively: So I think we all would agree that the current regulatory framework and the current statute as it's been implemented over decades by FDA values intervention over or much more so than prevention. We have a wonderful system where, if someone is able to show even a modest effect on an

advanced form of cancer or life-threatening disease, the FDA has at its disposal numerous tools to help bring that product to market. Paired with that, there are well-known incentives for sponsors of innovative interventions if they're successful in bringing the product to market.

On the other hand, if a product is designed to prevent that advanced cancer so that people never experience it in the first place, there are almost insurmountable regulatory hurdles to getting there. The risk benefit proposition that FDA is accustomed to working with doesn't really fit well. The type of evidence that would be generated for a healthspan type product, an intervention in healthy adults that's designed to prevent age-related decline in disease. It's just not tuned to the needs of the healthspan product or the practicalities of healthspan product. In our sort of basic conception, a healthspan product would be taken again by a healthy population. So it needs to be very safe. It would be taken over a long period of time and given its safety profile, its effects may be modest and may not be apparent until we've had a long time to see its effects.

And that means we would need large studies over long periods of time for ingredients and articles that likely have very little patent protection and are largely ubiquitous in either the prescription drug market or in other markets. And so it's really just a sinkhole for innovation, it just [has] all the arrows point[ing] against it. And so we've undertaken with the THRIVE Act to address those issues and create an evidence-based system, progressive evidence-based system that has adequate incentives so people will, sponsors will invest in it to bring healthspan products to market to allow for and give FDA permission to consider healthspan type claims. And then second to create the incentives that will develop a healthspan ecosystem where there's yeah, a pairing on the part of the developers and the regulators with sufficient certainty as to endpoints clarity as to endpoints clarity as to the evidentiary standards and incentives to protect the investment. So with that, we'll get into some more detail, but we've created what we think is a milestone map for FDA in terms of evidence and a suite of calibrated tailored incentives to bring healthspan products to market.

Thomas Seoh (00:22:07):
Thank you, Dave. I see that people are entering questions already, so that's great. I think we will shortly be reviewing elements of the Act and I think those questions are better dealt with that once we've shown you what is in the Act and what's not in the Act. So Zan, what makes healthspan products so different from other regulated products that they warrant new legislation?

Zan Fleming (00:22:31):
Well, first of all, these products aren't different. They're actually the same products by and large that are already under development, already approved, or will at some point be approved. And they're not just drugs and biologics, but they can be even dietary supplements and medical devices. And we'll talk about how that would work in a moment. The point is it's not what products are or are not covered by the Act, The Act covers any regulated solution that works. Most importantly, the Act lays out how these products can be evaluated, approved, and in the hands of people who would like to be able to prevent disease and not just treat them when they crop up.

Thomas Seoh (00:23:22):
What are the problems, David? What are the problems you're trying to solve with the THRIVE Act?

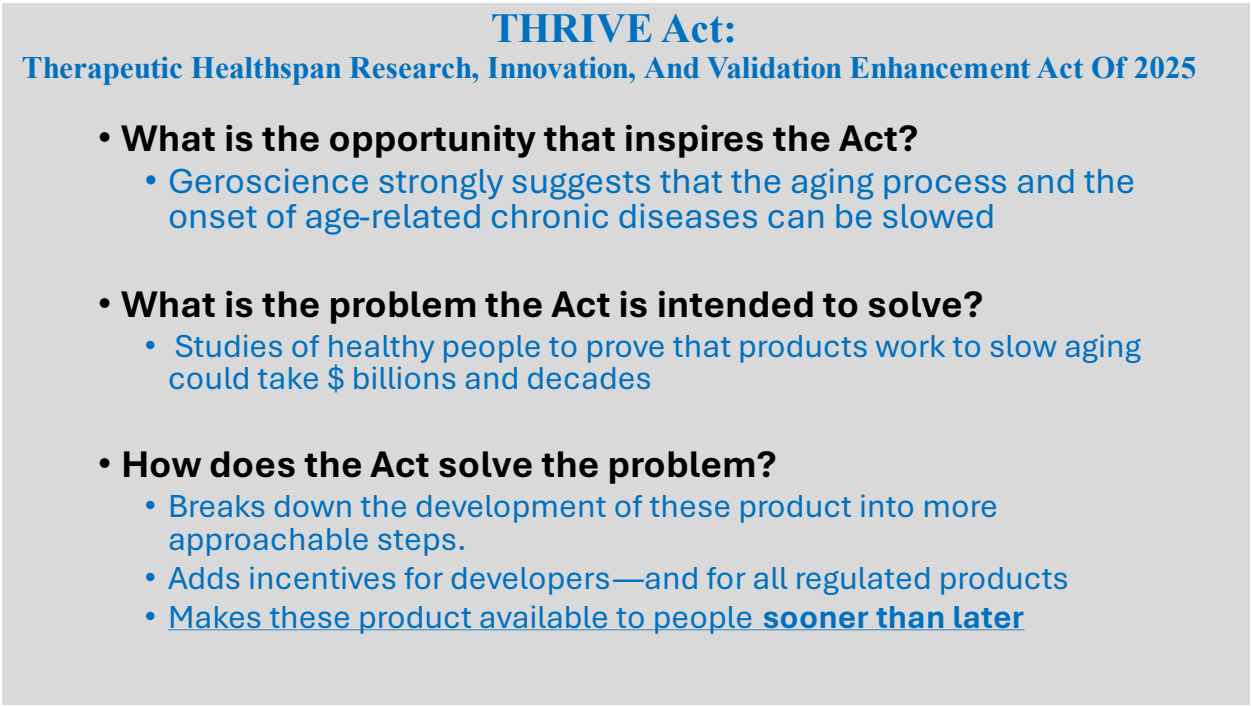
David Fox (00:23:29):
Well, I think we've already touched on them. The main problem is while the Food Drug and Cosmetic Act has always anticipated prevention as one of the functions of drugs and other regulated articles, the Act in its implementation has just been not been very good [at] recognizing prevention. And when it is

looking at prevention, when the Agency is evaluating prevention, it's usually [a] single mode, single disease paradigm. So what we are trying to do is layer into the Act across, as Zan noted, all product classes: foods, dietary supplements, drugs, biologics, devices, to layer into the existing Act, a concept of a healthspan claim and a healthspan outcome. And then most important to us is to do that in an evidence-based way to create tiers of evidence to support conclusions, scientific conclusions as to healthspan claims, and then to recognize that incentives are needed to encourage the industry to get behind these types of products and invest in the studies.

So, it's in the area in which without an evidence-based program and incentive, what we will end up with, and we've seen this already in the past, is a lot of unregulated, blurry, unsupported products. We don't want that. So what we're trying to solve for here is how do we drive towards a system that rewards doing the hard science so that we actually will know one way or the other whether these products serve a beneficial function. So we're trying to solve for the evidence problem, and we've talked about how difficult it is to develop evidence for these types of claims. So, we attempted to solve for the evidence problem and for the incentive problem.

Thomas Seoh (00:25:50):
Thank you David. Zan, in order to level set, not everyone has necessarily had a chance to see the draft. So what are some of the high level features?

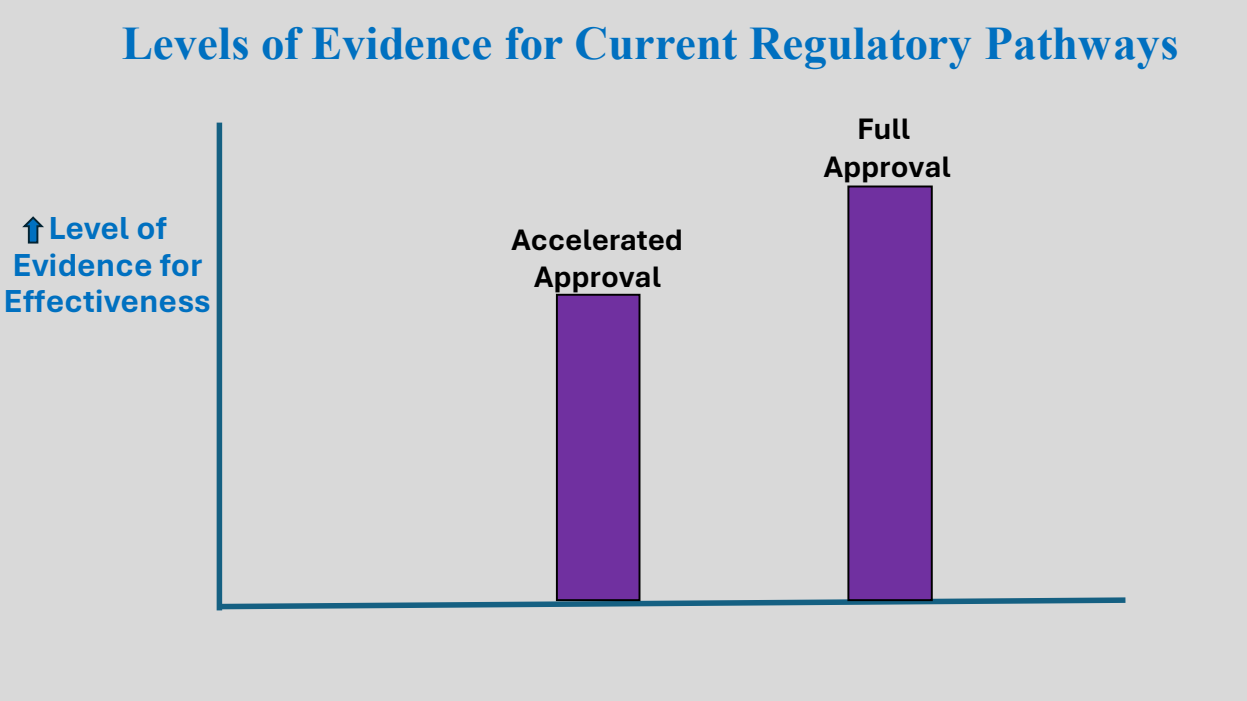
Zan Fleming (00:26:03):
Right, Thomas. Let's look at that and I'm going to share my screen. I don't want to take more than a few minutes to do this slide sharing. And by the way, if you read the THRIVE Act draft, you probably were struck by the ponderousness of it. You may not have even been able to figure out exactly what the key points are. It was written purposely as a legislative bill because that's where it's headed. It is in the convention of how Congress writes and passes law. And, so we put it in that form to make it ready for Congressional consideration. Now, let's talk about the THRIVE Act and what first of all is the opportunity that inspires it. First slide:



Many of our listeners understand this and firmly believe that science is strongly suggesting that the aging process can be modified and the onset of age-related chronic diseases can be slowed. And the problem the ACT is intended to solve, therefore is that studies of healthy people (as opposed to diseased people) to prove that products work to slow age-related diseases could take billions and decades. And so the way the ACT solves the problem, or at least attempts to approach the challenges here, is that it does break down the development of these products into more approachable steps, a progressive stepwise approach that David mentioned, and it adds incentives for developers and this is needed as it was in the Orphan Drug Act, and that's one reason we brought Steven Grossman on, a father of the Orphan Drug Act. We need incentives for developers to invest in the somewhat expensive studies or programs that will be required to have the evidence that is needed to support the effectiveness and safety of these products.

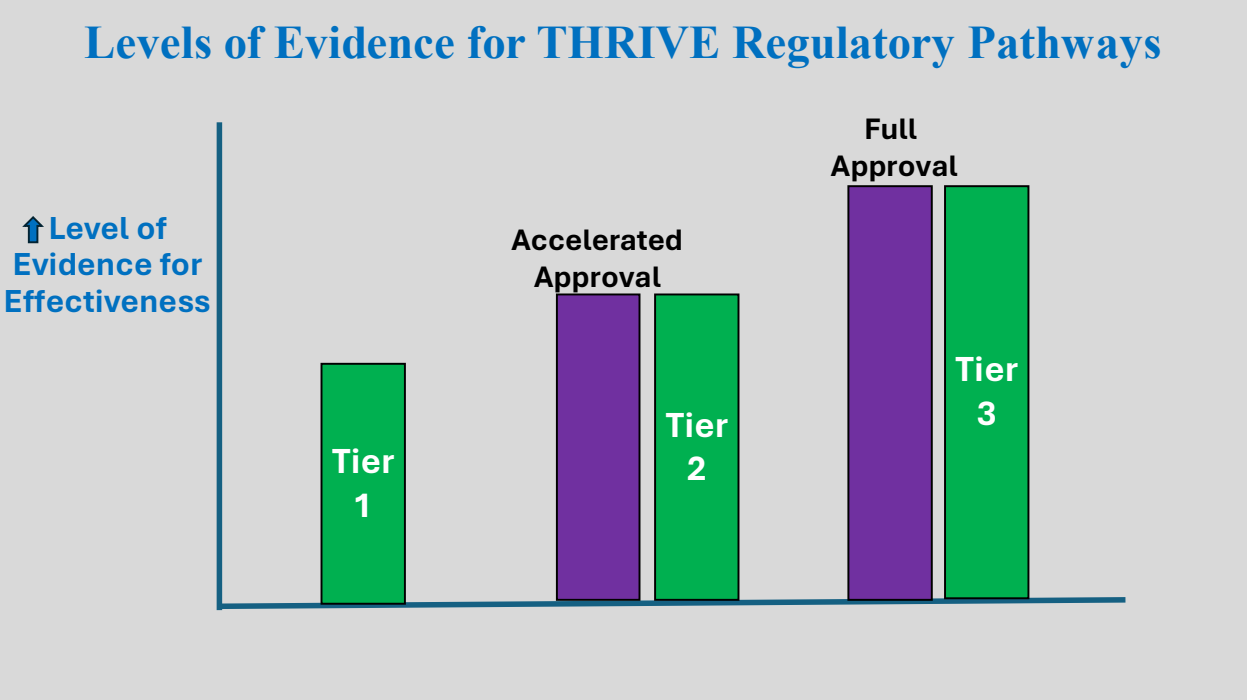
And the main intent of the THRIVE Act is to make these products available to people who want them sooner than later. That's really what THRIVE is aimed at doing.

So now everybody is, I'm sure, wondering about this term *levels of evidence*. What the heck are you talking about? Stay with me a moment as we express levels of evidence in high-level conceptual terms of how products are currently approved. Slide 2:



First of all, under the current system, we have products being approved for all kinds of disease and disease prevention indications on the basis of what is called substantial evidence of effectiveness (SEE). And, SEE enables a full approval or what FDA calls a traditional approval. SEE is a pretty high bar for any product that is being approved. We also more recently have at FDA something called Accelerated Approval. It allows products to be given to patients who desperately need them on the basis of evidence that suggests likelihood of benefit, but not definitively proven benefit. And so that is our system.

Now what we're proposing in Slide 3 is a regulatory pathway that starts off with Tier 3 being very much similar to a full approval and then Tier 2 being somewhat comparable to an Accelerated.



But the novel category is Tier 1. This is a first step where there is still extensive evidence required but of a totality that is less than would be the case for an Accelerated, or Tier 2, Approval. Just to quickly summarize the kinds of levels of evidence and the incentives for each tier, we go to Slide 4.

THRIVE Act: Levels of Evidence and Incentive for each Tier

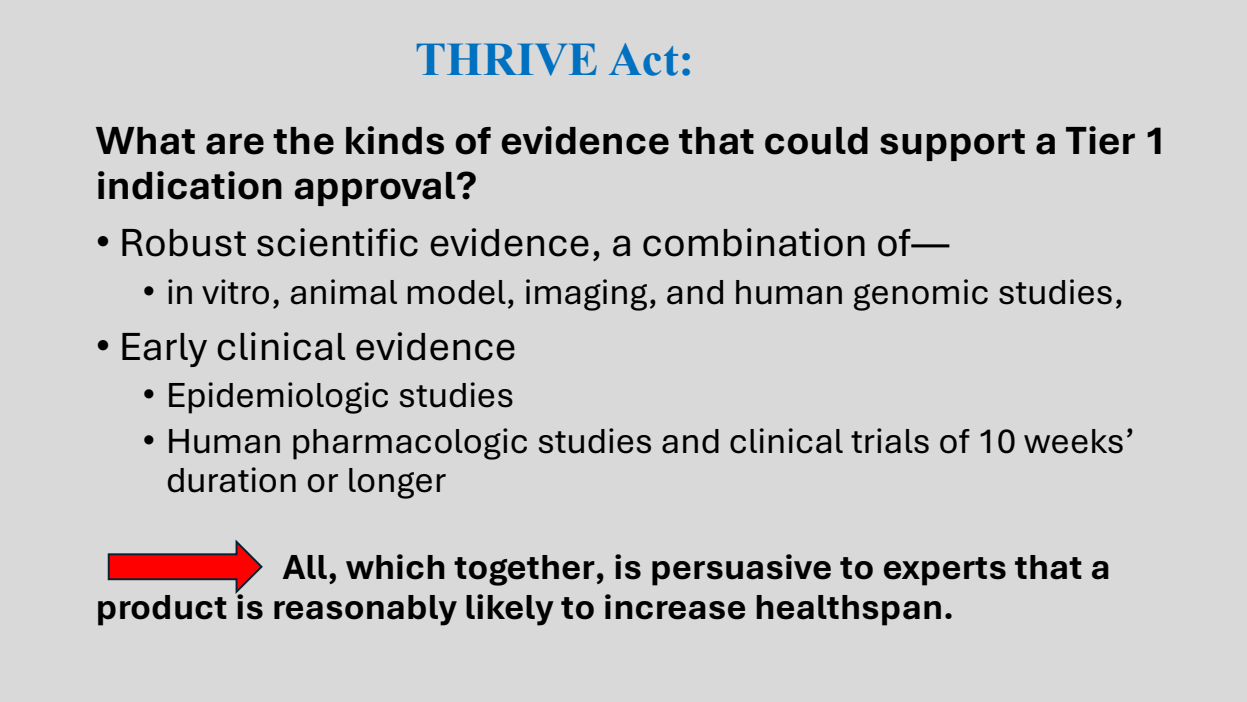
- **Tier 1**: Requires robust scientific and early clinical evidence that the product is **reasonably likely** to increase healthspan.
  - Approval exclusivity lasts for 7 years.
- **Tier 2**: Requires intermediate clinical evidence demonstrating the product is **likely** to increase healthspan.
  - Approval exclusivity extends for an additional 7 years.
- **Tier 3**: Requires **substantial evidence of effectiveness** from long-term studies, demonstrating significant healthspan benefits.
  - Approval exclusivity extends for an additional 7 years .

Tier 1 we say requires robust scientific and early clinical evidence that the product is reasonably likely to increase healthspan. And, a Tier 1 approval gives an exclusivity that lasts for seven years. Now David can

talk about what exclusivity is if that question needs to be addressed, but that is a way of incenting drug developers to get into the game. Tier 2 requires intermediate clinical evidence that demonstrates the product is likely to increase healthspan and that approval provides exclusivity for an additional seven years. -

We picked 7 years for the duration of exclusivity, but that is arbitrary [the same as Orphan Drug Exclusivity]. It could be less or more. Then finally, Tier 3 is essentially the same standard of evidence that is generally required for any conventional approval at FDA, and that provides additional exclusivity.

So, you're wondering what kind of evidence could support a Tier 1 approval? This is summarized in the final slide.



Tier 1 approvals would be, among other things, supported by robust scientific evidence, a combination of in vitro animal model data, imaging, and human genomic studies for example. It could involve epidemiologic studies. It could also involve early clinical evidence, but from studies long enough to be meaningful—clinical trials of 10 weeks' duration or longer. All this evidence altogether needs to be sufficient to be persuade experts that the product is reasonably likely to increase healthspan. So that's the essence of the THRIVE Act. We'll come back to more detailed questions as we go on.

Thomas Seoh (00:33:22):
Thank you Zan. Let's just, I guess, deal with sort of an elephant in the room. Some people have suggested that aging should just be legislated as a disease for which interventions should be assessed and approved by FDA. Why does THRIVE not take that approach?

Zan Fleming (00:33:41):
Well, the question is predicated on the belief of some that FDA doesn't have the authority to approve preventions for diseases. And of course that's not the case. We have vaccines for preventing infections disease. We even have products like statins that prevent cardiovascular (CV) disease, which I approved when I was there back in the day many years ago. So as David has mentioned, FDA has the authority to approve prevention products and they've done recently. We actually have prevention approvals for GLP-

1 agonists in people who have obesity or diabetes: These products reduce the risk of CV disease in T2D patients. So, a limitation in FDA's approval authority is not a reason to make aging a disease. There is a rationale for making aging a disease for purposes of paying for prevention care. The WHO has set up an elaborate system of codes for aging tissues and organs to support resourcing and payment for clinical prevention care. But here's the point: Making organ-based disease categories does not change at all the clinical trial designs and the evidentiary standards to approve organ-aging as disease indications vs. prevention claims. FDA needs to base approvals of feel, function or survival endpoints. Regulatory authorities cannot approve products for treating "aging of the heart" or aging of the brain. Whether it's a disease or a prevention indication, data are needed to support tangible clinical benefits—or persuasive data that these clinical benefits are likely. And, so for purposes of regulatory approval, it's not going to help FDA to make aging a disease.

Thomas Seoh (00:35:40):
Thank you Zan. I see various questions on this topic, but why would Pharma support a THRIVE framework if they've gotten good at negotiating the current system? What are other stakeholders going to be thinking about a THRIVE Act?

David Fox (00:36:03):
So first of all, it is evidence-based and that's Pharma's expertise. And second, it will significantly expand the range of targets and claims now available for developers. So it's a new frontier that plays to the strengths of Pharma because it's evidence-based and then there are some familiar incentives that go along with it. In addition, I'd say if you look at the Dietary Supplement Health and Education Act (DSHEA) from the early nineties, and you look at the expansion of and recognition of compounding under the statute, these light touch regulations have really been the bane of Pharma. And, so I think if we can design a system that directs us more towards the evidence-based system and less towards the gray market and unregulated system, I think that harnesses the true strength of Pharma.

Zan Fleming (00:37:29):
I might just add some concrete examples because Big Pharma or Pharma in general is already developing products that actually prevent chronic disease. We mentioned the GLP-1 agonists as a good example, but it's in people with obesity and T2D, not people who don't have diabetes, are healthy and don't have obesity. That's the big difference. It's the much larger non-diseased population that we're talking about. And so THRIVE presents an additional opportunity for companies that already have products with disease indications to go after indications for people who don't have the diseases yet. And that's a very attractive proposition. The only problem is that the kinds of studies that it will take to show that the product works in non-diseased people are going to be longer and larger than typically would be the case for disease treatment indications.

Eve Herold (00:38:51):
And I might just interject here also, when thinking about the insurance industry and their position on all of this, the cheapest way to treat a disease is to prevent it from happening in the first place. And so what we're looking at is trying to reorient the healthcare system from a sick care model which treats diseases in pretty much advanced stages. Given what kind of imaging technologies you used to assess the disease in the state and everything, it would be much more effective to intervene at the early stages. Now the question is we need to try to get the business community to look at the long-term benefits of these types of treatments as opposed to just focusing on short-term turnarounds.

Zan Fleming (00:39:48):
That's well said, Eve. I just wanted to mention that Jerry Colca just asked a closely related question: How is that going to work in our current system of reimbursement? And the devil obviously will be in the details, but we are encouraged by the notion that an ounce of prevention is worth a pound of cure. We will have to work out the details, but ultimately we can be confident that prevention will be shown to be economically favorable to payers and everybody else who's involved.

David Fox (00:40:42):
Let me throw in two other points. First, we have included, if we get into the minutia, some particular incentives for repurposing existing drugs. So the THRIVE Act provides an opportunity to go back and restudy and redevelop already approved products, and then there are particular incentives and rewards for doing that. Second, on the coverage issue and the approval issue, so not to belabor this, but even an Accelerated Aapproval is technically a full approval and should be reimbursed, although there are a lot of questions being raised about that by providers these days. But we've the system so that each tier of approval is a full approval. There are milestones that need to be met, but we would regard it as a full evidentiary showing for the particular claim that's being made. Now, I appreciate, and I'm not a coverage lawyer, that prevention so far is a very difficult term to accept under federal payment programs, and this is maybe more Steve Grossman's area of expertise, but this is where the new administration may come in and may help in creating a better reimbursement ecosystem for prevention.

Steven Grossman (00:42:27):
Let me step in and take a different slice of that, which is related to a column that I wrote yesterday for *FDA Matters*. One aspect of it was you have to have a regulatory pathway to have inventors and investors and you have to have inventors and investors and a product to challenge to bring to the reimbursement system. And I think that if you start at the end, you just get caught up in your head, and this should not be key to what will insurers pay, it's what can we create that's a value that insurers wind up seeing they have to pay for. And I don't want to prejudge how good these are going to be. I think the opportunity for products, and I think there was a question I want to touch on, which is yes, the Food, Drug, and Cosmetic Act does include prevention, but as it is practiced by FDA and in FDA law that is prevention of a disease. And what we're talking about here is a cluster of chronic diseases. We're talking about the aging process itself, and that is a much different, it's the same word prevention, but it's different. So I guess I would say let's worry about getting a system in place that creates some regulatory certainty, brings the investors, brings the inventors, brings the companies, and these things aren't going to be ready until a point at which the reimbursement system probably will be quite a bit different because it will have been challenged already by how do you address large scale populations like those at risk for Alzheimer's?

Zan Fleming (00:44:25):
Well, great point, Steven. We are talking about incentivizing acquisition of evidence to show that products do prevent multiple chronic diseases. And that's based on the supposition that there are shared root causes of the chronic diseases and that by targeting these root causes, you're going to have effects on multiple diseases. Now, there's nothing that prevents a company from pursuing prevention of single prevention indications, for example, for cardiovascular disease. The only thing is that for multi-disease prevention trials, you need to use people who don't have any of those diseases. The science teaches us is that we have the opportunity to show that multiple diseases are slowed or prevented. And if only one of multiple diseases is shown to be prevented, at least we will have evidence that will support the value of the product for that more limited purpose.

Thomas Seoh (00:45:57):
Maybe there's a lot of action going on in the chat and the Q&A, and we'll get to that very quickly. But just a couple of thoughts that are of interest to the geroscience community. How would biomarkers, biological clocks, Intrinsic Capacity, how would that be treated under THRIVE - digital intelligence, AI, machine learning, digital twin, things of that sort?

Zan Fleming (00:46:22):
Well, all that stuff can be very helpful. The devil will be in the details as to what is necessary and sufficient in a particular case to support a particular agent to have a healthspan claim. But I say yes, biomarker data can be very helpful and supportive. Now by definition, a biomarker is not considered in itself a way to approve a drug until it is validated as a surrogate endpoint, which can serve as a basis for approval. Validation is based on studies that show that the biomarker reliably predicts clinical benefit. Validation of a biomarker requires a treatment that has a similar effect on the clinical endpoint and the biomarker. That's a distinction that needs to be understood: biomarkers, until they become surrogates, will have secondary, supportive roles among evidence of effectivenes. But it's all the amazing technology that Eve mentioned and more that can be brought to bear. The computational technology applied to all kinds of -omics research can be supportive evidence that will help to achieve a Tier 1 approval.

Eve Herold (00:47:49):
I just want to say though, and you're absolutely right, Zan, all of those things need to be included and we need to be open to emerging technologies that are in development now because we can only expect the technological techniques to kind of, they're growing exponentially. So we need to be open to that. But I just want to say there is an impediment here and that is that there really is no universally agreed upon biological clock. So we have people working on different kinds of biological clocks and we're in the infancy of finding biological clocks. Some scientists think it's epigenetics, some people think it is DNA methylation. We don't really have an agreement, but I think as the science moves forward, we essentially will develop some kind of consensus. The other impediment is that we don't have internationally, nevermind nationally, agreed-upon metrics for measuring healthspan. So we can look at organs and disease states and things like that and kind of create a composite picture of a person's healthspan, but we need to incorporate accurate measures of biological age and all the rest of the technology being brought in to assess the totality of the organism because aging is a global condition. It's not just it affects your heart or your liver. It affects everything.

And I think the THRIVE Act is a huge step in advancing this kind of research and creating this kind of consensus. If it's out there. Eventually we'll get there. We need to take baby steps right now, but we are looking at a certain amount of uncertainty in terms of being able to precisely measure age, biological age disease states, life expectancy and all the rest of it.

Zan Fleming (00:50:13):
I just wanted to tag on to those are great points, and it also reminds me to stipulate that healthspan is a somewhat crude term, it's even controversial. For most people, it is at least very understandable at a high level. One can understand what it means to say it's the period of life that's free of chronic diseases, but how do you actually determine exactly when healthspan ends. There are few people who are really completely healthy by the time they're 40 or 50 and have no underlying detectable disease.. Healthspan is therefore going to be hard to pin down. It's an important challenge to come up with how we would in practice define healthspan for clinical trials purposes and for clinical practice. That's where there's a lot of work to be done.

Eve Herold (00:51:18):
Totally agree.

David Fox (00:51:20):
What we confront, I think, fairly directly in THRIVE is this issue of whether full clinical validation is needed of all the various models, Eve, that you're describing before we can move forward and rely on those. And if that's the position that we need for regulatory purposes, full clinical validation before we can move forward, we will never get there. And no one will, absent full government intervention, you wouldn't get private developers to invest in that kind of validation, at least to current FDA standards. And so there's a critical policy judgment that needs to be made and you put your finger on it, Eve, it's uncertainty. How much uncertainty are we willing to accept in order to advance healthspan product now rather than some mythical time point when we clinically validated everything and we won't get it. So all of these different regulatory tracks and evidentiary channels all come down to an acceptance of a certain level of uncertainty.

Regulatory science is not pure science. It's science bounded by rules of law and standards of evidence. And so we're trying to come up with a regulatory science approach for healthspan products, trying to surface what exactly is the level of uncertainty, what are the risks and how can we calibrate the approval pathway so we can stage it in a way in which we're learning along the way. And I think, Eve, as you and others have pointed out, that the tools available to us are so much more sophisticated than the tools that we could even imagine when the Food Drug and Cosmetic Act was first conceived in the early 1900s, then 1938, 1962, 1997, and 2012. I mean, we have to recognize that every 20 to 25 years, the Act from an evidentiary perspective goes through a significant change and we're ripe for another one.

Eve Herold (00:53:46):
That's exactly right, David. Some of the technologies that are coming down the pike like digital twinning have the ability to be much more precise, down to the molecular level, than any other technique that we have in our toolbox. So I agree that the Act and the whole movement needs to continuously evaluate and incorporate these developing technologies as well as, and I'm sure your listeners are thinking of AI-assisted research in the lab, things like that. Those things are accelerating change, and this is going to continue to accelerate for the foreseeable future and we need to prepare for that.

Thomas Seoh (00:54:40):
I'm itching to get into the Q and A and the chat subjects, but maybe one last question, David, you made a reference to building on regulatory science. The other side of it is a 'move quickly and break things' kind of approach. And Steven, I wanted to ask you this because I know in a prior conversation a little while ago you were kind of expressing the point of view, we kind of need to sweep stuff aside and start engineering something fresh. I don't know if you still think that, but maybe would you tell us, share with us your thoughts about the THRIVE Act and its approach?

Steven Grossman (00:55:19):
Well, I had a much longer answer though I'm not sure this is the right place for it. That starts with looking at the Orphan Drug Act and how that's evolved over time and trying to put that frame on both current events. So is this the moment to do that? I'll do it otherwise, let's wait until we're deeper into discussion.

Thomas Seoh (00:55:44):
Well, we're 45 minutes into a 90 minute session. I think we're in the guts of it.

Steven Grossman (00:55:48):
All right. And by the way, to make David Fox's point clear about how things evolve over years, for a lot of years I was asked, well, why didn't Hatch Waxman cover biologics? And I'm like, well, in 1984 there were a couple of biologics products in a couple of companies and nobody had any idea what we were doing. So of course it didn't include it. Now obviously any question about drug policy has to at least say, and what do you do with biologics? So times change, frontiers change, and that'll actually play into my point about the Orphan Drug Act. There was always all those, let's say 20 plus years after the Orphan Drug Act was enacted in which there was always this undertone, this sort of gossipy undertone that people with rare diseases were getting a break on the regulatory process, that the standards had been lowered and that somehow approvals of orphans was somehow less good, less final, less thorough, less helpful than approval of a drug for a larger product.

One of the things that changed that dialogue, Frank Sasinowski did an analysis in 2010, which he repeated again in 2020 in which he showed that standards had evolved in terms of interpretation, but that the standards by which orphan drugs were being judged were essentially the same and not different. And you still hear a little of that gossip, but not what it used to be because we do understand that. Now here's the thing. Now orphans drugs, okay, we can accept that premise. They really have been given some flexibility, but they really haven't lowered the standards for them. Well right now, the orphan drug field is dealing with two challenges that may not fit. We just evolved in our interpretation of law, one of which is the N-equals-1 trials. How do you figure out if an n-equals-1 works? And that has to take you at some point out of any semblance of the two controlled studies, et cetera, et cetera.

So that's a challenge that's still being looked at because you no longer say, well, it's an orphan drug and orphan drugs with some interpretation that'll help meet the full standards that the law requires. The other way in which the orphan drug field and the orphan drug standards are being challenged is progressive neurogenerative diseases which are heterogeneous, and good, solid well-conceived trials fail because the outcomes are so varied and what you have is so uncertain in a lot of ways, and that's a challenge that's also being taken on. Now my point here is that the orphan drugs paradigm worked for a long time and it still mostly works, but we're looking at situations that we're finally at where some broader thinking, some greater compromise with the acceptable standard is going to be needed. And I look at healthspan as the same situation, which is that we can do all the pushing and pulling and tugging. We can do our Frank Sasinowski studies, but in the end agree and that it makes sense to ask what gives the American people sufficient safety and efficacy data for some conditions that might differ from those we apply to more traditional drugs.

I make two further points on that. I see neurogenerative disease as maybe a lead blocker for healthspan because they're going to have to break the rules somewhere on that. And I think that provides an opportunity to challenge the system further and say just as there's just no way to put heterogeneous progressive neurodegenerative diseases into a box that looks like the Food Drug and Cosmetic Act. I think healthspan raises the same challenge. It's going to come later than for neurodegenerative disease. So, that is the lead blocker to me.

Looking where changes -- where more ambitious, more controversial approaches are being looked at as to what constitutes sufficient efficacy and sufficient safety. So that's sort of my picture where we are and why maybe we aren't going to wind up getting satisfactory answers without breaking the paradigm. The times are favoring that approach. This is clearly an administration that has no compunction about breaking paradigms, about looking at things differently. And so I like THRIVE, don't get me wrong. And I think the cause is a very good one, and I'm just raising the question as I have with Zan and the group before, which is you're going to be dealing primarily with people who have very conservative approach and you want to make it look as much like the current system as you can, but the reality is like

progressive neurodegenerative diseases, it may be when you get done, it may just not fit. And we don't want to say we can't do it because it doesn't fit. Enough said.

Thomas Seoh (01:02:16):
Steven, if I can feed back to you what I'm hearing, you're saying that precision medicine and precision health are different animals than the way in which drugs are approved for the general population in the past. And my question is maybe within the framework of a THRIVE Act, those kinds of decisions can be made by guidances or discussion or cultural change or what have you. I don't know what you can legislate from the standpoint of specific solutions to the problem that you just posed. But there are two topics that I see in the questions. One is how practical is it? How passable is the THRIVE Act? Who's for it, who's against it, et cetera., And then, does it actually solve the problem sufficiently? Will it incentivize? So can I throw that out to the panel? Please...

David Fox (01:03:04):
Let me offer a very basic answer to that and I think others can provide a more rarefied answer. So given my involvement with putting the initial draft together. With one or two very small exceptions, everything in the THRIVE Act is drawn from existing regulatory systems. So the concepts are, and the mechanics are all pulled from existing standards that are in use. So there's not a lot of things that are completely novel, it's just the way it puts them together and it's crafting a channel based on existing standards of evidence. It just arranges them in a way that makes sense for healthspan products. So in that respect, it's not as if somebody would open the THRIVE Act and say this doesn't make any sense under the Food Drug and Cosmetic Act. In fact, as Zan said, it builds off of the existing regulation of all the product categories.

The only not really novel aspect of it that that would take some explaining is that given the nature of some of the healthspan products that we envision and the fact that the products may already be available in other forms, it may be very difficult to protect one's exclusivity. And so we have included in the THRIVE Act, what we call private right of action to enforce or bring a Lanham Act type trade practice claim against somebody who's using your claims if you have exclusive rights to those claims. So you would not have to rely on going to FDA and begging FDA to bring an enforcement action. You'd be authorized to bring a very limited private right of action to enforce your exclusivity rights. And that would be new under the Food Drug and Cosmetic Act. Other than that, everything is drawn from existing authority, but that's the basic from passable from a political sense, I'd have to look to others.

Thomas Seoh (01:05:33):
I think that was a question, David, that people in chat were asking. So maybe Steven first and anyone else, are there congressional sponsors? What do we need to do? How practical is it? Who are the people who are going to oppose this?

Steven Grossman (01:05:48):
Let me take the first crack of that. Nothing like this just happens. It takes a bill,Everything requires a billthat, and so the question is, is it possible? Isn't the answer. You got to start, you got to get the reaction. You got to get the feedback loops. You got to consider the possibility that the THRIVE Act as conceived works in a completely evolutionary way. And we might find ourselves that what sells right now is revolutionary. You want to change it; you don't want to change it; I don't know. And I don't think we'll know until we have first what we have now, a comprehensive proposal, materials to support it. It then needs to be offered up for consideration by elected officials who have expressed interest in it. And we are definitely in an era in which chronic diseases as a topic is on an upswing. And so is it politically

feasible? Well, I would've told you a lot of things I've actually personally been involved in and succeeded weren't possible.

And even when we did the Orphan Drug Act, I think we all thought we'd done a good turn, but we didn't think we'd transformed the world. And I think we all would've been shocked to learn that it would still matter 40 years later because nobody thought that way. Well, I think we are starting to look longer, and this requires people to look longer. And that's also harder because people don't say, well, what's it going to be next year? I mean, one of the things that made Orphan Drug Act work was that worked in a three to five, five-year context. Here's what's going to happen, what people are going to do. I think that how you sell this really depends on the times, but the political process basically doesn't change. You got to work the system. You got to convince people; you got to build coalitions.

Zan Fleming (01:08:08):
But to be clear, we are the first to stipulate that this is not ready for Congress, that we need to do just what Steven is suggesting. We've got to workshop this and get widespread input and, ultimately, support. We've got to compromise probably in some ways. And so it's going to take a process to make this ready for congresspeople to consider. That will be a tortuous process. By the way, this bill just provides a framework. It doesn't get down into so many important details. It just can't, the Orphan Drug Act doesn't do that. No law that is passed by Congress gets into the kind of detail that will be required to be sorted. And so just as an example, for every iteration of the Food Drug and Cosmetic Act, there are probably tens of thousands of pages of guidances that FDA writes to show how they interpret the law and how it will be implemented. And so it's going to take FDA writing guidances that will help sponsors to understand what the expectations are. And that too is a process. It's not going to happen overnight.

Eve Herold (01:09:41):
And I would just add, this is the first step in a long journey. And part of that, what we need to do is to educate Congress because these are new concepts. They're all familiar to us. So we kind of assume that people know what we're talking about when we say healthspan. That's really not the case. Again, I want to say David is absolutely right in the sense that because there isn't a very detailed, precise definition with metrics and all that to define healthspan, we have to have a working understanding of what we're doing to move forward, and then we just take it one step at a time.

Steven Grossman (01:10:31):
Is there any room in this? And I haven't thought about this for some model demonstrations where Congress might authorize five Xs, I don't know what the X would be, and FDA then in conjunction with industry, I think then sort of works it out a little bit as to what it would look like and whether it can produce a viable product at the end. That's a little dramatic. Think about the history of the biosimilars.

Zan Fleming (01:11:04):
It's a great thought. It is really a great thought, Steven. And we're seeing in a way some models of pilots or initiatives. For example, ARPA H has a program that is aiming to move the needle in this field. And so they are attempting to catalyze development of endpoints that would facilitate the healthspan product development, including validating aging clock markers, which could ultimately become surrogates. And the XPRIZE has been set up to incentivize development among entrepreneurs or who are wanting to get into the game or willing to do so. And, so the point is we could really benefit from some of these early initiatives that allow us to get our feet wet and not have to jump in whole hog.

Steven Grossman (01:12:07):
Yeah, I think there's room for that. And the other model I was thinking about was biosimilars where FDA more or less steadfastly refused to provide general guidance for about five years, and their posture was we are not entirely sure what the rules should be. So we're going to deal with the first, I don't think they put a number in it, but it turned out to be the first 50 or so sponsors got personal service, if you will, until FDA felt it understood enough to do general rules. And that's a variation of the demos and the models, which is that one barrier to this is nobody's done anything quite like it before. And so maybe one way to slice it is can we create some pieces in the front that give people confidence that phase two and phase three are going to work?

Thomas Seoh (01:13:06):
I want to repeat the second question and then just make an observation. But the question is, does the THRIVE Act solve the problems it's identified? Does it go far enough? Will it incentivize people? I mean, why would someone with the THRIVE Act develop a rapamycin, for example, for TAMEtrial like indication? Why would a supplement company trouble to invest in a large clinical trial that gets the marketing exclusivity, but not sort of IP level exclusivity? But if you could think about that for a moment, I just want for the audience to comment on, elaborate on Zan's point. This is a framework and if others want to propose a framework, that's fine. We're happy to look at it and we'll choose the better one. But this is identifying issues. There are proposals out there like let's have an expedited process like Breakthrough or RMAT for healthspan drugs.

That fits in a certain part of incentives. We have incentives about vouchers, pediatric voucher, like vouchers or prizes. Those are hinted at, they're listed in the Act, and we'd invite people to look at the structure of the ACT and use them as prompts. And if they have a better suggestion, let's all throw it into the pot. But let me come back to the question I'm posing to the panel, which is does the Act actually solve the problem? Does it go far enough? What's the impact? Is it actually going to make a difference for developers?

Zan Fleming (01:14:32):
I don't think we can answer that question today. You need to ask the people who matter. That would be the developers, and that would also include investors and entrepreneurs, Big Pharma, smaller pharma, biotech, medtech. We can speculate on what would float their boats, but we have to ask them to know. We have put out some feelers. We've asked for feedback from various quarters, and now we've opened up the floor for as much feedback as we can get from those who are directly affected or would benefit as well as public minded people who would have concerns about what would be provided here in the Act.

David Fox (01:15:33):
Yeah, Zan's completely right. It's hard to know how people will react to the incentives and putting real money behind them, but we do have a lot of experience, and we tried to bring that experience to bear in the design of the THRIVE Act. So Steve started with the Orphan Drug Act. One could say today the Orphan Drug Act is more about the incentives than anything else. That's the way it evolved. The seven years. When I was at the agency, we tried mightily to come up with ways to incentivize the industry to do pediatric studies, but it was the BPCA, the Best Pharmaceuticals for Children's Act that added just six months of exclusivity, and then suddenly the farm industry couldn't do pediatric studies fast enough. Everybody came.

We know on the other hand, for example, the GAIN act for generating new antibiotics has been largely a failure. On the incentive side, it adds five more years to your existing exclusivity, but five years to a drug

that nobody wants to be used, that we want to lock in a closet and give very limited claims to, doesn't incentivize anybody. We know that pediatric rare pediatric disease voucher and also for tropical disease has been very successful because of its transferability. And so we have built into the THRIVE Act a variety of incentives, including something along the lines of a trade. We have the transferable voucher, but also the opportunity for transferable exclusivity. So to use a successful existing product for a rare disease or a disease population to subsidize in a way the development of a healthspan product. So, if the commercial viability of a healthspan product is relatively low because of the nature of the product and the protectability of it, you'd be able to transfer your exclusivity to somebody who has much better capability because the barriers to entry are higher of protecting that product.

So yes, it's speculative, but I think we are very cognizant, I've been at this for more than 30 years. Of what is an incentive for the industry and what is not. This is going to require a substantial incentive, and that's built in. We also include along the lines of what Steven was mentioning, we do have, we included an allocation of prizes for development in certain areas. So that's a little bit along the lines of a pilot, but people who go the extra mile and solve certain problems in the healthspan area would be eligible for prizes. So we build that in as well.

Steven Grossman (01:18:43):
I'm going to not only endorse the idea of, we don't know which incentive will work, but it is something you can focus group, you can meet with people. I want to put in a word for the good old market exclusivity, which seems to be diminished in a lot of people's mind because they see ways around it. And I do remember, I think this was GAO, but I could be wrong. I was surveyed on the question of, at the time of approval, most orphan drugs have more than seven years of IP. Why is market exclusivity of value? And the answers are twofold. One, market exclusivity is more certain than IP, and the other is market exclusivity can't be challenged in court the way IP can. So that notwithstanding the fact that there are incentives that are longer and would appear to be better, the reality is because of the element of certainty, in the case of marketing exclusivity, it's valued. And I think in this case, and GAINis a good example, we have to figure out what is the right incentive that will move, investors will move inventors to put the time and energy into this. But I think the case that incentives work in general is more than proven. And I would say that there's probably a reason to go back and look at GAIN and see how it should have been configured in light of the fact that it didn't work.

David Fox (01:20:13):
Yeah, yeah, quite familiar with that. Yeah, those surveys often net out, and this is an overall average that a new drug gets 13 to 14 years of exclusive marketing, including IP and regulatory exclusivity. There are obviously ones that go much longer and they're ones that are shorter, but it's about 13 to 14 years, which is also the maximum amount of patent term that somebody can get with a patent term extension under Hatch Waxman. So 14 years is something of a magic number. It's 12 years for biologics, but that is in the 13 to 14 years zone, and that's exactly where we net out in our progressive system, so you would emulate - if you imagine a repurposed drug that's being developed progressively for healthspan with no composition of matter IP and probably very tough to get enforceable method of use IP. We would compensate for that by emulating the IP that they would've gotten by giving them 14 years of exclusivity if they hang in there and go through the progressive system.

Zan Fleming (01:21:31):
And by the way, we even toyed with the idea of including IP proposal in the act, but that's a bridge too far.

David Fox (01:21:38):
Right. We kept that out. Yes. It's not the domain of FDA.

Zan Fleming (01:21:43):
's not the domain of FDA. And it's not to say that there shouldn't be a new look at by the Congress and provisions of the US Patent and Trade Office or US PTO, but that's another domain.

Eve Herold (01:22:03):
Well, I have a question for David and anybody really on the panel is that how does the exclusivity concept work with repurposing existing drugs?

Thomas Seoh (01:22:17):
How do the three tiers work? For example, for metformin or rapamycin or generic semaglutide or for that matter, tirzepatide which is currently patent protected?

David Fox (01:22:32):
Essentially for a repurposed drug. So we're assuming something older, there may be over to be generics available. There's no real IP estate. With each progression from Tier 1 to Tier 2 and Tier 2, Tier 3, they would get seven years of exclusivity. If it were a drug it would be a seven year bar and FDA approving the same drug for the same indication. But we recognize that there will be a significant amount of off-label use of that drug if it's already available widely in generic form. And so we include the private right of action. If anybody who makes that drug in any way expresses or implies the healthspan claim, you could go directly to court. You could initiate that action yourself as a private right of action rather than have to go to the agency and complain about it and fall into a kind of black hole of little to no hope of getting the agency to act.

So it's not perfect when you talk about repurposed products that are widely available. We can't go and pull all those products off the market. So you're playing into a space that may already be occupied, but you are given, you at least have the knowledge that FDA could not on-label approve anybody else during that seven year period for the healthspan claim that you proved up and that you'd have this private remedy. And the remedy is substantial, it's damages. Monetary damage is not just injunction and there is the opportunity we include for somebody who willfully tramples on your exclusivity to pay damages, triple damages, which is common in antitrust law. So that's also not new, but we try to create powerful disincentive for people to try to trample on your exclusivity,

Thomas Seoh (01:24:42):
But we recognize that free riders, if patients are buying generics not under that label for that purpose, that's an area that we cannot address for generics. What about other modalities? I mean a while ago, I think it was last year, we had a Targeting Healthy Longevity session from Mars for the Cosmos trial of a flavanol supplement. How would a supplement be run under the Tiers 1, 2, 3? And are these the same standards that are applicable across the modalities for devices?

Zan Fleming (01:25:24):
This is a good example of a kind of product that could get a Tier 1 approval and it's not a drug, though it could - you could easily make a drug out of a flavanol product even though it's now available as a dietary supplement. By the way, and this is very important, under THRIVE that product could have a Tier 1 indication approval and continue to be available as a dietary supplement. Nor, would other supplements—similar or identical products—be precluded from marketing as supplements. The only difference is if a dietary supplement wins a healthspan claim, only that product would be able to put

their claim on the wrapper or label. The flavanol product that we are talking about was the subject of a major cardiovascular outcome trial. The trial results were pretty convincing, although for some technical reasons we don't have to get into, it was not considered a positive trial, but it's the kind of evidence that would or could be persuasive along with other supportive evidence for a Tier 1 or 2 approval. There is abundant evidence that supports the effects of flavonol on cognitive function, on blood pressure, on lipids, and so there are strong priors that this product could actually increase healthspan. I'm not saying that the evidence reaches the level for approval. That's a job that would have to be done by the regulators, but it's just a good example of how a dietary supplement could be given a healthspan claim. And by the way, they would have to go through the kind of process that the drugs go through. They can't get a healthspan claim just by submitting their application and not having a pre-market review process. They're going to have to go through essentially a drug approval process, but the company can still continue to market the dietary supplement. This does not change DSHEA one bit. It just provides another option, an additional option for dietary supplements.

Thomas Seoh (01:28:24):
Can I call up one of the questions -, David, in Q and A asked comment, the novel feature of the Act seems to be the new Tier 1 approval mode. So how does it differ in practical terms from Tier 2 and 3 and what happens will approval, would you have to pass through Tier 2 and Tier 3, et cetera? Good question.

Zan Fleming (01:28:53):
Well, I'll just start out, and again, these are categories of evidence. We can't possibly get down into the details of just what would be necessary and sufficient for the totality of evidence. There is no single category of evidence here that would by itself support approval of a Tier 1 indication. This is just a framework. It's not the details.

David Fox (01:29:30):
Well, let me answer the second question first, which is that if a sponsor wanted to go directly to Tier 2 or Tier 3, they are not required to go through Ttier 1. So if they already are amassing clinical data, they could go ahead. They're not required to step through all three on the first question. I think what's different and noteworthy about Tier 1, and this is where I think you might want to speak to this a little bit more, is the nature of the evidence. And so Ttier 1opens the door to a form of marketing approval in which we don't have true clinical endpoint type data. We don't have classical clinical endpoint type data and we don't yet have what we about to a surrogate marker reasonably likely to predict under an Accelerated Approval standard. Instead, it relies on probably a totality of other forms of evidence, this developing field of evidence along with calibration to the safety profile of the product.

So we're thinking for relatively low risk products where there's compelling science but not clinical outcome types science, we'd be willing to let the product on the market to advance the policy of healthspan. And let me just emphasize if there's one thing to think about to draw all this together, why it makes sense now, it's that point that Eve raised the uncertainty point. So that's at the heart of regulatory science and what's the nature of the uncertainty? And I'd say from, I'm not the scientist here, I'm the last person to speak of the science, but what the scientists are telling us or telling me is that the nature of the uncertainty is much, much different today than it was when we passed prior versions of the Act. And we can look at the science at a much more granular level, and so we're taking less of a risk that we're completely off the mark and because we feel like we can control for that uncertainty in a wholly different way, it allows us then to go to market without the classical empirical evidence of, I don't know it until I've observed it in the human population.

Steven Grossman (01:32:10):
How would you compare this? I could see the question how is Tier 1 different from conditional approval, which has its own history as a concept and its own emotions that it generates?

David Fox (01:32:27):
This may be a little bit too abstract than what you're looking for, but it's the nature of the regulatory decision. It is a decision, it's a conclusive decision that based on this evidence, we believe there's truth to the level that Congress said we needed to find it in order to allow the product on the market. So while there are requirements that a sponsor would need to fulfill to maintain their place on the market over time and to get to higher levels, the initial, you'll see that in the Act, even if you don't reach Tier 2 or Tier 3, you still maintain your earlier approval. So the approval itself at each tier is not qualified or conditioned. It is a full determination based on the available evidence that Congress said is sufficient to reach that conclusion. I know that sounds, it's a little bit of, there's some circularity in there, but in some ways it's not conditional approval if we don't call it such.

Zan Fleming (01:33:41):
Yeah. Well, and what it's important to point out that the difference between Teir 1 and 2 in the actual wording of the Act is just “appears reasonably likely” versus “likely.”

Zan Fleming (01:34:04):
Appears reasonably likely versus likely, that's the difference in semantics. But, the devil is in the detail as to what that constitutes.. Let me also mention another consideration in taking the risk, the risk that the evidence is not ultimately going to be confirmed, and that is the safety of the product. It goes without saying that the benefit to risk relationship has to be acceptable at every tier starting with Tier 1. So you're not going to see gene therapies in Tier1, in all probability, at least in the foreseeable future, but you need to have a certain high level of safety. Maybe it's an endogenous metabolite, it's a commonly occurring product in the food supply, or we otherwise have abundant experience with it, even marketing experience like we have with GLP-1 agonists. But the point is you've got to have some high assurance at Tier 1 that there's not going to be a safety issue.

Thomas Seoh (01:35:22):
By the way, how about the question or claim that Tier 2 and Tier 3 is nothing new. It's a nothingburger. There is a difference obviously at Tier 2. It's not limited to serious life-threatening medical conditions and life-threatening diseases, or at least it seems to suggest preserving healthspan fits that criterion. But is it true that given the structure and direction of the Act and THRIVE Act, there could be more of a totality of evidence that could affect Tier 2 and Tier 3 so that they shouldn't be thought of as exact clones of Accelerated Approval and traditional approval?

Zan Fleming (01:36:02):
No, I don't think we have to make them exactly alike, but for conceptual purposes, we compare the Tier 2 level of evidence with that involved with an Accelerated Approval. Now, the reason the accelerated approval doesn't work for preventing chronic diseases is because the interpretation of FDA is that these diseases that are the subject of a accelerated approval need to be for imminently life-threatening conditions. And so typically you see most of these approvals for cancer drugs. Now ironically, the Center for Veterinary Medicine does have a provision that does allow for chronic disease prevention as a, what they call a conditional approval, though they don't use the word conditional on the human drug side, but it is used in CVM and it's actually kind of a model for a mid-level standard of evidence for approving the healthspan product.

David Fox (01:37:15):
On the CVM side, just to be clear, it's essentially a safety first approval and then you by law develop the efficacy evidence over time while you're on the market and that's what makes it, it's conditional in that it's more like a peri-approval. You're approved on safety, with efficacy coming later. And that's different from THRIVE, where even in Teir 1, FDA is making an efficacy finding. It's an efficacy finding that is based on the types of evidence on which the statute would place value, preclinical evidence and mechanistic evidence and other forms of evidence. But that evidence is sufficient. We're saying it's sufficient to make a full Tier 1 efficacy determination. Now, that's not a full ultimate healthspan determination. It's a determination within the parameters of a Tier 1 approval. So, that's the difference. That's different even from the CVM. It's not a promise of efficacy evidence later that you do have efficacy evidence even at Tier 1.

Steven Grossman (01:38:35):
Well, David, the way I was taught it, which doesn't make it the right way, is that some evidence of efficacy is actually a safety concern because if you give people a safe product that has no benefit, then...

David Fox (01:38:52):
Absolutely. Yeah, no, absolutely. Right. Even at Tier 1, which is why people demonstrated benefit passed outweigh the safety risks.

Steven Grossman (01:39:05):
So even at Tier 1 in the current system, people have to look for efficacy because otherwise the risk benefit balance goes off.

David Fox (01:39:17):

If the efficacy is so speculative and completely abstract and theoretical, it could not outweigh the safety risk of the product.

Thomas Seoh (01:39:31):
On the other hand,

David Fox (01:39:32):
The product, the product has no burden, it has no safety, then it has no pharmacologic activity. The whole thing is that's the Bob Temple saying, ‘There's no free lunch in pharmacology, right?’ If it's going to be effective, it's got to have a risk. Otherwise, it's a cosmetic.

Zan Fleming (01:39:50):
Cosmetics—that's the only products we don't include in the Act.

Thomas Seoh (01:39:54):
You look like you had a point. Go ahead.

Steven Grossman (01:39:56):
Yeah, I want to come back to what I think some of these questions and some of these answers miss, which is if we were doing it by diabetes and cardiovascular, the system is just fine if more than a little slow in getting the benefit to people. This is about having something that is novel relative to the existing system, something that is going to attack a biological mechanism, something that's going to have an effect on multiple chronic diseases. And again, as I understand it, I'm no statistician. If you go in and you

say, well, this helps cardiovascular, it helps diabetes, and it helps the liver or the kidney, and FDA is going to come back and say, well, if any of three outcomes is a positive, then oh, by the way, your level of proof is P 0.01 because you have to adjust for multiplicity. And so one of the things that lies in the back of all of this is that a lot of the products that might qualify under this pathway could move forward, except that what we're trying to prove for them would create multiplicity in a way that would make it almost impossible to run trial. Leaving aside the nwould have to be enormous.

Zan Fleming (01:41:32):
Yeah, well, that's the technical issue that is worth pointing out actually operates today in the evaluation of cardiovascular claims, multiplicity of composite endpoints is taken into account. Typically it's myocardial infarction that drives that MACE composite. And that would be the same consideration for a composite of multiple chronic diseases, as you say. But the way the THRIVE Act would perhaps address the issue is to lower the strenuousness of the multiplicity test. Again, we're getting down into the weeds, probably not worth doing that given we have so many questions and only zero time left in our session though, let me just say we'll keep going as long as people want to hang on. We're at time, but gosh, what a great discussion we've been having. I'd love to keep going for the entire afternoon, but..

Thomas Seoh (01:42:38):
Let me draw a formal close to the events here. This is the beginning of a long conversation on regulatory pathways, fit for purpose evidence and the incentives for healthspan products, and we'd love to hear from you. You can put your questions and comments. We'll probably transfer the chat ideas and the questions into our THRIVE Act discussion board@kitalis.org. So all registrants will receive the link to the recording within a day or so, as well as announcements for future Targeting Healthy Longevity 2025 sessions. We had a session with FDA officials and geroscientists plan for early this month, but it's being rescheduled to a little bit later this year because we need to give the new FDA leadership a chance to settle in. And we also have a workshop in planning for approaches to frailty and sarcopenia. So with that, the formal portion of this event is closed. I thank the panelists and you, the audience for your attendance. We will be leaving the Zoom webinar open for some minutes for those speakers and audience who are available to tarryand chat. So thank you very much. Have a great weekend. Closure end of scene.

Zan Fleming (01:43:50):
All right. We're now at the podium after the, well, we didn't have a podium. We had a round table

Thomas Seoh (01:43:57):
Virtual dais, but I did have a philosophical question and people please go ahead and chat for people who are staying in the room. But this is a philosophical question, and this builds on the safety discussion we had at near the end there. Under what circumstances could it be justified to give interventions to younger, leaner, healthy people when 85% of health seems to be due to lifestyle? Is that just an overly provocative question or is that a serious policy question?

Zan Fleming (01:44:33):
I think that is a conjecture that there isn't residual risk that cannot be relieved any more than 15%. I don't accept that that is the case, but let's say it's 50-50, it's still a concern. I would readily admit that. Why should we put the kind of effort we're doing now into regulated expensive products and not just mandate that everybody do what they were taught in kindergarten about eating healthy, being active and doing other things that are known to be good for you?

Eve Herold (01:45:21):
Can I just say I'm thinking ahead to what an Act ultimately would look like and what a regulation would ultimately look like once we get past all the initial stages of development and everything, and ideally in my mind, as science moves ahead, it's going to solve some of these problems for us. So for example, if you could say we have a verifiable, accurate biological clock that measures age, then that would be an endpoint I think that we could work towards.

Zan Fleming (01:46:01):
Well, if we had that endpoint, it changes everything because we have the precedent of LDL cholesterol with which we approve the statins. We have HbA1c by which we approve drugs for diabetes. So having those has made it so much easier to approve products for those conditions. So once we have a validated clock or any other biomarker, that changes things by a lot. But here's the road to get that validation means we have to have an intervention that actually moves the needle and that we can show there's a correlation with that readout. It's a catch 22, and it's going to take a good while to be able to show that we actually have products that we can in effect run through the validation procedure and to actually get those data.

Eve Herold (01:46:57):
And we need longitudinal studies to show comparisons between the state of health before that intervention and the state of health after a certain amount of time has passed. Sure.

Zan Fleming (01:47:13):
Yeah. Well, again, a lot of devil in the details and this is not going to make things happen overnight for sure. And as mentioned, we're not even ready to go to Congress yet. We got to workshop this thing until we have a consensus around it and broad support from all the stakeholders.

David Fox (01:47:37):
Also, I think part of what you're raising is what we call a drafting issue. So we want the legislation to be enabling, but we don't want it to be so detailed and prescriptive that it prejudges the science where the science is headed. So you want to kind of strike the right balance in the legislation of being sufficiently open-ended that as the science evolves, it will fit into the legislation without having to go back and pass new law. So right now, people can quibble over this, but right now we live in a regulatory system for drugs that's based on the 1962 substantial evidence standard.

Now, you could say that's a success because that standard has stood the test of time and has allowed FDA to incorporate all sorts of new science into it, but it's also become a problem because it leaves almost all the decisions on hard FDA problems to an ad hoc behind the scenes improvisational effort, flexibility. So we want flexibility, but so much flexibility makes the system unpredictable and subject to the proclivities of individual reviewers. So you're always trying to strike the balance between something that's broad enough that will stand the test of time and we'll be able to absorb new science, but something that doesn't leave it is not so open-ended that nobody really knows what the standard is. And so that's a legislative drafting issue, and Zan keeps reminding us we can only get so far with the legislation and then a lot is going to have to be offloaded to the regulatory development process of guidance and interaction with the industry and stakeholder meetings and that whole evolutionary process on the details. But I think we have a pretty good visual of what an Act would look like. It needs some refinement for internal consistency. There's a few more ideas that might want to incorporate. It probably is a reach in a few places, but if you want to visualize what it would look like, it's not really that far off the mark

Steven Grossman (01:50:00):
For anybody who's hung up on that. I think I may have been somewhere earlier in the chain, the one who pushed for it to be done in bill form, because putting it in bill form creates both a structure and helps you understand what it is you're missing because you're thinking immediately about what is it that various players in the future under whatever program we're advancing. And so I hope people don't get hung up on the fact that it's in legislative form, even though it's not ready to be offered as legislation. It is a very useful tool.

Zan Fleming (01:50:43):
That's right.

Steven Grossman (01:50:47):
And who knows if because we've got a Supreme Court decision that nobody really has had any time to implement that says we need a lot more detail in our laws so that they can be implemented by regulatory agencies with a minimum of ambiguity and a minimum of uncertainty, all that additional workshopping might prove to be essential and wind up in the end needing to be some of it move back into an Act.

Thomas Seoh (01:51:23):
Can I pose a question from one of the registrants? And the question was how does the THRIVE Act promote healthy longevity equitably for all? And that's not the main purpose, obviously, of the THRIVE Act, but the question deserves an answer I think.

Eve Herold (01:51:45):
Well, I mean it could be a long-term process because obviously if you're generating new cures and new therapies, they're going to be available to a limited number of people in the beginning, but then economies of scale kick in. So I mean, this is something that potentially affects every human being on the planet. So once we understand that and national health systems understand that and regulatory bodies understand that, then you're going to get economies of scale. We're a long way from that now, we're still in the early stages of a lot of these kinds of therapies, but the trajectory in terms of how cures and therapies have ultimately been delivered is that yes, they initially are available to a select few and over time the net widens until they become adopted by healthcare systems and universal coverage and things like that. So new treatments do become democratized with time.

Zan Fleming (01:52:52):
Yeah, I think that's so well said. Eve, in effect, if you bring the evidence, the payers will come and they will come for the larger populations. The Center for Medical Services will be there if the economic case is made based on the evidence. And that's addressing Thomas's question, why is this in effect helping to address inequities, health inequities in our society? And it would do that by, among other things, the economy of scale, that the products, the cost of the products would go down on a unit basis so that it would be affordable or reimbursed by

Eve Herold (01:53:46):
Healthcare Payers.

Eve Herold (01:53:48):
One of the things that I've been thinking about when I reviewed some of the questions that came in last night about the economy of about increasing the healthspan is that there's very little understanding of the fact that increasing the healthspan goes far beyond science and medicine. It goes well into all the

social, economic, every facet of society. So it's also very complicated because there are determinants, there are nonmedical, non-biological determinants of healthspan, things like social support and education level, lifestyle. Of course, we've mentioned that a lot, but we are working on one side of this and I think we need to look at how this eventually is going to spill over into multiple layers of education, social programs and things along those lines that have been shown to show a significant role in healthspan and healthy aging.

Zan Fleming (01:55:04):
Yeah, amen.

Steven Grossman (01:55:06):
I'd like to take on for a minute the question Alan Jakimo asks about patient advocacy and why hasn't anybody mentioned patient advocacy here? And I don't know on one level, I don't know. I don't know who David and Zan have been talking to along the way, but I do see conceptually there's a bit of a problem because you got to convince the American Heart Association, the American Diabetes Association, that there's a pooled benefit from healthspan products. I don't know that that's such a heavy lift, but it does put them in a different paradigm than they work on every day and every week.

Zan Fleming (01:55:51):
That unfortunately is true, Steven. It's really part and parcel of our challenge that it's easier to address the patient with an acute disease in front of you than it is to take time to counsel that patient to do what could help to prevent the disease. And so it is a whole misallocation of our resources towards, as Eve said, sick care that's much easier for the physician to do. It takes much less time on a per unit basis than preventive care, which is not sufficiently incented.

Steven Grossman (01:56:35):
So the physician is the servant of the disease model, and FDA is the servant of the disease model, and the disease groups are the servant of the disease model. And so I guess one answer would be this is more revolutionary than anybody thinks.

Eve Herold (01:56:53):
That's kind of the argument to be made for looking at aging as a disease because our whole system is predicated on this model of the disease process.

Zan Fleming (01:57:09):
Well, you can look at it either way. You can look at it from a negative framing or a positive framing. I would rather look at it as increasing healthspan versus decreasing risk of disease. Ultimately, it doesn't make any difference in terms of the clinical trials that would be necessary to approve any either form of indication, but I am more attracted to the positive formulation than to the negative.

Eve Herold (01:57:48):
Oh, I am too. I totally agree with you. And I think that really is part and parcel of just this whole concept of changing the entire way that we view disease progression and health along the lifespan.

Zan Fleming (01:58:08):
Well, that's right. And the other distinction between the population of people who have disease and may have very strong advocacy groups behind them is that we're talking about the would be non-

patient, the person who doesn't want to become a patient and doesn't have any kind of stakeholder status. And so a challenge when you're starting with a population that's diffused large, unorganized, not listened to directly,

Eve Herold (01:58:55):
But there have been in terms of surveys that are done of the public about 'would you like to live to be 120?' If you ask people that, most of them will say, well, no, because in their mind, being 120 is a catastrophe physically, biologically, medically, and in every way. But if you ask them, would you like to live to be a 100 in a state of good health and vitality, then overwhelmingly they would say, of course.

Zan Fleming (01:59:28):
Yeah. And you just described in another fashion healthspan,

Eve Herold (01:59:34):
And

Zan Fleming (01:59:34):
That's why the focus is on healthspan, not on preventing disease or not on treating aging as a disease.

David Fox (01:59:45):
How can healthy normals stay healthy and normal for as long as possible?

Zan Fleming (01:59:50):
That's right. That's the question.

David Fox (01:59:54):
The FDA system is just not geared towards healthy normals. And to the extent it is in areas that are not evidence-based, not to the rigor that we prefer,

Zan Fleming (02:00:05):
And Dave, it's because sponsors are not coming to that.

David Fox (02:00:10):
Yeah, of course. Yeah, yeah, of course. Yeah,

Zan Fleming (02:00:13):
They were. I think FDA

David Fox (02:00:16):
Talk about health equity. I mean, we basically have a system in which people who feel like they're relatively healthy, normal, they're in homeostasis and good balance. They have to basically find their own evidence and do their own work very imperfectly and spend a lot of their own dollars on things that probably don't do anything for them in order to try to maintain that state of balance. And then once they get off balance, we know it's virtually impossible effort to get them back into balance and they live the rest of their lives with healthcare costs and unfortunately an imperfect healthcare treatment system.

Zan Fleming (02:01:04):
Exactly

David Fox (02:01:05):
Right. I mean, I think that to me, that's the equitable case. On the patient advocacy part. And Zan has forbidden me from using the word patient, so a little constrained. But one thing that I have been pushing on is part of a cultural shift at FDA is FDA does have patient listening meetings and they have various patient stakeholder meetings trying to learn from patients what they want in terms of clinical endpoints. An agency brings in experts, and this is a regular process, and I would like to see at least an agenda item on all of those meetings in which at least some time is dedicated to thinking about the pre-disease and preventive period. I understand that is very disease specific, so it's not quite within our mandate, but I just think culturally it's just a blind spot that we've allowed to hold for much too long. And even if there is nothing to report, I think every meeting when FDA meets with patients should have some moment where they're thinking about, okay, is there something more we could be doing on that early stages or pre-disease or preventive part?

Zan Fleming (02:02:35):
Yeah. And Dave, I do agree that there's room in the act for addressing the subjective for including the voice of the would-be-non-patient.

Eve Herold (02:02:48):
Correct.

Zan Fleming (02:02:49):
And we should do that. We end the fullness of time. We were just pressed to the max, and I didn't think we could really credibly describe how this would be done without just making it look like it was wind dressing.

Thomas Seoh (02:03:09):
Well, there was a draft section that ended up on the cutting floor, but maybe we can throw it up on our discussion board so that people can comment on it.

Zan Fleming (02:03:19):
Yeah, it's a great idea. Let's put it up for discussion. And we hope there'll be a lot more in the coming weeks. We'd like to follow up at some point with another get together and we'll do it as a web meeting so people can actually get up and yell at us.

Thomas Seoh (02:03:48):
Maybe this is a good time to close. We look forward to being yelled at by, in a town hall setting and I thank everybody who stayed with us in the audience. And can again wish everybody a great weekend. Thanks for event.

Zan Fleming (02:04:06):
And thank you all.

Thomas Seoh (02:04:07):
Thank you so much.