FDA Commissioner Robert Califf, MD participated in a virtual 'fireside chat' webinar on: '***The regulation of healthspan products'***. Dr. Califf was interviewed by **diabetes research leader Jay Skyler, MD** of the University of Miami, former President of the American Diabetes Association.

A roundtable discussion by leaders in geroscience and healthy longevity followed the webinar and was moderated by **Alexander Fleming, MD,** Founder and President of the Kitalys Institute, and Founder and Executive Chairman of Kinexum.

The 'fireside chat' with the FDA Commissioner is the **inaugural conference session for Targeting Healthy Longevity 2023**, organized by the Kitalys Institute. For further details, please visit: www.healthy-longevity.org

Meet the Speakers & Moderators:

Steve Austad

Dr. Austad is Distinguished Professor and Chair of Biology at the University of Alabama at Birmingham as well as Senior Scientific Director of the American Federation for Aging Research. He has previously held faculty positions at Harvard University, the University of Idaho, and the University of Texas Health Science Center in San Antonio. His research explores the evolution of life histories with a particular focus on the comparative biology of aging. Dr. Austad's research ranges from comparative demography to molecular mechanisms of aging and he has a long-time interest in variation in both cognitive and physical aging rates among primates and other animals. The long-term goal of his research is to develop treatments to slow the aging process, thus keeping people fit and healthy longer. Dr. Austad's laboratory works with different animal species, especially those which are more successful at aging than humans, such as clams and hydra, to discover such treatments. Dr. Austad earned an undergraduate degree in English literature from UCLA. After doing so, he left academia for several years during which among other things, he drove a taxicab in New York City, worked as a newspaper reporter, and trained large cats for television and movies. His interest in science was awakened by his time in animal training, he returned to academics to study animal behavior more formally, receiving his PhD in biology from Purdue University. After postdoctoral research at the University of New Mexico, Dr. Austad accepted a position as assistant professor in the Department of Organismic and Evolution Biology at Harvard University in 1986. Leaving Harvard as an associate professor in 1993, he moved to the University of Idaho where he became a full professor. From 2004 to 2013, he was a professor at the University of Texas Health Science Center at San Antonio. Dr. Austad served as interim director of the Barshop Institute before moving to his current position in 2014.

Alexander Fleming

Dr. Alexander Fleming is Founder and Executive Chairman of Kinexum, a company of professionals from across the world with diverse expertise in developing drugs, biotech products, medical devices, and digital health technologies. He is also President and co-founder of Kitalys Institute. Dr. Fleming received his M.D. and internal medicine training from Emory, fellowship training in endocrinology at Vanderbilt and metabolism at National Institutes of Health, where he was a senior fellow. At the US Food and Drug Administration from 1986-98, Dr. Fleming was responsible for the therapeutic areas of diabetes, other metabolic and endocrine disorders, growth and development, nutrition, lipid-lowering compounds, and reproductive indications. He led reviews of landmark approvals including metformin and the first statin, insulin analog, PPAR-agonist, and growth hormone for non-GH deficiency indications. Dr. Fleming oversaw clinical review of the earliest biotech products including human insulin and growth hormone. He helped to shape FDA policies and practices related to therapeutic review and regulatory communication. He was a major contributor to FDA's Good Review Practice (GRP) initiative and led the committee responsible for education and training at FDA's Center for Drug Evaluation and Research (CDER). He conceived and directed the first FDA pilot project to utilize the internet for regulatory communication. His regulatory and technical expertise has been requested in numerous international settings including the World Health Organization, where he was stationed by FDA during 1991-92. Dr. Fleming was a member of the expert working groups on Good Clinical Practices and General Considerations for Clinical Trials of the International Conference on Harmonization (ICH) and participated on other ICH committees including the Common Technical Document working group. Dr. Fleming has frequently authored scientific articles, books, and book

chapters. He has been a member of many corporate and advisory boards to academic and commercial institutions and professional societies. He serves on the joint technology working groups of the European Association for the Study of Diabetes and American Diabetes Association. Dr. Fleming coined the term 'Metabesity', which refers to the constellation of cancer, heart and neurologic diseases, diabetes, and the aging process itself, all of which share common metabolic root causes and potential preventive therapies. He organized the first Congress on Metabesity in London in October 2017, which has since been followed by annual conferences in October. Dr. Fleming founded in 2020 the not-for-profit Kitalys Institute as a means of producing Metabesity conferences and advancing all measures that can improve health and healthspan.

David Fox

Mr. Fox currently serves as a Partner at Hogan Lovells, an American-British law firm that specializes in government regulatory, litigation, commercial litigation, and arbitration, corporate, finance, and intellectual property. He advises management teams, from start-ups to the largest global pharmaceutical and biotechnology companies, on matters before the Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA). Mr. Fox is closely integrated with funding sources for the industry and is frequently retained as a strategic advisor on assessing the value of life sciences assets. Known for his collaborative approach to complex regulatory issues, Mr. Fox has successfully resolved numerous disputes between sponsors and staff at the FDA on products that raise novel regulatory issues. As a former senior lawyer for FDA and throughout his career in private practice, Mr. Fox has been deeply immersed in the regulatory side of the Hatch-Waxman Act, including pioneer-generic disputes and numerous cases of first impression involving exclusivity issues, Orange Book listings, and patent term extensions. Mr. Fox previously led the Pharmaceutical and Biotechnology practice group of Hogan Lovells and now serves on the firm's global Life Sciences management team.

Steve Grossman

Steve Grossman is Executive Director of The Alliance for a Stronger FDA, former Health Staff Director of the Senate Labor and Human Resources Committee, former Deputy Assistant Secretary for the Department of Health and Human Services, and former member of the Board of the National Organization for Rare Disorders (NORD). As Executive Director, Mr. Grossman is responsible for communications, budget and political analysis, and the smooth running of the organization. He also lobbies on the group's behalf and works with the media.

Steve Kritchevsky

An internationally known expert on nutritional influences that affect trajectories of health and disability in older adults, including vitamins, protein, energy balance, exercise and obesity, he has more than 450 peer-reviewed publications, lead Wake Forest University School of Medicine's NIA-funded Claude D Pepper Older Americans Independence Center (OAIC), and co-directs the Sticht Center for Healthy Aging and Alzheimer's Prevention. He has participated in some of the most important aging-related multicenter studies in the past 20 years, including the Health ABC study and the Lifestyle Interventions and Independence for Elders (LIFE) Trial, and he is the past editor-in-chief of the *Journals of Gerontology: Medical Sciences*. He leads the Research Centers Collaborative Network (RCCN) with the American Federation for Aging Research. The RCCN's goal is to build research collaborations among the six NIA Center's programs through workshops, pilot awards, and educational activities. Through his service on the National Advisory Council on Aging, he helps shape

national research priorities for aging research. His recent work focuses on translating the new discoveries in the biology of aging to prevent age-related diseases and extend health span in older adults.

Joan Mannick

Dr. Joan Mannick, an expert in the field of aging, is the Co-Founder and CEO of Tornado Therapeutics. Joan has served as the Head of Research & Development at Life Biosciences and as the co-founder and CMO at resTORbio, recently acquired by Adicet Bio. Before that, she was the executive director of the New Indications Discovery Unit at Novartis Institutes of Biomedical Research, where she led the clinical stage mTORC1 program licensed by resTORbio. Prior to joining Novartis in 2010, Dr. Mannick was a medical director at Genzyme Corporation leading an investigator-sponsored program for early-stage oncology products. She has served as a faculty member at Harvard Medical School and University of Massachusetts Medical School. Her NIH-sponsored laboratory focused on the role of protein S-nitrosylation in physiology and pathophysiology. Dr. Mannick received her BA from Harvard College and her MD from Harvard Medical School. She completed her residency in Internal Medicine at Brigham and Women's Hospital and an Infectious Disease fellowship as part of the Harvard Combined Infectious Disease Program. She is board-certified in Internal Medicine and Infectious Diseases.

Kate Rawson

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

Thomas Seoh

Thomas Seoh is President and CEO of Kinexum, a strategic advisory firm that provides regulatory, clinical, CMC and other translational guidance for life science product development. He is an entrepreneur/executive who has held senior leadership positions in public and private pharmaceutical, biotech and medical device companies for over 25 years. Mr. Seoh began his career as a corporate attorney in New York and London, then assumed legal management positions with the Consolidated Press group in Livonia, MI, then the ICN Pharmaceuticals group in Costa Mesa, CA. He next became VP, General Counsel and Secretary, and later, SVP Corporate and Commercial Development, of Guilford Pharmaceuticals, a NASDAQ-listed company in Baltimore which commercialized GLIADEL® wafer for glioblastoma multiforme and developed the propofol pro-drug LUSEDRA® and small molecules for Parkinson's disease. He then became CEO of venture-backed Faust Pharmaceuticals in Strasbourg, France, with a repurposed compound in Phase II for Parkinson's patients, a re-positioned molecule for Duchenne muscular dystrophy and a GPCR drug discovery platform. Mr. Seoh subsequently served in leadership positions of medical device startups developing an ex vivo liver dialysis device, a novel mechanical thrombectomy device for Deep Vein Thrombosis and stroke and a state-of-the-art neurocatheter, and a plant-based skin substitute wound dressing. He has served on industry-university advisory boards at Johns Hopkins School of Medicine and the University of Maryland Baltimore County. He holds an AB in Philosophy and History and a JD from Harvard University.

Jay Skyler

Jay Skyler is currently Professor of Medicine, Pediatrics, and Psychology in the Division of Endocrinology, Diabetes, and Metabolism at the University of Miami. He is also Deputy Director for Clinical Research and Academic Programs at the Diabetes Research Institute, University of Miami. For 22 years, Dr. Skyler was Study Chairman for the National Institutes of Health (NIH)-sponsored Diabetes Prevention Trial for T1DM (DPT-1) and its successor, the NIH T1DM TrialNet Clinical Trials Study Group (TrialNet), which were clinical trials networks aimed at preventing T1D or interdicting the T1D disease process. Dr. Skyler had continuous grant support from NIH from 1979 to 2015. Dr. Skyler is closely involved with many scientific societies and has served as President of the American Diabetes Association, the International Diabetes Immunotherapy Group, and the Southern Society for Clinical Investigation; and Vice-President of the International Diabetes Federation. He was founding Editor-in-Chief of Diabetes Care (an American Diabetes Association publication with a current impact factor of 15.270), founding Scientific Editor of the International Diabetes Monitor, and currently is Senior Editor of Diabetes Technology & Therapeutics. Dr. Skyler is the recipient of the 1992 Banting Medal for Service from the American Diabetes Association, the 2014 Distinction in Endocrinology Award from the American College of Endocrinology, the 2015 Distinguished Faculty Scholar Award from the Faculty Senate of the University of Miami, the 2015 Mary Tyler Moore/S. Robert Levine Award for Distinction in Clinical Research from the Juvenile Diabetes Research Foundation, the 2016 Distinguished Alumnus Award from Jefferson Medical College, and the 2017 Josiah K. Lilly Award from the American Diabetes Association. Dr. Skyler received his MD from Jefferson Medical College. He did postgraduate training at Duke University and NIH.

Lawrence Steinman

Larry Steinman is a professor of Neurology and Neurological Sciences, Pediatrics, and Genetics. He also served as the Chair of the Stanford University Interdepartmental Program in Immunology from 2003-2011. Dr. Steinman's research focuses on what provokes relapses and remission in multiple sclerosis (MS), the nature of the molecules that serve as a brake on the brain inflmmation, and the quest for a tolerizing vaccine for autoimmune diseases like type 1 diabetes and neuromyelitis optica. He has developed two antigen specific therapies, using DNA vaccines, for MS and type 1 diabetes. He was senior author on the seminal 1992 Nature article that reported the key role of a particular integrin in brain inflammation. This research led to the development of the drug Tysabri, which is used to treat patients with MS and Crohn's disease. Dr. Steinman received his BA from Dartmouth College and his MD from Harvard University. He was a post-doctoral fellow in chemical immunology fellow at the Weizmann Institute of Science in Israel. Dr. Steinman returned to Stanford University Hospital as a resident in pediatric and adult neurology and then joined the faculty at Stanford in 1980. Dr. Steinman has received numerous honors and awards, including the John M. Dystel Prize from the American Academy of Neurology and the National MS Society for his research on MS, and the Charcot Prize for Lifetime Achievement in MS research. He has twice been awarded the Senator Jacob Javits Neuroscience Investigator Award by the National Institute of Neurological Diseases and Stroke. Dr. Steinman is a member of the National Academy of Sciences and the National Academy of Medicine, formerly called the Institute of Medicine. Dr. Steinman holds several patents in the areas of immunology, and for therapies of Huntington Disease, type 1 diabetes, and MS. He cofounded Neurocrine Biosciences, Bayhill Therapeutics now named Tolerion, Nuon Therapeutics, Transparency Life Sciences and Atreca.

Session transcript:

Zan Fleming:

Well, I think we have everybody for our so-called anchor desk. We can kick off the 2023 version of Targeting Healthy Longevity. Great to have everybody. We've got a small gathering audience, but it's going to quickly get larger as the FDA Commissioner comes in at the top of the hour. But great to have all of you. I'm here with co-founder and co-chairman, Professor Larry Steinman from the Junior University, as we call Stanford University. Larry, great to have you, and as we go back to 2017 when we started this off.

Lawrence Steinman:

Thank you Zan. I remember actually taking a red eye into London and attending the first meeting at a nice venue next to Wembley Auditorium. Now, with AI, I don't know whether I would've taken the red eye and just phoned it in.

Zan Fleming:

Well, it's been great to have you all along the way and certainly we think back to London with great nostalgia. I'm here also with Thomas Seoh, CEO of Kinexum and a senior official in the Kitalys Institute along with Joan Mannick, one of the first movers in the geroscience therapeutic development field, along with Margaretta Colangelo. Margaretta is also a board member of Kitalys and she is responsible for getting at least half of the audience here. So we are indebted to Margaretta. Then, Joan Mannick is one of the real leading lights in the field and probably has gone further than anybody else in taking the therapy forward in this space. So great to have everybody on.

Thomas, we've changed the name and the format of the conference, so you might say a few words about that.

Thomas Seoh:

Sure. I don't know how many of you know about what a neologist Zan is, but he coined the term 'Metabesity' we think at the biotech showcase in 2013, to refer to that constellation of chronic diseases of aging that have common roots and therefore could be addressed by common solutions. But over the years we've received feedback that it's a weird word, it's hard to remember. It could be confused with obesity or could be limited to metabolism.

So, this year we are calling the conference, instead of Targeting Metabesity, Targeting Healthy Longevity, putting it out right there in front so people know exactly what we're talking about. Instead of three or four days in a row in October as we've had in prior years, we're spreading it out over sort of a monthly format of free virtual webinars, culminating, we're planning to an in-person event at the end of the year. So, please keep tuned to it. You can check it. Check out the conference and news about the conference at healthy-longevity.org. or follow the Kitalys Institute and be alerted to developments.

Zan Fleming:

Thanks Thomas and Joan, great to have you back. You really had been a terrific co-chair of the conference and so glad to have you today.

Joan Mannick:

Delighted to be here and it's going to be an exciting session.

Zan Fleming:

Well, thank you for all your support and Margaretta, you are quite incredible and your over 50,000 followers, really one of the founding people in this geroscience space and an expert in AI. So, that's a multifaceted, almost singularity among people in this field. Great to have you Margaretta, and thank you for all you've done.

Margaretta Colangelo:

Thanks, Zan.

Zan Fleming:

Well, you can say a few words.

Margaretta Colangelo:

Well, there was tremendous interest in this. I received hundreds of messages from all around the world and people were excited that we're having this, but also, they were excited that Kitalys was hosting it. There are many people who can't attend because they're in a time zone where it's in the middle of the night. But I'm going to write a recap and send it to everybody who showed interest. But I think of all the conferences I've been involved in the last 30 years, I received the most positive, excited messages about this conference.

From the ministries of health, from hospitals, from universities, from scientists, of all ages. So lots of interest in this conference.

Zan Fleming:

And as you say, it's global. People from all over the world and you've done a lot of global work. You're showing up in conferences all over the world and it's quite remarkable that we have such a worldwide community.

Last but not least, Jay Skyler, who will be conducting the fireside chat with the commissioner. Jay, great to have you. You're actually down in Costa Rica, but the technology allows you to be present and that's great to see.

Jay Skyler:

It looks like people are scattered all over. Larry's at Stanford, I see Amanda Adler from Oxford being on, so lots of people around the world.

Zan Fleming:

Yes. Hello, Amanda. There are so many people I'd like to acknowledge. I see my old friend and colleague, Ron Hart, who was at FDA. It's been many years since we were there together. But we enjoy getting back together when we can.

Ron Hart:

Thank you, Zan. Good to be here. Interesting conversation on AI. David Frank and I, who heads the medical section of AAAS, which has 38,000 members, have just been discussing that problem about trying to develop a special workshop. Because medicine especially is based upon the shoulders of those people who came before us, and we've heard that many times in the past. But we have to depend also on the data presented in publications being honest. That we may disagree with a theory or interpretation, but we can always trust the data presented.

But that's no longer the case and with AI being able to generate papers with or without scientific information puts us all at risk relative to the quality of the database from which we're making diagnoses. If we have false data, we're trying to make diagnoses from then we have problems with patients dying because of that fact. So, while AI is wonderful and we use it all the time in our labs to do our biomarkers and all the rest, it's also very frightening that it may be generating estimates of up to 10 to 15% false publications.

Zan Fleming:

Many thanks for that, Ron. In fact, this is a subject of great interest and concern for the commissioner. I know he really does have a concern about misinformation in the field of health and that may come up shortly.

I see the commissioner is actually on a few minutes early. So, instead of keeping him waiting I think we'll slowly bring him into the meeting. Rob Califf, can you hear us all right?

Rob Califf:

I can hear you just fine. If I'm too early, let me know. I got plenty of work to do here.

Zan Fleming:

I know you do. Well, you're probably going to be multitasking while you do this. But it's just terrific to have you and your old friend and colleague, Jay Skyler. You both go back to early days at Duke and you respectively are experts in clinical trial design, cardiology and diabetology. So, I can't think of two better people who can discuss the important issues related to preempting chronic disease, slowing the aging process, and having a greater degree of healthy longevity for our country and the world.

So, again, we can't thank you enough Rob and I'm going to go ahead and ask Jay to take over. We'll start just a few minutes early, but that's a good thing. Gives us a little more time.

Jay Skyler:

Well, thank you Zan and Rob, welcome. As a way of background for everyone, **FDA's policies, practices, and planning related to drugs, devices, diagnostics and nutritional products aimed at risk reduction of age-related diseases and disabilities, basically creating a healthy lifespan, is the subject that we're going to be discussing today.**

My first question for Rob is, **what kind of evidence would be required to support healthspan-related indications and product labels across drugs, devices, and nutritional products?** We usually see that endpoints are related to a specific disease, and aging is not a disease, and we want to create a healthy lifespan. So, what are your thoughts on what kind of endpoints one could use? **Could you use a multi chronic disease composite endpoint** or what would you be thinking?

Rob Califf:

That's a very broad question to start with, Jay. Let me just note, when I was a mere medical student, Jay was a dashing young sort of paradigm of a young faculty member on the way to success. So gosh, that was a few years ago, but a lot's happened since then.

First of all, let me just make clear, I think you all know this, but **the commissioner doesn't make decisions about individual products, but has a role in policy that those decisions are made by full-time civil servants reporting up to center directors.** So, I have opinions but don't take anything I say as official policy unless I denote it as such.

First of all, what I'd say is in my career I helped develop on the other side of the fence, on your side of the fence, and I used to be involved in developing endpoints as we developed cardiovascular outcome trials. I would say the laws tell the FDA that we need adequate and well-controlled trials and the opinion of experts in the field. In my outside experience and my knowledge here in the commissioner's seat, when there really is a consensus that's very broad, and the experts in the field in the relevant areas agree, then it's common for the FDA to also be in agreement. That's actually what the law says. But when there's disagreement and disarray and some experts say one thing and some say the other thing, and then the FDA will typically revert to where there is common ground.

So, in this area, I mean you're all experts and you know that it's particularly difficult. I would **say job number one is to find out where there is consensus and work on it. Within that frame of thinking, a lot of things are possible. Multi morbidity indices are possible. Organ function measurements are possible.** But there's something that I think has tended to vary depending on the year you talk about and that thing that's very important is that the charge to the FDA is benefits for the entire human being, not one part of the human being. I would argue a lesson that I was very involved in, the push to do longer term outcome trials on diabetes, I think the payoff has been stupendous because I don't know how long it would've taken us to distinguish the type 2 diabetes drugs that reduce death and major events from those that lower glucose but don't have much additional impact.

So, even if you use a measure which is a surrogate or an intermediate clinical endpoint, I think as we go forward, the trials are going to have to be robust enough to give us the other information that we need about the outcome for the whole human being. The place where I make an exception is if it's a rare disease where the numbers of people are small, and the outcomes are critical in the short term. So, that's at least my view of it. But again, I'm just a commissioner, I don't make these decisions.

Zan Fleming:

Rob, on that point, the great one about the value of the cardiovascular outcome trials that have been done with diabetes, we are now seeing the prospects that these clinical agents will be targeted or even being targeted against other chronic diseases, including neurodegenerative diseases. The only problem is doing one indication at a time will take literally decades, as an effect taking now, to work through the lifecycle of developing these agents for multiple indications. So, that brings us back to the multi chronic disease composite. Would that make sense as a way to register an indication for age-related reduction and risk of multiple chronic diseases?

Rob Califf:

I think it makes a lot of sense, but I would add in the context that if we think about gating information content, as Bob Temple used to teach me in the good old days, the hardest thing is to show that a drug has a beneficial effect at all. **Because 90% of drugs that get into phase 1 don't make it to market because they either have off target toxicity or they engage the target, but without the effects that were expected, or other things happen along the way.** So, the hardest thing is just to show there is any benefit.

Once you've done that, as you accrue information with larger numbers of people, I think we will be able to expand the aperture because we're just entering the era now where I think we are much more confidently going to be able to use things like electronic health records and personal devices. We all have cell phones. I spent five years at Alphabet. **I feel like the technology's been there for a while and we're just developing now the rigor and standards of methods to be able to use these data for regulatory purposes and that's going to open up the ability to do much larger trials.**

I was just on a call with the India Consortium, this US-India consortium, and it's a different angle, but it's the same general idea. Their question was, why don't you do the trials in India? My answer was, if I lived in India, I would want a representative Indian population in clinical trials for drugs and devices that I was going to use, just like if I'm living in the US, I want a representative US population.

Also, increasingly, just to throw in another example that's in play right now, **this is an interesting day for Alzheimer's because Lilly press release came out and Zan, you know that I'm obligated and duty bound to say that we have to wait and see what the data shows, not just the press release, but If you assume that the data is going to look like the press release, now we'll have a mountain of data about reduction in the rate of decline of cognitive function.**

But then there's the question of who should be treated? Is it everybody? Is it a particular subgroup based on amyloid or some other characteristic? We're now at the phase of technology where I feel like we shouldn't be using marketing to make those decisions. **We ought to be generating evidence in the post-market phase. T**hat's not primarily in the FDA's lane, but I think around the world, whether it's CMS in the United States or tech assessment in Europe, there's going to be a push to get much more evidence and, we used to say, well, it's impossible because it would be too expensive, but we got 320 million Americans with electronic health records. I think it's pretty hard to say it's not possible to do it.

Zan Fleming:

But you are an expert in big data. Sorry, Jay.

Jay Skyler:

Yeah, but I was going to say that big data is great, but one also must be sure that there is compliance with whatever intervention one is looking at and perhaps big data can find that through the two kinds of sensors and apps but you'll recall, Rob, you were involved in the EXCEL trial where 41% of the people on the pragmatic trial were 41% of the people on the tested agent and discontinued and that

complicated the interpretation of that. So, how do we get around those things in a pragmatic and real-world approach?

Rob Califf:

Well, Jay, because of my current position, I can't get into an argument about the EXCEL trial, but I think if you look back, it came close to the...

Jay Skyler:

I agree. I count it as positive even though technically.

Rob Califf:

Yeah, and if you look at like long-term statin or ACE inhibitor trials in cardiology over time, people for a whole variety of reasons people discontinue the medication. EXCEL wasn't that different if you look at units of time as a metric.

But having said that, I want to be clear that **when I say pragmatic studies, I don't mean just taking observational data and trying to figure it out in hindsight. I'm really talking about, the word I've been using lately, is evidence ready systems.** If we look at the UK with COVID-19 compared to the US, the UK said we got systems, we have electronic health records, we can ask a question. We don't have to collect much additional data because we've got most of it in the HER but there is study specific data, and one element of study specific data is, did the person get the treatment that was assigned? For a very low cost, they reeled out study after study that showed us what worked and what didn't.

Meanwhile, in the US, the tendency was to do small studies that were not adequate to answer the question because the cost per patient was so high. Now I agree with the one point you made, when you get into chronic trials, it's harder because people move around. Things happen. You can almost certainly do better with adherence with study medication that people are coming in seeing the study coordinator. So, there's a trade-off there that we'll have to learn more about.

But I'm looking at things like gene editing is just an amazing disease modifying approach to children with rare diseases, but we won't know the impact of editing one gene on the sum of other genes until we got 20 or 30 years of follow up for these diseases. **So, we're going to have to develop the systems to measure things over time and the only part of this I'm a hundred percent sure of is that technology is not the limitation.** It is the human factor that's the limitation.

Jay Skyler:

Well, if you talk about wanting to have a healthy lifespan, that's going to be true for all these, that we need to have long-term follow up because it's not like testing a drug in rodents that have a short lifespan. We're looking at human beings and saying we're going to expand the healthy lifespan, but you need to follow them for their entire lifespan to know whether you achieved that. So, that is long-term follow up and you're going to need those kinds of large databases and sensors and medical records to be able to do that.

Rob Califf:

Couldn't agree more and I mean, I know throughout the questions that you all sent me in advance that you were thinking about, this is an underlying issue that we've just got to come to grips with. I think we have in rare serious diseases where the question was, **can you use accelerated approvals where there's more uncertainty by definition and confirm and follow up?** The answer is, at least in America, people have said, if there's a disease that's going to kill my child before they're even 10 years old, I'm willing to take more risk to potentially get a benefit.

But when you're talking about healthy people, we haven't come to grips with that yet**. There's a question, how much uncertainty is reasonable for people to tolerate?** I don't know. Your questions cause me to get philosophical, so I'll go ahead a bit and do it.

Zan Fleming:

Please.

Rob Califf:

I mean, you're aware that my career is, my academic career was mostly doing late phase clinical trials. I had the fun of spending a lot of time on portfolio selection and trying to understand preclinical and early phase data. But the work I did was mostly large clinical trials.

So, I saw so many things, 90% attrition rate, I was able to observe that happening. And every single one of those trials had some smart group of scientists who were a hundred percent sure that this darn thing was going to cure some disease or have an amazingly positive effect, otherwise you couldn't raise the money and get IRBs to agree to phase 1.

So, I think just having an expert's opinion that they're sure it's going to work is not enough. Then you say, well, if we got to wait 30 years to find out, that's also not going to work. Which is a point that I think we all agree on. I just say, between those two extremes, for therapies intended to prevent deterioration, that discussion, I'm glad you're having it, I would just say it's unsettled. **I would also say it's unlikely that the FDA is going to be the primary instigator of a decision about where to draw that line. That's got to be an argument among experts in society and a whole variety of people.**

I'll also point out that the Alzheimer's data begs the question, doesn't it? How early should you start, if you're at risk?

Zan Fleming:

That's right.

Rob Califf:

Who knows? Cause here's a treatment that has risks.

Jay Skyler:

Yeah. Well, it brings up an interesting point that if we're going to really move the needle in the field, we need geroscience's experts and regulatory science experts and policy experts, perhaps even from

Congress to get together and have some sort of dialogue and come up with a dedicated report that really lays the groundwork as to what directions we should be going. Would you buy that?

Robert Califf:

Sure. That's the American way and I think, I wish I knew 30 years ago what I know about Congress now, some of you did, but it is a system and you need to understand it to have an impact but regardless of any cynicism about politicians, et cetera, it is a fact that if there's a consensus in the population, it's likely in a democracy like ours to eventually end up with Congress passing a law and that's what happened with accelerated approval. As you know, it's also what caused Congress to add to the omnibus some new teeth for the FDA to sort of fix some of the things that weren't going right with accelerated approval.

Jay Skyler:

Can we think about also getting Congress to change its approach for nutritional supplements so that if they do a large-scale outcome trial, Cosmos enrolled 21,000 people and although did not reach the primary endpoint, they found a significant benefit for both cardiovascular death and for standard MACE and yet they really can't do anything with that, with the current rules. **Could FDA, with a little bit of push to Congress, approve carefully done studies with supplement and nutritional products like that?**

Zan Fleming:

Jay, just because even the commissioner may not know what Cosmos was, it still is ongoing, we're talking about a large trial of a nutritional product, the Flavanol extract. It's the largest trial you've never heard of and just so Rob knows, what we're talking about, in this case, a nutritional product and this brings up how do you have incentives on the food side who are doing these kinds of trials so that we do get the evidence?

Robert Califf:

Well, I did read your stuff and I went and found the trial. It's not published in the most widely read journal, I'll say that, although it has a nice,

Zan Fleming:

Well, I missed their primary end, which is [inaudible 00:31:53] numbers.

Robert Califf:

Yeah, and so I read it and we could have one discussion about what it means when you miss the primary endpoint and you hit a mortality endpoint. That's an interesting topic, but **I think I would surely agree that it's time to update the supplement legislation.** It's very old. There's a lot of resistance to updating it. It's on our legislative agenda that's publicly known. It didn't make it into the omnibus. **There are some very prominent politicians that are opposed to any changes because as you know, you can market a supplement now without any real notification of the FDA. There's no list of all the supplements that are sold and what's in them. There's no requirement for adverse event reporting**, and I think for foods in general where I've spent most of my time, I think all of you have probably read about that.

This year, part of the discussion we had about large trials, I actually think this Cosmos trial is in a way a groundbreaking thing because it was done by that Harvard group. My wife's been a participant in the nurse's health study. They do things at a low cost. They use a lot of the methods that I think are the way of the future, so I think **for a lot of things that people believe about foods, it's going to be possible to put those to the test also and we're going to need a regulatory framework to guide how people can promote those things.**

The simplest way I can say about my concern is if you can tell me what good for your prostate health actually means, then I might accept that the way we handle supplements right now is the right way. I have no idea what that means, but it's all over a number of products, so these structure function claims, they're not interpretable in a health context, but for that law to change, it's going to take enough people agreeing with me, which right now there's not.

Jay Skyler:

So, one of the things I hear you saying and agreeing with us is that Kitalys needs to convene a group of geroscientists, include some regulatory people, some policy people, and come up with some sort of overlying document that would give direction of what might be desired in this space.

Robert Califf:

Someone should convene and what my advice is make sure that if there are prominent naysayers and legitimate disagreements that those are accounted for, because it's not a consensus if you have a group that anoints itself as a consensus group and then excludes people who have status in the field, and I recognize that can be difficult. So that's my only advice about, and I used to spend a lot of time convening groups like that as I think you know. I think it's kind of fun because when the question is, it's not just theoretical, you're going to apply it to something that might be a treatment, the discussion gets interesting quickly.

Zan Fleming:

Well, that's great advice Rob. We definitely tend to work in our own silos and hear our own opinions being echoed in working with those but we do need to hear a wide range of opinions.

Jay Skyler:

So, I think we've hit a few of the key things, one of them that we came close to when you were talking about big data and collecting those things is whether AI might have a role in all this in terms of looking at the data sets at least, or of coming up with directions to go in. What's your thoughts about AI in the future?

Robert Califf:

Well, again, considering that I worked at Alphabet for five years and I'm far from a technical expert and I'm not a coder, I'm not a computer scientist and in fact, most of my career has been working with people that are in that field and statistics to get clinical trials done. So, I feel like a sort of intuitive sense of where things are headed and the first thing to point out is **AI is pretty much built into so many things we do already, and we just don't realize it** because it's been in installed into systems that we routinely use. If you're trying to figure out where you're going to drive, you're probably asking your phone or your car and that's like one of the best examples of use of continuous AI you can

possibly see, because it's adjusting your route in real time based on data coming in and its knowledge of your preferences which accrue over time in the instrument.

I give credit to things that were done at FDA when I wasn't here, was the general schema for how to regulate algorithms in AI, which is very focused on something that I saw in real time at Alphabet, which is no matter how good your algorithm is at point A, by the time you're three months down the road, if it's applied in real life, the operating characteristics to that algorithm are going to be different and so, you've got to measure the operating characteristics of the algorithm, which means in essence that you need a learning health system in place to make sure this doesn't go awry.

Now, when we take large language models in generative AI, we get into an acceleration sphere that even, you probably saw that Hinton retired from Google, not because he was scared of what Google was doing, but he felt he needed to speak out and he didn't want his opinions to be conflated with opinions about Google specifically. **Generative AI is the big game changer that we've been waiting on, but it also has a real risk of getting out of control in a way that none of us will understand and so, we're like a lot of people having to think about what we will do to regulate this.**

I don't see AI replacing clinical trials because I think causal inference is still just a very difficult problem. I see it making clinical trials easier and easier to do, modeling clinical trials so you can do the right clinical trial will be better and some of the greatest issues just going to be like doctors may actually be able to talk with patients now because they won't have to be copying and pasting all their notes that can be generated using large language model and doctor can just check it, which is one of the biggest problems we have and also one of our biggest problems in clinical trials, if you survey practicing clinicians now, they're under so much pressure to complete their charting that they don't have time to talk to patients about risks and benefits of new potential treatments.

So, I'm really excited about it, you can tell, but we need to be wary of the risk involved in this new generation of AI, which I sort of saw happening five years ago, and it's amazing how quickly it's coming into play now.

Jay Skyler:

Indeed. So, since everything here that we're talking about, if we're going to be successful as cross-disciplinary, are there other federal agents who should be involved in developing the consensus documents that we mentioned and for example, the FTC might have authority on what supplement companies say, the other agencies, you mentioned CMS earlier. **In diabetes, we have a trans government task force for type 1 diabetes, which covers that, which includes FDA, CDC, CMS as well as several NIH institutes. Is that kind of cross-government activity potentially going to be an approach that we could use to help in generating a consensus statement and where we ought to go and how we approach Congress?**

Robert Califf:

Yeah. I would take it for granted that if you're going to have a consensus, it's going to be persuasive. **You got to have CMS and NIH and probably CDC.** I mean CDC is less generally involved in therapeutic interventions, but you're talking about prevention where CDC has a major role. Thoughts about FTC are interesting. I'm more and more aware of FTC. So yeah, I think there's sort of a core group of trusted

entities that need to be on board. I mean, one other thing I'd say, in addition to being inclusive, I think you'll find that sometimes the best way to proceed is to clearly identify where there are differences of opinion so that you can over the course of some reasonable period of time, resolve those differences or come to some consensus, but having the other federal agencies involved I think is important.

You're aware that the nomination for NIH director has not been made yet, but there's certainly intimations that it may be someone who's very involved in clinical research and clinical trials, so there may be a real opportunity here for collaboration on a broad front.

Jay Skyler:

Indeed, cancer clearly is one of the things in aging that we need to think about differently than some of the other chronic diseases because there's so many different cancers, but obviously needs to be considered. Zan I think we're at the time that we said we would have Thomas...

Zan Fleming:

Well, that's right. We allotted 15 minutes for Q&A, and we will start with our panel, which we've assembled. We've got a diversity of experts and we even have a professional journalist, Kate Rawson, who co-founded the Pink Sheet. We'll give her the first question for Rob.

Kate Rawson:

Thanks everybody so much. Zan I would be about a hundred years old if I had co-founded the Pink Sheet, but I did help launch the Pink Sheet Daily.

Zan Fleming:

Sorry for the mistake.

Kate Rawson:

No, no. The Pink Sheet was founded in 1939, and I dabble with provision policy but contribute to the Pink Sheet and I know Sarah Carlin Smith is on here as well, so good to see her name. Commissioner, it's always great to see you. This is an interesting topic and one that we haven't delved into a provision policy that much, so happy to be here and learn some things about healthspan products. So I guess my question would be: 'I hear what you're saying in terms of the importance of outside convening, that this is something that the connect maybe the Duke-Margolis or the National Academies need to work out, but I wonder if it's also an opportunity for FDA to get involved and where do you see the agency's participation and as a first step?'

Robert Califf:

Well, I'll just say **wherever there's scientific discussion and policy discussion about medical interventions, the FDA is and should be involved, but I don't think FDA should be leading a field of science.** I think the best view of the FDA is that we're referees and we have opinions, and it's good for FDA scientists to stay abreast and to be involved in the opinions but I think there's a reason that we have an NIH and that we have a vibrant industry that invents and tries new things and that's where the push should come. There's one special area where I think FDA should lead when there's a clear pathway and I would just point to Rick Pastor as a shining example of that, but Rick was not inventing

the drugs or inventing the scientific paradigms, but he was looking at where the field was headed and providing runways that you could say enable industry or help industry go down a pathway that has been very successful.

That's a particular area for FDA, but what you're talking about, **FDA should participate, but we're not here to be a research science organization. We do research, as you all know, but it's regulatory science, not discovery science.**

Kate Rawson:

Can, if I could just add one follow on, and then I'll mute myself. So, we have some industry folks and drug sponsors on this call. If I'm a company that's interested in this field, how do I get started? Who do I reach out to at FDA to make sure that if I'm thinking about trials or endpoints, who's my best person for that kind of expertise at the agency?

Robert Califf:

It so much depends on what the product is that you're dealing with and if, you brought up supplements, if it's a supplement, then we're going to have to invent something new to deal with this, because there's not a pathway for what you described as you pointed out, but if it's a biologic or a drug, you'd have to ask the question: 'what is it primarily oriented to do' and just go to that part of the FDA. I think most companies know where to go with that.

Zan Fleming:

With that point, Rob, almost inherent in this field, that if it's truly a geroscience intervention, it would hit across multiple therapeutic areas. So, the question comes up, **should there be a division or even an office at FDA that would take care of these approaches as well as age-related standard indications like frailty, cachexia, and related metabolic conditions?**

Robert Califf:

Well, it's a hope of mine, Zan, that we'll develop an approach to aging, not for this part of it so much, and I'll come back to that, but as you said what's the right dose of a drug for a 90 year old person in general, I don't think we have much evidence to get this right now and it reminds me of, I was very involved in the pediatric rule and all that work, which I think has been pretty successful, still some more to be done. **I think we do need to focus on aging more.** I was part of a group that was advising the FDA and we wrote a paper on it. So, I've got a written record on this. For what you're describing, I don't think the time is right yet to allocate those kind of resources, but I think as the field evolves, it's a possibility.

Zan Fleming:

Steven Austad is the scientific director of the American Federation of Aging Research and an expert scientifically in other ways and I'm going to bring Steven up for a question.

Steven Austad:

It's true. Thank you. I think the pathway for certain types of, let's call them anti-aging drugs, just drugs that presumably are targeting fundamental aging processes in terms of addressing specific diseases, I think the pathways are clear; what's unclear to us in the field is there a way to approve drugs to give

perfectly healthy people, so far as we can tell, to slow their progression. It's almost like who do you give the Alzheimer's drug? Let's assume we have an Alzheimer's drug. Does everybody get it? Does somebody, only people with MCI and how do we define MCI? So, do you see any way to think about drugs that are not directed at specific diseases and would have outcomes that are not directly related to specific diseases or disabilities?

Robert Califf:

I've been in many discussions about that. Remember that Calico was a branch of Alphabet and I spent a lot of time talking to Hal Barron when he was there, and I don't have any particular wisdom on this. It hurts my head to think about it and if people think that there's going to be a drug that will reduce aging without affecting any particular disease any more than any other, we're going to have to come up with some way to deal with that. I don't have a magic potion for that right now. We do have something called the National Institutes of Aging. I spent three years on the council of that organization and like I say, I think **FDA-NIH collaboration is going to be a big part of whatever happens in this field.**

Steven Austad:

Thank you.

Zan Fleming:

We have another very well-known expert in the science field, Dr. Nir Barley, who I hope can come off mute and ask a question. Nir, if you're not able to do that immediately we'll come back to you. I'd like to ask a professional drug developer, Dr. Joan Mannick, who has probably taken an agent as far as anybody else in the field of neuroscience in her case aiming at reducing the risk of upper respiratory infection. Joan, how about a question from you?

Joan Mannick:

Sure. So, I was really interested in the comment about evidence ready systems that were available in the UK but not in the US during the COVID-19 pandemic. Do we now have those systems available, because part of the problem, when we try to do trials, geoscience trials where we're usually trying to prevent something, we need these huge expensive trials and the costs are formidable, but if we could decrease the cost, as you suggest, are the systems in place; and two, lots of times the FDA wants a lot of safety monitoring, which becomes tricky because you'll keep on having to either go to the homes and get blood or bring people into sites, which adds to the expense. Is there any shift in how people are being monitored in trials within the FDA?

Robert Califf:

Well, so there's no such an evidence ready system now, that's a goal and I was trying to get across it. If we end up with an NIH directory who's interested in this, and I know there's interest at CMS for the reasons that we've discussed, there's a possibility that, and now with the technology where it is, this is something I wanted to do my whole career. So, I'm hoping that we'll develop such a system in the United States. I mean, another thing to keep in mind, the way I say it often is for COVID-19 treatment, the UK set the pace. We all know that with the recovery trials, but when we wanted to know what to do with the next dose of vaccine, we called Israel because they have just in time electronic health record data on the whole population-essentially that's kept up to date and they add extra things to it if needed, but the minimal amount necessary so that it's within a cost range.

Now, I'd have to say if you got a novel molecule that you're going to give to human beings on a large scale, the early part of it, the first X number of patients, whatever X is, there can be a healthy discussion about that, I don't see that changing because you don't know what's going to happen. If there's anything I'm a hundred percent sure of is that mother nature is a lot smarter than we are. Just ask any drug developer who's been through the mill, but I think the difference is, for whatever reason, we've tended to say for the next 50,000 people, you still got to collect everything and get all those blood tests and I think that's where we can use things like artificial intelligence and technology to do things remotely. This is old Zan, and you were part of these discussions way back. If you've measured how often people get hiccups in 1500 people and it looks like the general rate of hiccupping in the general population, you don't need to measure hiccups anymore.

You're just going to have to look for rare events that can happen once in 10,000 people. It may turn out to be important. **There are so many ways we can reduce the cost to make these studies possible, but I don't see it changing in the early phase. We need to do all that stuff.**

Joan Mannick:

That makes a lot of sense and I'm wondering, Zan that is in part of this group's initiative that supporting the evidence ready systems and that in the phase 3, after you've established safety profiles, having less monitoring, so that it's feasible to do these healthspan trials with prevention endpoints. It'd be a nice thing to get consensus on.

Zan Fleming:

Yeah. The large pragmatic, well controlled trial.

Robert Califf:

Yeah.

Steven Grossman:

Commissioner, I'm interested in the issue of NIH-FDA coordination here because there's a risk as there have been in other fields **where NIH is funding research that makes perfectly good sense but is completely unaligned with what will be needed in the regulatory process** and in this area where it's all over the place to begin with; is that something FDA would participate in, if there was a conference on that? Is there somebody who could be appointed? A point person who could respond to these inquiries? Because we can't call you every time, I know that.

Rob Califf:

I never had trouble getting FDA people to come to the meetings that I had, so I'm sure you could find the same thing. It is a hard question to know which person would be best, but we've got some. **The medical policy opposite FDA right now is first-rate in my view, and they'd probably be the place to go for general discussions about policies that are not yet baked.**

Steven Grossman:

Chief medical officer.

Rob Califf:

We got a great chief medical officer, Hillary Marston, who is new and a phenomenal internist who also worked closely with Tony Fauci for some years and then in the domestic policy council. She knows a lot more about the federal ropes than I do. I'd also recommend our chief science officer, Namandje Bumpus, who gave up an endowed professorship at Hopkins, was the department chair of pharmacology to become the CSO at FDA. She is a phenomenal person. I feel like we got an arsenal of great people who can think very broadly and also deeply about the science and clinical issues, but I'll grant you, we got 19,000 people, so you got to think about who you engage on what topic.

Zan Fleming:

We'll tell them that you sent us, Rob, when we ask for their participation. There are so many questions in the chat. We would love to get to all of the questions, but I know that you're going to have to run in a minute, Rob. I wonder though, Rob, do you have any other closing thoughts that you would like to say?

Rob Califf:

As you might imagine right now, to be completely transparent, we have the pandemic preparedness hearing with the Senate tomorrow, so that's what I'm mostly thinking about. You guys are second in my thoughts right at this moment, but in terms of your interest, this new class of Alzheimer's drugs, again, I want to be perfectly clear, sometimes the press releases and, when you see, the actual data turn out to be different. I don't think that's going to be the case here, but we'll see. With that caveat, that is going to raise a huge number of questions, which I think are closely related to what you're talking about. **If I had a family history of early Alzheimer's and I was not yet affected, I would be asking the question: "Should I be starting this?"**

Of course, we don't know, because the trials haven't asked that question. They're going to be addressing some of the things that you're raising. As you well know, **the first big obesity without diabetes outcome trial is going to be reported soon and it's going to raise a lot of the same questions. As far as I know, the mechanisms there are very complicated, so we know the systems that are involved but we don't really know how the mechanisms play out, but it seems to be a general effect on a lot of things that are impacting chronic disease**. It's a fertile time to be talking about this and I'm glad you're doing it.

Zan Fleming:

Rob, we can't thank you enough for spending this time, particularly on the eve of a big hearing for you. Gosh, you've got so many issues swirling around. We admire what you're doing, it's great to have you spend some time with us. We have a lot of people who are going to hang on, we'll keep the discussion going, but you gave us great food for thought. Again, we thank you so much.

Rob Califf:

Thanks so much, have a good rest of the meeting.

Jay Skyler:

Thanks, Rob.

End of FDA Commissioner 'fireside chat' on healthspan products

Roundtable discussion by a panel of geroscience experts and other stakeholders in healthy longevity products

Jay Skyler:

In his last comment, Rob raised the issue of basically **the GLP-1s and their spinoffs that have been looked at for obesity. They've already been shown to work in type 2 diabetes, but once you point out they're being studied for nutritional liver disease, NASH and NAFLD. They're being studied for neuroprotection and neurodegenerative disorders. They're being looked at across the board for so many of the things that contribute to aging and they may be the first shot on goal that we have of things that may take multiple approvals, that would get through for a potential anti-aging approach.**

Zan Fleming:

Yeah. Jay, as you know better than anybody else, because you were right in the middle of it, the first GLP-1 agonist was approved back in the early 2000s.

Jay Skyler:

April 28th, 2005. 18 years ago last week.

Zan Fleming:

There you go.

Jay Skyler:

I've won one ever since.

Zan Fleming:

Yeah. We've been 20 years since then and we've added DV and weight loss indications, but it's taken us that long to get to what could be as multimorbidity global indication.

Jay Skyler:

We've got Nir on the line and he's doing the TAME study, we're leading it, which tries to look at multiple chronic diseases simultaneously. The questions are: “Can you get approval if you just stop one of those? Do you need to stop several of them? How long do the trials need to last before you can really get a regulatory decision?” I don't know. Nir, we're now seeing you on your iPhone, so welcome. Maybe you'd like to comment.

Zan Fleming:

Yeah. Nir, we tried to frame you on earlier, but go right ahead.

Nir Barzilai:

I heard you. I didn't know that there's a plan for asking questions and I was dumbfounded by the fact that Steve Austad's question caused him a headache. There's nothing I could do then increasing his headache. In fact, in retrospect, we could have started by presenting rationale for a TAME trial and then asking him to say something, because obviously, he's not educated in geroscience like us. I wish we could have used it better, but if you would come back to me, I would maybe try to ask it differently.

There are several drugs, the GLP-1 was mentioned, Metformin, SGLT2 inhibitors who are target for one disease, but when you give them to animals, they live longer, when you give to humans, they affect cardiac, kidney outcomes, overall mortality. So, maybe to think of studies where we can repurpose a drug for an endpoint that Steve Kritchevsky will talk about later, I'm sure.

That would be my question. I don't think he really got the fact that we're talking about prevention and it's better to prevent sarcopenia, frailty, it's much harder to treat them. These would be the points of discussion that we missed, but let's get better with time.

Zan Fleming:

Yeah. It is a lot to take in, and to be fair to Rob, he does understand that we are looking for deep roots that drive these multiple chronic diseases and the aging process in general. He is being pragmatic and saying: "You've got to have evidence that the product works and we don't know how to call that yet," so that's a big challenge for him.

Mark Mattson:

Yeah. This is Mark Mattson. It's not surprising that a drug, like the GLP-1 agonists, were developed at NIA when I was there. Josephine Egan and Nigel Greg took the lead in developing these for neurodegenerative disorders and collaborated with Tim Toltini on the Parkinson's trial. If a drug improves insulin sensitivity and reduces obesity, it's going to extend lifespan assuming there's no long-term side effects, because we know that obesity and insulin resistance shorten lifespan. The animal studies, the control animals are unhealthy in the sense that they're overfed and they don't get any exercise, so their lifespan is presumably less than it would be in the wild, assuming they didn't get killed by predators. You're talking about targeting pan-aging things that affect all organ systems. You had such short time with the FDA commissioner, but biomarkers is still the key thing in the aging field. Are there clear biomarkers of aging that can be reliably measured and have been established to..

Zan Fleming:

Mark, we do want to go back to biomarkers in just a moment. That's a really hot area and very important. First, let's have Steve Kritchevsky, who is a preeminent biostatistician, has been very much involved in this geroscience field, and has done a lot of deep thinking. Perhaps he could take Nir's remarks and maybe appropriate some of your own thoughts, Mark. Steve, talk a little bit about the concept of a multimorbidity composite endpoint.

Stephen Kritchevsky:

Sure. Thank you for the promotion of biostatistician, I'm really trained as an epidemiologist, but notwithstanding. When we started thinking about the **TAME trial, convened quite a big group to try to talk through an endpoint for any intervention that slows aging, with the mind that it should be something that the FDA would also be interested in. In our conversation with them many years ago, they would not recognize or didn't think aging, per se, was a philosophical issue and not something that they were that interested in, but a composite of clinical endpoints was very much in game and very viable as a way forward.** We started modeling that as a potential endpoint and our design for TAME represents our thinking on that, and that is you need about 3000 people for about five years to see a 20% difference in the emergence of new multimorbidities from a list of 5.

Now, that endpoint is a subset of several potential indices that are made up of many more kinds of endpoints than the 5 or 6 entities figured in the TAME endpoint. We're also working on those in the hopes that it would require somewhat less people, but FDA's interest in it is less clear, because it is a mixture of things that are clearly clinical, "Yes, no" situations, and some functional ones as well. This is an important discussion to have, because **if we don't know what an endpoint is for the trial we're going to do, we don't know how to tune our biomarkers to predict it and we don't know what biomarkers to include in our studies to see if they could serve as surrogate biomarkers.** These are a knot of considerations, a knot of things is all tied up together, and the answer to one unlocks several of the others, so, we cannot have a validated surrogate outcome biomarker until we know what the outcome is. That's all.

Zan Fleming:

On that point, it's so important**. A lot of progress is being made in developing biomarkers and we have biologic clocks that are very well correlated with aging and clinical outcomes, but as you say, and you make the key distinction, they've not been validated against a change affected by an intervention.** That's the big hold up, that's the big challenge of developing biomarkers for use of surrogate endpoints.

Steven Austad:

Could I just say something here?

Zan Fleming:

Yeah, Steven, go ahead.

Steven Austad:

When we went to the FDA about the TAME trial, we were successful at convincing them that we could do a trial that would tell us something about preventing multiple diseases. The much tougher question, we were purposely choosing people that were not very healthy for that trial. That was the whole goal. We were thinking: "God, what would happen if we got a bunch of health nuts in the trial? It would destroy everything," but in fact, what we want to do is preserve health. **Ultimately, we're going to have to find a way to address people not that are obese or already have lots and lots of risk factors, but people who are also quite healthy, but want to stay that way.** That just seems to me like a really tough nut to crack.

Zan Fleming:

That's right. From the standpoint of event rate and healthy population, it's going to be very hard to move the needle.

Joan Mannick:

I was going to say, that gets to his evidence-ready system and decreasing the burden of those late-stage huge trials. I do think that's at the center, when you think about it, of **what's stopping us from being able to move forward in a health span, disease-prevention indication in healthy is decreasing cost of trials.** It's major to be able to push for that. Since Rob already seems on board with that, that seems like a politically good torch for us to start carrying. I don't know what the right phrase is.

Stephen Kritchevsky:

Carry the banner forward.

Joan Mannick:

Yeah.

Stephen Kritchevsky:

The first trial of a cholestyramine was in men only, in the 95th percentile of LDL. Once that happened, as news of better treatments got discovered, what became treatable kept lowering, lowering, and lowering. Same with hypertension. The definition of it went from 160 back in the '50s, incredibly high levels. As treatments became safer and better, what was hypertensive got redefined down. Now, probably 60% of the US population qualifies for treatment. **If we had something that worked in a high-risk population over time, that would work down through the population to cover more and more people**, but you can't do the efficacy trial on average people, because you couldn't afford to do it.

Zan Fleming:

Not with conventional trials. Go ahead, Jay.

Jay Skyler:

Steve, that raises an interesting sidelight issue. In the 1970s, up until early 1972, we in the United States used the World Health Organization definition of hypertension of 160 over 95. In 1972, the US alone, without the rest of the world, changed to 140 over 90, and the overall cardiovascular death rate declined in the US over the next 10 years and not in any other country, showing that that was wise. The reason that it became so effective was we had the National High Blood Pressure Education program, where people went into churches and schools all the time to know your number for your blood pressure and to get people on board to do those things. Maybe, **as we talk about aging things, we need to think also about the communication strategy or how we bring it out to get everyone involved, so that they really are interested in seeing products that will create a more healthy lifespan**, or really paying attention to keeping your physical activity, your mental activity, and your diet in mind, so, that you can do it with lifestyle issues.

Zan Fleming:

Again, it relates back to the point the commissioner made and then Don, in effect, seconded. We need systems that are ready to affect the results, whether it be a clinical trial that can answer the question or whether it be implementing the use of the scientific knowledge we know that will improve health. I want to back up a little bit to bring in Dave Fox, who thought deeply about the regulatory structure and function in facing healthy longevity products along with Steve Grossman, who was involved in developing the Orphan Drug Act. One could imagine that there could be such an act that would facilitate or incentivize the development of products for achieving healthy longevity. David and Steve, you were at the FDA and the Department of Health and Human Services, respectively, in key positions. You've thought about this. How do you see the differences between developing therapies for disease and actually preventing, or we should say, reducing risk of chronic diseases and in general slowing the aging process?

David Fox:

Thanks, Zan. Actually, Jay's last comment really was an eye-opener, or really puts his finger on it. If I understand that, the public health community in the US made an adjustment to the goal, to the target, not knowing necessarily that it would have an effect, but then validated afterwards through actual experience, that it significantly reduced death rates. So, the public health community looked at some metric that they thought was reasonably likely to have a positive impact, but they didn't have the data, but they went ahead in the face of uncertainty. Not naked uncertainty. The commissioner talked about consensus among experts sitting around a table but looked at the metric and thought: "We can do better, and if we do better, people might live longer or be healthier", and they were right.

I thought it was very interesting, the commissioner started his presentation talking about uncertainty and accelerated approval, and how we tolerate a high level of uncertainty when the outcome is so immediate and so dire. **It all comes down to whether we can encourage the regulators in the absence of congressional action to also allow for a degree of uncertainty in another area where people have an interest, which is in living longer, healthier lives.** Also, who is the guardian of that decision? Is it the staff at FDA? The commissioner admitted he has no control over the staff at FDA. Is it the commissioner's office, or is it the community at large?

Steven Grossman:

In terms of who, he answered the question. If we go to scientists and the chief medical officer and say he sent us, we've got our entry point.

David Fox:

Yeah.

Steven Grossman:

I was more taken with his initial comments about: 'You need to have it really well-thought-out and with some evidence before FDA's going to engage in path making'. This is still a problem, because I don't think people know where we need to get to. What was I taught? When you don't know where you're going, any path will do. **There is much of that in the field that needs to be conquered, it should be conquered in concert, in conversation with FDA and NIH, but we need to be bringing it to them to a degree soft-packaged. I thought that's what I heard him say and I think it's right. We need our path. They're not going to tell us.**

Zan Fleming:

Okay. Saima Khan, your question.

Saima Khan:

Hi Dr. Fleming. Thank you for that and for pronouncing my name beautifully. I'm, from the regulatory angle, a little bit disappointed with the approach that the FDA's hands are tied, we need consensus from the clinical community, and you guys lead the way on technology. It's the same rhetoric we use on here and it's a little bit passive. We've learned so much in the space of all the diseases that you covered here, cardiovascular, metabolic, Alzheimer's, et cetera, and we know that there are certain interventions that the majority of responders will benefit from, and we've taken risks. We've had big cohorts of data from Framingham studies to other large trials that have helped us to qualify that the

risk or the uncertainty was worth taking and that you can make a treatment, a pharmacological, a diet and exercise intervention based on risk factors.

We also seem to be in this inertia for decades around cardiometabolic disease and the metabolic syndrome, and we know full well that there is a relationship and a correlation between metabolic health and neuroprotection. Certainly, from my point of view, we should continue to request the FDA to invest in pathways that will enable geriatric drug development, and we might have to bucket this. There's lower hanging fruit, there are broader implications, longer-term earlier intervention, and access issues, but it doesn't mean that you just don't do anything. If we take it by disease state, and I think one of the questions was around, where do we go? Who do we contact? It was very much: "You pick a disease, and you pick a division."

There are so many good examples in the FDA where, for example, centers of excellence, accelerating certain technologies and disease types, or looking at different pathways. Even maybe if we look at the pediatric regulation and how that came about, is there something that we could be pushing the FDA to do in terms of having an above division approach to certain conditions that we know either there's a clinical pharmacology, there's a disease prevalence, there is a bigger clinical consensus around certain biomarkers? Take it in that multi-pronged approach to get them to sit at the table, and B, less didactic about disease A, disease B, endpoint this, and acceleration that.

Sorry to wax on a bit, but I do feel as though we need to continue that pressure, keep asking that, and that the consensus and partnership with the FDA should be in parallel to the FDA taking a slightly different lens to how they are treating this population. It's not just about healthy living, it's about addressing high morbidity and mortality issues that we have with a population that is either defined as elderly, over the age of 65, or whatever, cutoff you want. Sorry to sound quite passionate about it..

Zan Fleming:

Saima, we will sign you up. Great to hear from you.

Saima Khan:

Thank you. Thank you.

Zan Fleming:

Please, stay in close touch. Carl Pledger, I see you've got your hand up, we'll come right back to you. Since Saima mentioned what FDA should be doing, I don't think we should be too parochial, there are other major regulatory authorities in the world. I don't see anybody from MHRA or EMA on the call. I may be missing it, but Tina Woods in London: “What do you know about what MHRA is doing in this regard? Can you bring any light to the MHRA approach if there is one?” You've done wonderful things in other sectors in Britain. But great to see you, and tell us what's going on there.

Tina Woods:

Great to be here, and to be part of this fascinating discussion. So, yes, I mean there's quite a lot on the cards from a regulatory perspective in the UK. Coming out of Brexit, there's a huge plan linked to our science and tech ambitions to become a superpower, et cetera. So, there's quite a lot of items

sort of being looked at and being passed through legislation now from sort of looking at personal data marketplaces and looking at creating a more effective digital market.

We're looking at digital clinical trials. One of the seven health challenges in the life sciences strategy is on the biology of aging. In fact, a call that we had last week at the Office for Life Sciences, they're very keen on looking at aging biomarkers in clinical trials. So, we're having ongoing discussions around that and of course, linking it up with other sorts of reforms in finance, for example, pension funds being able to invest in more high-risk sort of innovation areas and the MHRA, of course are revisiting sort of device regulation.

So, what we're interested in is **linking up the science and the technology with the possibilities to unlock innovation and sharing data at scale to fuel our ambitions to achieve increases in healthy life expectancy**, minimizing health and wellbeing inequalities, all linked into the government manifesto commitment, which is very much at the heart of policymaking. Also, linking up to some of the innovation clusters that we're trying to unveil around the UK in sort of more deprived areas. So, it's all trying to join everything up around the possibilities of science, technology, linking health and wealth and so forth. So, there's quite a lot.

It's an interesting time and we've just launched a healthy longevity innovation mission and speaking to colleagues around the world. In fact, I was just on a call before this one, meeting some people out at the Foresight meeting last week in San Francisco, and trying to galvanize attention. Seeing the UK sort of ripe to become a sort of so-called 'world test bed' for health.

So, I'll be reaching out to many of you on this call and very interested in looking at the possibilities in the UK situation and teaming up with what's happening in the US. I know Zan, with Thomas, and we've been having lots of conversations about learning from each other, which will continue, and I think it's a really interesting time right now to look at all this, certainly in the UK context, which is ripe for lots of possibilities.

Zan Fleming:

Tina, thank you for that wonderful summary. You've actually taught us more than we've taught you, for sure. The UK is leading the world in its national policy formation and action, and largely in part to you and the All-Party members who have gotten behind this across the nation [inaudible 01:30:21]-

Tina Woods:

Well, there's a huge community behind us, which we've been growing substantially. So, I take my hats off to many people who have been committed to the cause.

Zan Fleming:

Well, thank you so much and we will keep working together. Let me now go to Karl Pfleger, who's eight times zones away in San Francisco. I know Karl, you'll have a point about biomarkers.

Karl Pfleger:

No, I want to ask the question that I asked in the chat, which was never directed at the commissioner, it was more directed at the rest of the community here. There's a lot of argument about whether aging should be considered a disease. **I think as a practical point of view, the better way forward is to look at these subparts of aging cause we know that it consists of a bunch of different molecular pathologies, and I think that many of those, if you look at them, look like they should be considered to be diseases.**

So, I'm not an expert on how things get classified as diseases, but I want to know whose job it is in the community, in the field to work on this? So, for example, accumulation of persistent long-lived senescent cells, everybody thinks this is hugely causally influencing a lot of different important health endpoints and just like accumulation of cancer cells is bad, accumulation of senescent cells, cannot be a disease but it seems like it can.

Fatty thymus disease, the thymus involutes, and everybody knows that it is important for immunity and T cells and lots of clinical outcomes and just like we have fatty liver disease, it seems like the analogous disease for the thymus should be a clinical indication itself. So, who should be making that case? Who in the field should be pushing that and how?

Zan Fleming:

I must push back a little on that premise, Karl. There's a difference between cancer cells, which we know will kill you, and senescent cells, which we have good reason to believe are harmful. Yet we don't know exactly what will happen when we get rid of the senescent cells or whether there may be off-target effects in doing so. So, I take your point that there is a kind of continuum-

Karl Pfleger:

The bar for off-target effects is broad if the analogy is chemotherapy.

Zan Fleming:

Well, again, it's matching the problem with the solution. For a life-threatening disease, you have to be willing to take more drastic measures. But here's the essence of the problem. We're talking about preempting disease with a healthy population, where you have a very different benefit/risk consideration. That's the real challenge. It's not that it's right or wrong, it's just a statement of fact.

Karl Pfleger:

Some people who have fatty liver seem healthy, apparently, but we know they're not really. The same thing is true of thymic involution. There's no such thing as a

Zan Fleming:

People with fatty liver disease die mostly of cardiovascular disease and so it's not necessarily the liver disease that kills them. It's complicated. I'm not going to say that you should treat everybody who has fatty liver disease with a drug that has a dicey safety profile, it's probably not true.

But thank you, Karl. You surprised me. I thought we were going to talk about biomarkers. I would like to have our panel turn to biomarkers and that is a hot topic, one that is so important to developing

therapies or intervention sooner than later for preempting chronic disease. So, let's start with Steven Austad, who is certainly in the thick of this area of endeavor.

Steven Austad:

I mean, it's clearly at the top of the list I would say of basically aspirations in the field to get a panel, or in the best case, a single biomarker that can track the rate of aging. We have some candidates. The trouble is how do you validate them? It's not the same as validating a cancer biomarker. But, again, I think there's a lot of effort. AFAR has got a major initiative to try to develop biomarkers and tons of people are working on them.

I'm sure that Altos Labs is working on it. I'm sure that Calico is working on them. But it's the number one thing that we're missing that we need to develop. The NIA put a hundred million into developing biomarkers 20 years ago and came up with nothing, but in fact they didn't have the tools that we do now and I'm quite convinced that we will be successful. But right now, if I had to say, the number one thing that we want to throw money at to figure out everything else about aging, is going to be biomarkers, because that would accelerate the pace so much.

Zan Fleming:

Well, back to Steven Kritchevsky, who understands the challenge on the practical level of validating biomarkers against clinical outcomes. Can you, walk us through that, Steve?

Stephen Kritchevsky:

Yeah, I will. I would just mention that there is guidance from a joint NIH/FDA working group that delineates seven different uses of the word 'biomarker'. I think it's relevant here because I'm not sure when anyone says that word on this call, it's the same thing that someone else is hearing when they're on this call. The biomarkers that is the holy grail are surrogate endpoint biomarkers. So, these are things you could measure quickly after an intervention that would give you a reliable readout of whether that intervention was likely or was going to have a benefit for whatever clinical outcome it's tuned to.

So, we don't have those in this field because we don't really have an intervention that is shown to be proven effective. We need that first. Now, one step back from that are what are called reasonable surrogates or reasonably likely surrogates and you need a couple of things for that. One is it has to predict the outcome and your intervention has to change it.

So, the intervention you're proposing deflects it, and high and low values of that predict the outcome that you're trying to affect. But you still have to do the whole study to validate it completely. But it is a place to get started. We went through that exercise in TAME, and there's a paper applying those criteria and there's a paper by Jamie Justice that shows the result of that activity, and it is a framework. We're not saying those are the only potential biomarkers.

Is there going to be one biomarker? Probably not. It's probably going to end up having to be an index. It's complicated by the fact that different organs may age at different rates, that there is not

necessarily unitary aging across every aspect of us and so that would also push you towards some kind of composite or index.

But we've got a ways to go. So, there's a lot of promise. **I do come back to a point I made earlier. It'd be nice to know what the endpoint of the clinical trial is that we want the surrogate for, so we can start looking for biomarkers related to that a**nd are trying to start a process to develop some consensus among clinical trialists at least of what some elements of that endpoint might be.

Zan Fleming:

Thanks Steve. Joan, you were on the bleeding edge of developing a surrogate sort of as you were flying the plane and you had some, oh, gears switched by the FDA on you. Walk us through how you were dealing with this issue and what it came down to.

Joan Mannick:

I would say we could always see that mTOR inhibitors upregulated the antiviral gene response and what we wanted as an endpoint, so I'm not sure this was a biomarker issue, was lab confirmed viral respiratory tract infections. It just happened the FDA, this was pre-COVID-19, wouldn't let us do nasopharyngeal swabs, because they said no one in the real world got a nasopharyngeal swab when they got a respiratory tract infection. So, we had to just use symptoms as an endpoint that were noisy, and we missed the endpoint.

Back to what Steve was saying, I'm not sure the problem is we don't have biomarkers. I think **what we're missing in the field is an endpoint to validate the biomarkers against, which was what Steve was getting. So, we're stuck being unable to validate surrogate biomarkers right now. So, the clinical is what's holding us back.** We need more successful trials showing that we are moving aging related conditions, and either preventing or treating that, then we can use the biomarkers to see if they're correlating.

Todd Lorenz:

No, the question becomes how do you validate an endpoint? Which is a very tricky business. From talking to the FDA in previous situations, I can say, what they've informally said: "We'd like to see more than one clinical trial, a group of clinical trials enrolling more than 100,000 patients before we validate an endpoint," which is clearly impractical in aging. So, there needs to be another path.

We do have this spectacular technology with artificial intelligence, and I'm wondering if there are databases that follow people over longer periods of time or probably a number, there's probably a number, if we could download several databases into a program and have them pieced through artificial intelligence. I don't think it's going to be industry that does that. I think that it's going to have to be academia or some of us here on this call that take that. Zan, are you aware of a number of these databases that might be used in that kind of way?

Zan Fleming:

To some extent, I couldn't agree more that we need to put them to work. But again, it comes back to Steve Kritchevsky's point that ultimately you can generate a biomarker, a biologic clock, for example,

that has excellent correlation with aging or some clinical outcome but validating that it moved in the same direction in response to an effective therapy, now that's the big challenge.

Todd Lorenz:

Well, they're going to have to go to a different model here. Ultimately, I think even Rob understood that.

Joan Mannick:

Could I just jump in, Todd? There's a difference between validating the endpoint and validating the biomarkers. So, we could use validated endpoints in a clinical trial targeting aging to validate the biomarker as a first step.

Todd Lorenz:

No, I mean biomarkers. Biomarkers is what needs to be validated in that way.

Joan Mannick:

I know Steve.

Todd Lorenz:

An endpoint is anything that fixes how a patient feels or survives or functions.

Joan Mannick:

Exactly. Right.

Zan Fleming:

Perhaps Steven Austad, you could tell us what AFAR is doing specifically about working with industry as large have come trials.

Steven Austad:

Yeah. Well, what we're trying to do is exactly what's been described, which is compile enough studies and enough data already, with enough collected samples already that we can go back and retrospectively do this. **One of the things that I think we're lacking and maybe something that this group could help out on, so I think we have our hands on some things in the US, on some studies in the US that have samples, but I think this would benefit from an international level. Because a lot of countries have done a lot of studies that have stored tissue samples or blood samples that could be used in this way.**

One of the things that we're working on at AFAR is the samples from the diabetes prevention study. There are also the samples from the CALORIE study that would be a big interest. But again, internationally, there's probably a lot of stuff that if it were collated and organized in one place, and maybe Todd can do this, and use artificial intelligence to help with it. Because I think we're missing out as long as we're sticking with our own national available information.

Thomas Seoh:

Steve, how would such an international collaboration come about? The ideas being discussed here to get to a stage where several years forward, various databases from different countries have been put together and people are gaining the learnings from that? I mean, I don't know that the Kitalys Institute could do that. **Who here can do it? What are the steps that would be needed for that to catalyze and get started?**

Steven Austad:

Oh, well, that's a good question. I mean, that takes a very high level of international connections, facilities. I mean, it requires people that are familiar with the people who control the data. It turns out it's not as easy to get the data as we originally thought that it might be, because people are protective of the data. But exactly what we need is overcoming those barriers, and whether that's a financial issue, whether it's a political issue, I'm not sure, but it needs to be done.

Todd Lorenz:

I think if there were a concerted effort to do this by a party like a major university or perhaps AFAR, I mean by some third party that doesn't have a major... I think people might get to be embarrassed into volunteering their data for such an effort.

Steven Austad:

Well, I hope you're right, Todd, because one of the advantages of AFAR is that we're not running an agenda. We're simply trying to benefit the field.

Todd Lorenz:

Yeah.

Zan Fleming:

Well, let's go to another subject, which is, again, very challenging, but we just don't have the technology to incentivize the activity, particularly on the dietary supplement side, the nutritional product side. But if get data that will support the use of a product for increasing health span and we heard from the commissioner many times that FDA just doesn't have the current structure to give dietary supplements or nutritional products, a prevention claim as a proprietary product.

They can give general sorts of class claims, but they are very limited in what they can do. So that's just one small example. Maybe we could bring back Dave Fox and Steven Grossman, along with Thomas, to talk about how can we improve the landscape for developing these therapies and not just therapies, but interventions in general, of course, dietary, and other lifestyle interventions or first principles, but when it comes to actual drug device or nutritional product development, how can we do that?

David Fox:

Go ahead, Steve.

Steven Grossman:

If I could just unmute. The more I've listened, the more I've thought about this over the last couple of days as we've prepped, the commissioner said: "Go talk to chief scientist, chief medical officer and the goal should be to get somebody inside in one of those offices to take on the role similar to what

the office of combination products does." It sources out who should get responsibility for regulation of any given product, when there's a combination product, and it could work for this, you need people besides the commissioner talking about this, thinking about it. You need a point person.

I know that seems very tactical, but it's the iteration that gets these things to a higher level. Can we bring NIH in? Can we do an endpoints conference? I don't think there's any straight path, but I think that it's iterative and it needs to be planned again. We need an iterative plan, if you'll. David? Thomas?

David Fox:

Yeah, thanks Steve. Just to be clear, **I think there's incentives that need to be addressed in completely different directions. So, one is how do you incentivize the regulators to open their minds and use their flexibility to look at things differently**? Then how do you show there are adequate protections over the investment to cause people to want to spend money on these programs? When, as the commissioner noted quite right, that: "If you're going to be administering something to a healthy population to keep them healthy, it's going to have to be very safe."

We're typically not talking about new chemical entities with robust composition matter IP around them, talking about things that are largely generic, ubiquitous, and so, harder to protect. On the incentivizing the regulators, again, it's a revelation to hear the commissioner so frankly say that: "The civil servants are the ones who really are determining this," and that he can only speak from a plot policy platform. Even then it's not policy unless it's memorialized in writing somewhere. So, there's a very large gap between the Office of the Commissioner, as well as Dr. Bumpus, Chief Medical Officer, what they can do from the commissioner's perch as opposed to what's going on at the staff level. We know the staff level is very dug in on field function and survival, on hard outcomes. So, it's a tough situation.

It was very interesting what he said, I think, about the Lilly data and Alzheimer's, and how that could end up forcing the agency's hand on early intervention. Now, they're going to have to write a label, assuming the product plays out, that's probably going to balance and restrict who can use it, when there's certain onset of symptoms. But I think **maybe between the two cases he mentioned, the GLP1RAs and the Alzheimer's products, it could be that we will see the agency's hand forced by people who can pay for those products out-of-pocket and make the decision themselves. Then the question will be, when will the regulators have to catch up to that?** Because we're seeing that with the GLP1RAs, with people using it who don't fit the BMI criteria for weight loss within the labeling, who are going out and buying it, literally, out-of-pocket, and large amount of money.

It's another thing that, also just to bring it into the mix, raised the issue of equity here, **healthcare equity. That there are going to be people who are going to force the use of these products for potentially health span by seeking them out and paying for them for themselves and then we would hope maybe that eventually the regulatory system will catch up to that, so that the products become more available to more people.** So, that's just one observation.

On incentives for having people invest in the products, I mean, I think IP is one, but you're not going to see composition matter IP, which is what drives investments. So, some form of regulatory barriers

to entry, which probably is going to require a legislative solution. Zan, as you know, we've been working on that hard and even also extending some kind of proprietary protection to people who do that kind of experimentation in the food and dietary supplement area.

So, he's right that the dietary supplement law, DSHEA, completely discouraged, disincentivized developing real evidence about these products. Even the commissioner doesn't really understand what a structure function claim is for an everyday dietary supplement and that's noted. I like that**. The answer to that, I think, short of changing the law, which is not going to be an easy lift and the politics probably are not right for doing that, is using the flexibility that we know FDA has within the drug regulatory system to create a pocket, a lane in which they could look at products as drugs and encourage the development of the evidence, and then reward it within their exclusivity system.**

I mean, the pieces are there. **It's the institutional will to use the flexibility for something other than unmet need and rare disease.** He talked about accelerated approval that was not originally a creation of Congress, that was a creation of the FDA status and they said: "We're willing to accept more uncertainty and use unvalidated, surrogates, surrogates reasonably likely to predict a positive outcome. But we don't know. But we're willing to take that risk, that chance, because of what cards on the table are for these patients."

I think the day has come for them to think about how we can also use flexibility and some tolerance for uncertainty to affect the broader population, not just, I mean, certainly, I'm a champion of rare disease targets and treatment. But I think the issue is can we bring that kind of thinking, which the agency is capable of doing and has the authority to do, can we bring that into how do we affect larger groups of people who are facing chronic illness for a long period of time? It's very expensive to treat, it affects all levels of society.

So, as Steve says, we must keep pounding away at that. I've said this before, I think every time the FDA has a stakeholder meeting on a disease to look at endpoints for a disease, there should be a pre-disease segment of that conversation. We should be going into the agency every time they're looking at endpoints or issuing a guidance and say that, even if you come up with nothing, they should be required to dedicate time to thinking about the pre-disease state. How do we keep people never having to face this disease in the first place?

Zan Fleming:

Wow.

David Fox:

We must institutionalize or socialize that conversation every time FDA does a guidance on endpoints for disease.

Zan Fleming:

David, you made about 6 or 8 crucial, important points in just a few minutes' time. Hold those thoughts. I want to bring a few other people in, but we need to say goodbye to Jay Skyler. He's going to have to jump off. Jay, you did a great job in getting the commissioner to talk, to confess that he

gets head pain when he thinks of some of these issues. That's a great technical term I'm going to remember. But many thanks, Jay, for bringing that off and we'll be in close touch.

Jay Skyler:

I think we need to get all these efforts underway of consensus groups and let's get it done.

Zan Fleming:

I want to thank you, Jay, and Godspeed. Let's bring Larry Steinman into this discussion. We're talking about not only the what, the how. Larry, you chaired a Blue-Ribbon Gulf War Commission, so you know how that worked. You saw its efficacy. What are your thoughts here about the kind of a mission that would sweep across various parts of the government and the private sector?

Lawrence Steinman:

Yes, I think we'll take a lot of organizational skills to come close to sweeping through all the various gates that need to be addressed. I was very struck by commissioner's responses to Eli Lilly's press release this morning about the positive results on the Alzheimer's trial. In the second or third paragraph, they mentioned that about 30% of people exposed to the biologic for 18 months had small brain hemorrhages and brain edema of no great consequence according to Lily, just small brain hemorrhages and brain edema and although the P-values look stellar and I would certainly predict that the drug will be approved, it gets to a very tricky point for geroscience, so that if there's a drug with potentially significant side effects, early intervention is always going to be the best course of action to block any disease from progressing. But the big question is, will it come along with significant risks?

He mentioned significant risks, and I think it all depends. If you live in a family where there was early onset Alzheimer's, let's say in the late fifties or early sixties, I'm talking about years of life, one thing to remember is that homo sapiens living in the United States and mid to upper socioeconomic groups are not like our parents were in their fifties and sixties. Lifestyles are very different, and it's just hard to make those assessments. But since commissioner is a good surrogate for how this is going to be accepted, it will probably sweep through. This is a drug that is going to potentially have a lot more serious side effects in a large population than other well-known interventions that help us live longer like statins and angiotensin modulators. So, all I can say is we had better fasten our seat belts. It's not going to be easy.

Steven Grossman:

Well, what I didn't see in the press, in the write-ups of the press releases, what the background rate for Aria is in a population of X with these comorbidities, are those kind of fatal side effects common? I mean, there was no sense of proportion there.

Joan Mannick:

If you have the vehicle group, it’s like half of what's in the active group.

Thomas Seoh:

Okay. So you're using the placebo, but I don't know, it is possible to get a placebo group that's not representative, and on every dimension, this might not be one of them.

Joan Mannick:

But all the drugs of this class have this similar side effects, so it's probably real.

Zan Fleming:

It's real.

Steven Grossman:

So, then we're talking about risk/benefit, and I think part of it is for Alzheimer's, they're willing to do risk/benefit and say it's worth it. We need to justify risk/benefit for lifespan drugs.

Zan Fleming:

Well, I think this comes down to the crux of the problem. If it does work for people who have advanced disease, that's one thing. The question is how far could you go? Could it be somebody at risk who has relatives with Alzheimer's? Should they be treated? Probably not. That's what would be an affected geroscience approach; if indeed it's affecting other organs and not just the brain. But the problem will be where do you draw the line and the populations that should be treated?

Steven Grossman:

We do such a great job with rationing in this country of healthcare, so ...

Zan Fleming:

Yeah. Well, that's true. Kate, you have fresh eyes to this field. I would like to bring you in and maybe get some of your thoughts about how we could be effective at changing the current situation that is not favorable for developing interventions for people that don't have disease yet. But let's see, Kate, are you on mute?

Thomas Seoh:

Is Kate still on? She may have just dropped off.

Zan Fleming:

She may have dropped off. Margaretta, you're still on. You have anything but fresh eyes. You've been in this field from the beginning. What strikes you as interesting or maybe concerning about what you've heard today? You're on mute if you're saying something, but I do see your picture.

Thomas Seoh:

Maybe I can fill the void for just a moment.

Zan Fleming:

Yeah. In fact, I wanted to turn it over to you to give us some of the best questions that you've seen in the chat.

Thomas Seoh:

I can get to that in a moment. But I was struck by the commissioner seeing himself as a referee as opposed to what he was saying in opposition to an advocate for a science or what have you. But I

guess I see him more as a guardian than a referee. It's a cultural issue, as Dave Fox mentioned. They have the means. They've approved preventives like vaccines and statins. They've even regulated interventions that are for conditions that are not diseases, like pregnancy. So, if they wanted to do it, they could, or at least there's precedent for doing it. But you and I have discussed, Zan, that the transition from reactive disease treatment to proactive precision health, the question is: 'What role is the FDA going to play?' I heard the commissioner say they're not interested in being in the lead. Will they go with the flow or are they going to get-this is the uncharitable way of saying-dragged kicking and screaming or being very careful about the steps that they take.

I think that's the tension I see with geroscience. We talked about the treatment of a disease and now we're talking about focusing on the pre-disease state, which I think is important. But at the end of the day, the geroscience dream, I guess, is to take younger, healthier people and delay aging. I guess if the industry and geroscience came up with a real reversal, then that wouldn't run into that issue because you can go to the FDA and say: "Hey, look, we're restoring sight," or hearing or wrinkles if they regulate that. But the stuff that you don't see that's going on at core in the cellular and molecular levels, that's the great insight of geroscience. I guess I'm interested to hear from this panel, is it the FDA's job? They seem to be regulating medicines and I'm not sure whether those kinds of interventions in the ultimate state are medicines. So, I'm curious to hear what people have to say.

David Fox:

It's a treat, cure, prevent, mitigate disease.

Thomas Seoh:

So, what about healthy people who are younger, who are not at levels of excursions from their molecular and cellular and organ processes that rise to the level of being recognized typically as a disease?

Stephen Kritchevsky:

This happens now with hypertension. I mean, people in their twenties are started on agents.

Zan Fleming:

That's right.

Stephen Kritchevsky:

Because it's considered to be a lifelong risk, and the longer you're treated, the lower your ultimate risk is. So, there's precedent there too. It's just having to break out of the mindset of one pathway, one disease.

Thomas Seoh:

One patient population.

Steven Grossman:

Thomas, I was there when he had another event when he gave a little longer explanation. I think the longer explanation is good for us, which is that FDA is involved in setting the rules and then for specific products, it's the referee as to whether or not those standards have been met.

Thomas Seoh:

Right, okay.

Steven Grossman:

Seen that way, we need to get the rules set and it's all over the place. I don't know if that's avoidable, but that should be the main thing: trying to get these questions down. Here are the four things we need the FDA and the dialogue on. Then you get to the rules and then they are the referee. I think we're about to see that the rules for Alzheimer's for the first time have been met. It's fascinating.

Zan Fleming:

I see our colleague Pepper Landson has her hand up. Will Pepper come on and join us?

Pepper Landson:

The conversation has certainly made strides since the last time we had this conversation, and yet we're still kind of swirling in the same eddies. I think it was Steven who just commented essentially that focusing on the things that we can move the needle on will have value to us as a community. But the thing that strikes me as being kind of my background of being an operator and a pragmatist is there's all the science that the community is generating right now, and yet where are we aiming the science? We need a road to put it on. Folks like Joan, folks like me and a variety of other folks who are probably on this call are moving agents into clinical trials for healthy aging. Again, that road isn't built yet because endpoints, biomarkers, et cetera, that's all amorphous too. But I wonder, since we're already giving a lot of time and energy and talent to the effort as a community, is there a leading effort, I'm going to frame it in the concept of, is there a drug in clinical trials right now, whether it be Metformin and TAME, which could be in clinical trials if funded, that we as a community could say: "Look, it's not perfect," but what if we got behind it as an entity, a united front and said: "We want to help company X move the needle for all of us and you are going to be the pioneer in front," right? You are Lewis and Clark for us, and we will support you. We don't have to love necessarily the science, we don't have to love the mechanism. But if it's the right thing that says FDA, this is the best shot we have come up with as a community and let's work together to make this happen so that the road is paved for those coming behind it. Is that something we could do as a community?

Zan Fleming:

Well, we sure could advocate, the problem in that case with metformin is there's no company. Metformin is way off as it never was patented in the US.

Pepper Landson:

Right, but that's just an example of a good plan, but perhaps not a great business strategy.

Zan Fleming:

Yeah. But the low hanging fruit are the drugs that have been approved and used for many years and typically will not have corporate sponsorship. So, that is an issue.

Joan Mannick:

The other thing I was thinking, Pepper, is Rob was mentioning 90% of the trials are going to fail. So, it'd be nice if we could have multiple shots on goal so that we don't put all our eggs on the one that fails or all our eggs in the basket that isn't going to get approved.

Pepper Landson:

Okay. Joan, how does this sound as a strategy for what you're working on at Tornado and perhaps what Praetego will be working on soon? Should the companies who seem to be in the same arena help each other as it relates to regulatory pathways? So, that although we are all small bundled together like sticks in the biblical story, we are stronger.

Joan Mannick:

Absolutely. I mean, I think even look at what FDA does for oncology, they sort of have templates of how the trials should be run. It would be great if we had templates for different aging related endpoints that people could use.

Thomas Seoh:

How do we get there? Do we facilitate discussions with the FDA or is it individual companies that have them? Dave, you're shaking your head. Maybe you can tell us, guide us what you're thinking.

David Fox:

We've talked about this before. There are just a lot of barriers for individual companies going in and you can have those conversations like a pre-IND. There are these different technology type meetings, but you get a lot of listening from the agency, and you don't get anything back, or you go in as a company and you must have a specific product and specific questions, and everything is very tightly held. But this is one place where I think just to toot our own horn, the Kitalys Institute can help. **It would be much easier for us, as the Kitalys Institute, with representatives from the companies to go in as a consortium for discussion than it is for an individual company to get in.** If wanted to meet, for example, with Dr. Bumpus or with the chief medical or chief scientific officer, it's much easier to get on the calendar as either a consortium or as an independent institute than as a specific company. Just to start the conversation, see where their minds are, and then you can go in and try to get more specific. But it's a world of difference going in as an individual company then going in as an association.

Thomas Seoh:

You could imagine conversations about the role of biological clocks, what the agency would need to treat them more seriously. Just a question for the panel, what did you think of Rob's answer as to whether it was ready for prime time to be thinking about a dedicated center or office or division or something? I was disappointed, but I don't know that I was entitled to any particular expectations. I would imagine the geroscientists think we are ready. What does it take to get the FDA to think differently than what the commissioner just said? Joan, you look like you're about to.

Joan Mannick:

Well, I was dying to ask him. He goes: "Oh, it's not ready yet." And I wanted to go: "What's required to be ready?" Because it wasn't clear to me, is it that we must get this consensus because it's the sort of the outside world that pushes the FDA to do this, or is it that we need a trial that works? I don't know. Zan, did you have any sense of what he might mean by: 'it's not ready yet?'

Zan Fleming:

Well, yeah. It's, I guess, multiple things probably. But we should control what we can control. We can't necessarily directly get in the mind of Rob Califf. We need to take some positive steps forward in some of the ways that have been outlined. I think Dave Fox, you've certainly plotted us a laundry list of ways we can go forward.

Steven Austad:

I think it's clear that the FDA does respond to external pressure if the external pressure is right. I don't think the first Alzheimer's drug would've been approved without external pressure. Probably the same with the early anti-HIV drugs. So, I do think that they could be responsive to pressure, and I thought that his comment about not being ready yet just showed that he didn't have that much familiarity with the field, which is understandable.

Thomas Seoh:

Steve, not to be argumentative, but the examples you gave were from patients, sort of a tsunami of patients, asking for relief.

Steven Austad:

Yes.

Thomas Seoh:

What is the constituency for anti-aging?

Steven Austad:

Anybody over the age of pick X.

Steven Grossman:

That works if you have an 'it' and we have no 'it' to get political behind.

Joan Mannick:

I have sometimes gotten on the phone with these very wealthy older people, maybe age 80, who are still in good health. They're willing to take so many risks that I'm always shocked**. They'll take with no data all sorts of stuff that I would think is too risky. So, that is an interesting population, the healthy eighties, because then it really is a life-threatening disease in the short run and if you're still healthy at 80, there may be a runway there.**

Stephen Kritchevsky:

I'm also concerned or think that the penetration of ideas of geroscience and the rest of medicine is something that's important. We talk to each other a lot, so we're all convinced, but I'm not sure how big this world is. I still talk to people who are at Wake Forest and tell them: "Oh, I do geroscience" and they respond: "What is that? That's very interesting." **So, I think there's a communication problem, and that's important. I think in building a constituency and support for FDA to react to, that there's a biomedical community, that this is a thing.** I know Jim Kirkland is almost tireless in writing articles about senolytics and I think this is part of the long plan. **The long game is to make sure that this keeps**

coming up and kept presented to people in consciousness, not in journals called geroscience, but in general medical journals.

Zan Fleming:

Well, folks, all good things must come to an end. We've run over a little bit. It has been terrific and how great that we could have this community discussion. To Steve's point, we are a kind of self-selected group which don't represent the larger scientific community, and that's a challenge that we need to address. There's some many other things that we can do. We've started to learn specific ways we can get the FDA to turn its attention towards this field, but we need to roll up our sleeves together to do that.

We are going to provide the recording of this session and also a transcript, so to all of you that have registered, those will be coming automatically to you. But we also want to hear from you. We'd love to hear your thoughts of how we can improve our conference at the technical level. We've got room for improvement for sure, but we're also building our calendar for the sessions to come, and we would love to hear from you about ideas that you'd like to see presented in the conference that is going to run until the end of the year. We may even have a one- or two-day physical conference, so stay tuned for that. So, we in general would love to hear from you and we'd love for you to stay in touch. So, with thanks to our panelists, to Jay Skyler, to Commissioner Rob Califf, we'll say goodbye for now.

Thomas Seoh:

Bye-bye.

Joan Mannick:

Bye.