Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

March 27, 2026

Docket No. FDA-2026-N-2047

PRESENTERS

Kyle Diamantas, Deputy Commissioner for Human Foods, FDA

Cara Welch, Director, Office of Dietary Supplement Programs (ODSP), Human Foods Program (HFP), FDA

Jensen Jose, Regulatory Counsel, Center for Science in the Public Interest

Daniel Fabricant, Ph.D., CEO and President, Natural Products Association

Phil Yeager, Director of Research and Evaluation, ODSP, HFP, FDA

Weslee Glenn, Vice President of Innovation, Ayana Bio

Duffy MacKay, Senior Vice President of Dietary Supplements, Consumer Healthcare Products Association

John Deaton, Vice President of Science and Technology, Biohm Technologies

Tony Pavel, Partner, Keller and Heckman LLP

Frank Romanski, Global Vice President of Strategic Growth & Revenue Management, Lonza Capsules & Health Ingredients

Betsy Jean Yakes, Identity and Status Branch Chief, DRE, ODSP, HFP, FDA

Elvira Gonzalez de Mejia, Professor, University of Illinois Urbana-Champaign

Linda Neckmar, Senior Vice President Human Health, Novonesis

Andrea Wong, Senior Vice President & Chief Science Officer, Council for Responsible Nutrition

Gregory Leyer, Founder, Biotic Solutions Consulting

Amy Smith, Sr. Director, Medical Affairs North America, Kerry ProActive Health

WELCH: I want to give a welcome to everyone who's joining us, joining us by live stream. We have an exciting agenda today, and I want to reserve as much time as possible for that. So I am going to get us started, with some housekeeping notes. And I'm, I'm sure you recognize that. So, my name is Cara Welch. I'm the director of the Office of Dietary Supplement Programs. In a moment, I am going to turn it over to, well, thank you, the Deputy Commissioner for Human Foods, Kyle Kyle Diamantas. So, as a note, this meeting is being live-streamed and transcribed. The recording, transcription, and the slide decks that you'll see from the presenters will be posted on our website. That takes some time to prepare them for posting, so please give us a moment. If you're interested in accessing these materials, I would suggest you monitor the FDA meeting webpage specific for today's meeting.

Wi-Fi is available. Next slide. Wi-Fi is available. Thank you. On FDA's guest account. Also, please take this moment to silence cell phones and any other devices. I will do that when I turn it over to Kyle to ensure our transcription is accurate and that our live stream participants can hear. Please be sure to speak any questions or remarks into the microphone. There are microphones on either side of the room for Q&A and for the open public comment period at the end. Please begin your remarks by stating your name for the record. And then for folks that are joining us, we do have some people monitoring the live stream. Inevitably, there will be issues. We ask that you give us a little bit of time, but please know that we are, we are monitoring the information as best we can.

Restrooms. As you exit the auditorium at the top of the stairs, there is a men's and women's restroom located down the corridor on your right. We have a morning break and a break for lunch. There is sort of light fare, snacks, and beverages available in the Wiley Cafe. It is the House of Mac Cafe that is located outside the entrance of the building to the left. Seating is available in that cafe or, well, it really depends on the weather. Yesterday was lovely. Today is rainy, so if it is dry, you could sit outside. Just let you know. Please use the front door to enter and exit. Don't use the one at the top of the stairs. Also, please remember to wear your name tag, maybe not when you're wandering College Park, but when you come back, because you will have to go back through security. For any media or press questions, we would ask that you direct inquiries to the HHS press room on hhs.gov.

Thank you. And then as you can see from the agenda, we're having a public comment period, at the session four for the day. We've asked commenters to target three minutes for their remarks. If we have extra time after the list of people who've pre-registered, others can absolutely give up to three minutes of remarks. If you otherwise have any questions or need assistance, please see our team members at the registration desk where you got your name tag. And with that, I am very pleased to welcome to the

podium, Kyle Diamantas, FDA's Deputy Commissioner for Foods and Senior Counselor to the Secretary. Kyle. Next slide.

DIAMANTAS: Thanks, Cara. Good morning, everyone. Welcome to the Human Foods Program and our Wiley Auditorium. I'm really grateful for all of you to be here on a rainy Friday, nonetheless. You know, for those of you that may not know, I was an attorney in my prior life. I now consider myself a recovering attorney. But over the course of my career, you know, I touchpoint on nearly every aspect of food law, working across the portfolio from dietary supplements, conventional foods, infant formula, and other specialty products, beverages, novel substances. And here at FDA, my role is now focused on the business of ensuring food safety and advancing nutrition. That's really work that reflects the mission and the goals of everyone in this audience and the themes that we'll hear throughout today's discussion. The dietary supplement industry is really a great example of a healthy industry, with annual sales that have impressively increased year after year, which I believe is a testament from consumers of the benefits of these products in the category as a whole. The breadth and range of the dietary supplement products have also expanded over the years, thanks in part to remarkable advancements in technological innovations, really to an extent far broader than what was on the market in 1994. This growth, from an estimated two to $4 billion industry to an over $60 billion industry today, is really a testament to consumers' desires to take an active role in their own health and wellness. Today, more than three-quarters of American adults use dietary supplements, by our estimates, reflecting a fundamental shift in how Americans approach their own health and wellness. This isn't just market growth. That really represents millions of Americans making daily decisions to support their nutritional needs and take advantage of their own personal health goals. Against this evolving backdrop, the FDA has diligently worked to maintain an appropriate level of oversight within the bounds of the authorities granted to us by Congress. As you all know, the Dietary Supplement Health and Education Act of 1994 was deliberately crafted to establish a careful balance. On the one hand, it helps protect consumers' right to access safe products and accurate information. And on the other hand, it preserves the FDA's authority to protect the same consumers against unsafe and otherwise unlawful products. While the fundamental goals underlying the statute have not changed, the reality of implementing those goals has grown to a magnitude far beyond what it once was in 1994.

It's crucial that FDA be nimble and adaptable as we advance our regulatory frameworks in keeping pace with the rapidly growing commodity and related technological and scientific advancements that all of you are well familiar with. We're also interested in taking a hard look at our own regulatory framework. The industry has grown and changed tremendously in the last 30-plus years, yet the regulatory framework has

largely stayed the same. It has not, is not adapted to the change in your level of innovation. It's a goal of mine to modernize our oversight, addressing some of the shortcomings that have allowed unscrupulous actors to thrive to the detriment of the overwhelming majority of players in this space who follow the law and regulations, and to ensure the rules that are in place are serving a purpose and helping ensure a safe, high-quality dietary supplement marketplace for all. This administration has prioritized identifying and cutting out red tape. And by doing so, we'll be setting up the agency to lower costs and enabling regulatory industries to increase access to innovation. Modernizing our agency's oversight is not about stifling the industry or consumers. It's about addressing shortcomings and ensuring that rules that are in place are serving their intended purpose. And that's to ensure a safe and thriving dietary supplement marketplace for all. The food program has already made some meaningful progress on this front. As you all know, last year we issued an enforcement discretion letter with respect to the disclaimer on product labels. As needed, we'll continue to work on rulemaking to adjust this requirement, which we believe will reduce label clutter and unnecessary cost for manufacturers without compromising consumer understanding. We're also examining other areas where regulatory requirements may have become unnecessarily burdensome to industry without providing commensurate public health benefit. For example, we're evaluating our approach to certain notification requirements and exploring whether advancements in technology and data systems can help streamline compliance while maintaining appropriate oversight. As we continue to explore deregulatory opportunities, we look forward to working with all interested parties on these modernization efforts. Improving the regulatory framework for dietary supplements is something we're committed to, but it's also a shared responsibility. It requires collaboration between our agency, the regulated industry, and the consumers we both serve. By working together, we can ensure that this industry continues to flourish while providing consumers with safe, high-quality products they can trust. So I want to turn our attention back to 2024, when the FDA's Foods Program underwent a major reorganization to transform our programmatic structure. This restructuring was a necessary evolution, driven by the need to be more proactive and strategic in our mission to protect and promote the public health. Our previous organizational structure often meant we were responding to problems after they had already emerged, rather than proactively identifying and preventing them. We were often operating in silos that sometimes prevented us from seeing emerging trends or connecting dots across different product categories, and in ways that prevented us from focusing on things like regulatory innovation. We moved from a structure that was often reactive to one that is centered on three key risk management areas that now guide our work. These three areas where offices are the Nutrition Center of Excellence, the Office of Microbiological Food Safety, and the Office of Food, Chemical Safety, Dietary Supplements and

Innovation. As you all know, this last office now houses the Office of Dietary Supplement Programs, led by the terrific Dr. Cara Welch, as well as our pre-market additive safety and post-market assessment offices. And really, the establishment of this broader office or risk pillar is a step forward from my perspective. It allows the dietary supplement program to better leverage the deep expertise across the entire food program. We're now structured to align our surveillance efforts and safety assessments through the same risk management approach. This not only advances the efficiencies of our existing programs, but also provides crucial opportunities for the early indication of potential public health threats that may affect different commodities. Now, the Food Chemicals Office has integrated the scientific expertise for evaluating the safety of substances, both in conventional foods and supplements. We have also, however, been careful to maintain the distinct perspectives required in applying the appropriate statutory authorities to the scientific conclusions reached for both. So this alignment has already proven beneficial. We think it fosters greater coordination between the programs on post-market assessments of substances, and we think this is the right path forward for both conventional foods and dietary supplements. An example of this, of this enhanced collaboration, is our recent work to address 7-hydroxymitragynine products. Going back to last year, this was an emerging public health threat that required close coordination and response from experts across the Food Chemicals program. The result was a series of actions, including the issuance of several warning letters last summer and significant product seizures late last year. And I think this success underscores the power of leveraging our collective expertise to protect consumers from harmful products. We're also working across the Food Chemicals office to identify opportunities to align our premarket review programs to maximize efficiencies and effectiveness. We're working to streamline processes where possible and coordinate between programs to ensure a more efficient and effective regulatory process for all. When it comes to things like proposed GRAS reform as an example, our focus is to ensure that safe ingredients are available for use in both conventional foods and dietary supplements. We want to hear from you all, our dietary supplement stakeholders, to better understand how potential changes to the GRAS framework would impact dietary supplements, and identify potential improvements to facilitate the safe introduction of new ingredients in the marketplace. Specifically, we're interested in understanding things like how do you currently navigate the intersection between GRAS determinations and new dietary ingredient notifications? What challenges do you face in determining the appropriate regulatory pathway for innovative ingredients, and how can we design a system that provides clear guidance while best supporting innovative approaches? In fact, today's meeting provides a forum for us to hear directly from you all, our stakeholders, on these issues and many more. The insights gathered today and throughout our continued dialogue and engagement will inform our efforts to modernize our regulatory framework, refine our approaches, and help ensure that we can

conduct thorough and effective ingredient assessments that protect public health while continuing to support innovative approaches across the marketplace without unnecessary restriction. It's an exciting time at FDA. You know, there's more focus right now on foods and nutrition, I think, than ever before. We certainly have a commissioner and a secretary, that have increased their attention and focus on both conventional foods as well as dietary supplements. And I really think the grassroots efforts behind that has coalesced passion and interest in this area. And at the FDA, you know, we are excited to be at the tip of the spear when it comes to reform in the nutrition and dietary supplement space. And really, dietary supplements are a great example of the health and wellness opportunities that the Secretary's MAHA strategy is highlighting, that the MAHA movement recognizes that preventing chronic disease and promoting wellness requires a true multifaceted approach, and dietary supplements certainly play an important role in helping Americans address nutritional gaps and supporting their health goals by ensuring appropriate oversight, while at the same time removing unnecessary burdens and barriers to innovation. We can better support an industry that empowers consumers to take charge of their health. This aligns with the Secretary's vision of making healthy choices accessible and affordable for all Americans. When the statute was written in 1994, the bill recognized the importance of nutrition and the benefits of dietary supplements to health promotion and disease prevention. The statute goes on to discuss how the promotion of good health and healthy lifestyles improves and extends lives, while reducing health care expenditures, a matter of paramount importance to the future and economic well-being of our country. Of course, the legislative history of the statute isn't new to this audience here today, but I think it underscores why we've all gathered here. Ingredient innovation is critically important to the supplement industry, including your efforts to promote health and wellness. Today's meeting is an example of how FDA is working to modernize our programs. It's a first step, one of many, and I'm optimistic that the expert panels and public comments that we will hear today will leave our team with new ideas and fresh thoughts to evaluate. Success today means we'll leave with a clear understanding of the scientific and regulatory challenges you face in bringing innovative ingredients to market, and you'll have a better sense of how us at FDA are thinking about these very issues. Most importantly, we hope to identify concrete opportunities for improving our processes to better serve both public health and innovation. The presenters you'll hear from today are experts in the scientific and technical advancements that are being applied to the science of dietary supplements, as well as the new and innovative bioactive ingredients being developed. We hope today's discussion will facilitate FDA's assessments to better serve, excuse me, to identify the safety of these new and novel, innovative ingredients. I'm confident the conversations will be thoughtful, detailed, and productive. We're really grateful for everyone here today and online, and given the interest in the packed agenda, I think I'll turn it back over to Dr. Welch

and allow the conversation to begin. But I do want to again, thank all of you for the participation today and for your commitment to supporting FDA. Thank you.

WELCH: All right. Thank you. That was great. So we are going to head into session one. And this is our opportunity to explore the scope of dietary supplement ingredients, literally the name of the meeting. But specifically the scope of the phrase "dietary substance for use by man to supplement the diet, by increasing the total dietary intake." That's the phrase that was used in DSHEA. I'm going to try not to repeat that phrase too many more times. Just know that when I'm referring to "dietary substance," that's really what I'm referring to. Oh, good. The clicker works. So the scope of the phrase, where are we going with this? In DSHEA, we have a list of what is a dietary supplement. And top of mind, and what is a dietary supplement is what it contains. I mean, after the "other than tobacco" part. So, intended to supplement the diet, bears or contains one or more of the following dietary ingredients, and then the statutory text proceeds to list out what are dietary ingredients. A lot of these are fairly well-established terms: a vitamin, a mineral, an herb or botanical, an amino acid. Skip over to F where we talk about sort of variations or derivatives of all of the dietary ingredients. But we have this term in E, which is a "dietary substance for use by man." I'm going to skip over the "by man" part and just assume we mean "by human." And so FDA, when we are looking at statutory text that is provided to us, it's important to understand what the term means. To say there was not a lot of legislative history, as far as statutes go, it's fairly short. Kyle's remarks touched on some of the findings of DSHEA. And then there's, there's the text, and that's pretty much it. And so when we're handed this text, it's important for us to understand what is meant by the phrase. And so if we're not provided explicit language, if we're not provided, legislative history or intent, we look to the dictionary. So what is meant by a dietary substance? So a dietary substance for use by man, naturally, a substance that is used as food. So we have a substance that is commonly used as human food or drink. The phrase, of course, goes on to say, "to supplement the diet by increasing the total dietary intake." It sort of reinforces the idea or is further evidence that it's meant to be foods and food components that humans eat as part of their diet. Right? It is both in the diet and then increasing what is in the diet. To be clear, we also state that dietary substance, you can't put it into a supplement and then say, "Oh, now it's part of the diet." That would be a loophole. So we do say that a dietary supplement use as a supplement doesn't then make it a dietary substance. So we are looking at substances in conventional foods or in foods. And I think for a long time, this working definition worked, right? There were a lot of substances that were in foods that were coming into supplements, and that all made sense. I think we are seeing a few, developments at play in the supplement industry and in the food industry that dig into this topic. And really, it's important for us to understand, is this actually the extent or is this the scope of what is meant by this phrase?

So that's, that's the point of our discussion today. I will say we actually started this discussion back in 2019. And I have mentioned to a few people that I was looking at the transcription from our 2019 meeting. So in May, we held a public meeting on innovation in supplements. And you can see that it was actually a broader agenda than what we have today. It's not a complete repeat, but we started off that May 2019 meeting with a discussion of the scope of dietary ingredients under DSHEA. I led that session as well. And so, we then went on to discuss new dietary ingredient notification requirements, how to promote compliance with the requirement, etc. But on that session one, some of the, the themes that we were hearing, are actually, so I have them sort of scattered across this slide, right? We have, FDA talking about, so FDA is talking about, yes, as legislation goes, it's fairly short, but the provisions are there for a reason. And every one of those provisions was in there for a reason. Most of the people that were around in 1994 will tell you what that reason was. But that was 30 years ago now. So, we, it is important to understand that the provisions, this was a theme that came through from industry as well, talking about the exact wording of the statutory language is important. I think it was well accepted that she envisioned a dynamic dietary supplement market. So, and with a role for innovation, that's important to keep in mind because there was also some sort of criticism of that where, you know, we hear from, I believe it was Scott Bass that was talking about if, if a dietary substance only includes substances already present in food, then nothing new can get in under this problem. So is it actually encompassing innovation? And is that the innovation clause? I think there was some discussion of, you know, is it a nutritional substance or is it a dietary substance? That's sort of getting at some of the, iterations of, 1994 laws. The idea that the authors intended to remove the concept of nutritional, and just make it open to dietary substance. And then the conversation was, was pretty strong on modernizing the approach to compounds that are used in supplements, regardless of their source. And this is one where I think that we're absolutely going to explore and expand out over the rest of today. So we take, that one session in 2019 and we expand it out to be today's meeting, where we are taking the opportunity to understand more, again, the scope, but the scope of dietary substance specifically and how it was used in DSHEA. The session two talking about the methodologies to produce existing dietary ingredients. We talked, we heard from Kyle about the scientific and technical advancements. And it's important to understand how they intersect with dietary supplement assessments. I'm sure you're going to hear this again from my staff, because I've asked them to sort of reinforce this, but we're seeing these new ingredients come in in NDIs, right? We have 75 days to review these notifications, 75 calendar days, and hopefully not with a government shutdown in the middle. So the time is tight and we really need to make the most of the review time. So ensuring that we have a good understanding of the various methodologies that are already coming into our program is important. And that's really why you're going to see a whole

passel of, of ODSP and other reviewers at the top of the auditorium, because they really want to hear from the experts. Session three is sort of talking about specific ingredient types, proteins, peptides, enzymes, and live microbes. Actually, microbial is not just live microbial. These are ingredients that are not, that are A, are key to the dietary supplement industry, but B, are not explicitly listed in the statutory text. So where, what provision do we look at when we are determining if they are a dietary substance? Oh, excuse me, a dietary ingredient. And that is dietary substance. So understanding what are the critical attributes we should be reviewing when we are reviewing the identity of these substances. So for today's session one, we have, distinct perspectives from a consumer advocacy group, so Center for Science in the Public Interest and, and the dietary supplement industry, the Natural Products Association. And those were chosen specifically because it's really important that this conversation be held across the spectrum of stakeholders. Right? Obviously, regulators, we are in the room. It's important that we sort of learn from the experts, industry who are dealing with these questions, grappling with these questions day in and day out, but also consumers, right? Because they are our ultimate audience. And it's it's important that the statutory framework, as well as how we implement the statutory framework, works for consumers. We have asked our panelists to, hopefully look at the meaning of the phrase "dietary substance," but also how emerging ingredient types fit within that framework. And I can even go beyond. So this next slide is a number of questions that my, that, that my staff has, brought up that I really hope if we don't necessarily answer them today, which, for the record, we probably won't, we set the stage for the conversation and the dialogue to continue. Does the source of a dietary substance matter? That's something that came up in 2019. I think that's something that regularly comes up. Does it matter if it is synthesized in a lab versus, you know, actually from the, the source, whatever that may be? Does it matter if we're talking about using yeast in the fermentation or E. coli? And there's sort of downstream steps to understand then how does, how do these different production techniques, impact the resulting ingredient? So the provision, does it, does it depend on the production method? What happens when you produce these ingredients in a new environment? I am a chemist by training, and so, microorganisms are a bit of a stretch for me to understand, but I do find the conversations fascinating. The idea of something that is alive and it evolves. If you are talking about a microorganism that you isolate from a food or a microorganism you isolate from the gut and then you grow it up in a different medium, obviously not the human gut, it's going to adapt and it's going to adjust. And then how do we handle an ingredient in that respect? Is that important? When is it important? Is even, is even a better question to ask, right? Identifying this is when it is important and this is when it is not. Or this is an attribute that we should care about. I need to keep moving here. I thought it was so interesting, the question about does it matter if a substance is actually present in foods as intentionally

present in foods and unintentionally present? And so, you know, the idea that, a microorganism might be purposefully used for fermented foods, but in another food it is, it is the attribute of insanitary conditions. So, does that matter? Are there any limits to what this category can encompass? Which is, that's the question of the day. And I do, I, to be clear, I think, you know, as we want to say, the science, the safety of the ingredient is what leads the day. And I agree, we want to be able to give these, dietary substances a thorough review in our program, review the safety of it, and weigh in on the safety of the substance when used in supplements. But it is important to understand that sort of threshold question of are there any limits? So tons of questions. Very excited about today's conversation. I've already received a number of questions about what's next. Where do we go next? And I don't know. This is step one. It was a really big step to get here, but it is step one. Of course we have a comment period that will extend until April 27th. Would love for everyone in the room who's listening to the conversation to sort of take this back and apply some of the conversation to hopefully their written and submitted comments. I heard what I heard from Kyle is, and it's something we definitely hear, right? The goals are ensuring a robust safety oversight, but also removing the unnecessary barriers to innovation. And I think that is a message that is really important to reinforce. However, I'm going to reinforce this last point as well. The statutory language was there for a reason. And so if we're going to explore what is meant by the scope of dietary substance as it's used in the statutory text, as we proceed wherever we end, we need to be able to say, this language, this is how this, this working definition or this scope fits in with this language. We need to be able to connect the dots, connect the words, the phrasing as to how we got to wherever we end. Because, because there are some guardrails or train tracks in this case, right? And the train tracks are always going to be the law. And so ensuring we keep that in mind is really important. I am actually going to save as much time as possible for our panelists. I am going to first welcome Jensen Jones from the Center for Science in the Public Interest. Then we'll hear from Dan Fabricant, and then we will have a Q&A portion. So Jensen.

JOSE: Is not working. All right. Oh, there it is. Okay. Thank you, Cara. And good morning, everyone. My name is Jensen Jones, and I'm Senior Regulatory Counsel at the Center for Science in the Public Interest, your food and nutrition consumer group. I'd like to thank Cara, Kyle, and FDA for the opportunity to speak on such an important topic and for being the first panelist to speak. I don't know if that's going to be a good thing or a bad thing, but I'm looking forward to the discussion. CSPI's mission is to advocate for evidence-based, community-informed policies and on nutrition, food safety, and health. One of CSPI's goals is to make sure dietary supplements are safe and actually do the thing they claim to do. Many consumers may seek out dietary supplements to improve their health. Certainly, supplements like folate help with preventing neural tube defects. Iron can help with

anemia, and certain supplements can slow vision loss for people with macular degeneration. While there are certainly useful, useful supplements of which we are very much appreciative of, the current market contains about 90,000 unique products and is estimated to be worth about 60-something billion dollars. Not all 90,000 supplements are needed, nor do they all make people healthier. In fact, many supplements do the opposite and harm people. That is in large part because FDA is unable to regulate such a large industry, an industry that utilizes online tools, social media, which is often difficult to monitor and is filled with misinformation, especially when it comes to the wellness space. Expanding the definition will certainly expand the scope and size of the market, and FDA should focus on making the current marketplace safer instead of allowing more chemicals and substances in supplements.

With that, I appreciate FDA asking CSPI if dietary supplements include substances that are not in the diet. We believe that dietary substances are limited to substances commonly used in human food or drink because, according to Webster's Dictionary, "diet" means that organism's usual food and drink. This is a common sense definition that is in line with FDA's current interpretation in its draft NDI guidance. Now, I understand that the common and regular usage of words may not always be the same as the legal definition. For that, we can look at legislative intent.

Certainly, industry has been vocal that dietary supplements are meant, sorry, that dietary substances are meant to be expansive. In other words, dietary supplements, dietary substances are not only substances that are in the diet, but are also substances that are not in the diet.

When looking through the legislative history, Senator Orrin Hatch's Committee report says that the definition of dietary ingredient and substance is intended to encompass substances from the food supply, and were present in the supplements when this was passed in 1994. While much of DSHEA is fairly expansive, it's clear that the term "dietary substance" was intended to be limited to substances in the food supply. Conversely, if dietary substances, if, conversely, if dietary substance can pretty much mean anything outside the diet, then what was the purpose of having the definition tied to the diet in the first place? The definition eventually becomes moot. Putting congressional intent aside for now, the question is also whether an expansive view is good for consumers. On one side, we have industry that has put a lot of value in what an individual believes is useful for their health. But what happens when consumers believe that supplements are regulated like drugs? Pew Charitable Trust found that about half of the adults overestimated FDA's regulation of supplements. Consumer Healthcare Products Association found that almost half of consumers mistakenly believed that supplements were regulated the same as

prescription and over-the-counter drugs. Consumers aren't making choices about health based on fact when they mistakenly believe that the government has vetted supplement claims to be true and vetted them, vetted the ingredients to be safe. As a result, consumers often take the claim at, at face value. But simply, consumers cannot trust supplements in the way that they trust drugs, in the way that they actually believe.

Since 2007, there have been 2,147 entries in the FDA's health fraud database. What's worse is that FDA says that this list only includes a small fraction of the potentially hazardous products marketed to consumers. Now, I'm not saying that all supplements are unsafe and fraudulent. Not at all. But it's hard for consumers to identify the supplement, the supplements that are, in fact, actually safe and effective. The problem stems from the fact that the market is so under-regulated. Supplement companies don't have to disclose their safety data or rationale for new ingredients under GRAS. They don't have to disclose the evidence substantiating their claims. In many cases, they fail the basic requirement of notifying FDA that they actually made those claims in the first place. FDA rarely inspects supplement manufacturing facilities and often finds problems with the few that they do inspect. Now, on top of this, industry doesn't want to even show that their ingredients are even tied to the diet. We have a system where supplement companies are essentially policing themselves. We don't ask restaurants to do their own health inspections and grade themselves. We don't ask builders to do their own building inspections. However, we're expected to just trust the dietary supplement companies, that are worth billions are doing their job in evaluating their claims and their ingredients. A system where no one is looking under the rug leads to unsafe and fraudulent products. And we're not the only ones that think that. In the end, the goal of expanding the definition of dietary substances is to include peptides, proteins, enzymes, and microbiomes. It is in line with Secretary Kennedy's fight against FDA's war with alternative medicine, stem cells, vitamins, and peptides. As the Secretary concedes, this expanded access to experimental therapies could risk, could result in risky and fraudulent products. Secretary Kennedy stated, "Of course you're going to get a lot of charlatans." We already have plenty of risky and fraudulent products that consumers cannot navigate. Adding more to the problem is not the right direction. In addition, such a system will stifle drug innovation as more drug-like chemicals come to the market as supplements. The less incentive there will be to, there will be to do extensive, rigorous research into therapeutic benefits in the hopes of drug approval. The Council for Responsible Nutrition already told the FTC that it believes that randomized clinical trials are not required for most supplements, and that there is no requirement for full product testing of dietary supplements. The rigor at which industry is policing itself will not produce the evidence-based solutions to our health problems. For that, we need these experimental drugs to go through the FDA drug approval process.

Through GRAS, any chemical can become a dietary ingredient without FDA knowledge. FDA needs to know what chemicals and ingredients are in the dietary supplements. I don't think the industry will stop using GRAS just because FDA expands the scope of ingredients, regardless of the scope. This loophole needs to be closed if and when FDA releases its proposed GRAS rule. The agency should be clear that GRAS is not the appropriate pathway for new dietary ingredients.

Another fear that we have is that the definition of dietary ingredient will be expanded to the point of including substances like tianeptine or phenibut, which FDA has declared are not dietary ingredients currently. FDA officials have previously said that chemicals that fall outside of dietary substances make it difficult for FDA to regulate them as supplements. While I am sympathetic to that argument, I don't think it's worth the risk of allowing more companies to claim drug-like chemicals are legal supplements, especially when FDA doesn't know, doesn't know these, when these chemicals are coming to market and when they are on the market. However, I do think that legislative changes can better address these supplements that are in this regulatory limbo. In conclusion, the FDA should really focus its efforts on closing GRAS, better regulating claims, and focusing on drug innovations instead of putting its limited resources into figuring out how to regulate additional chemicals and ingredients. Again, I thank everyone for their time. I thank Cara, and I really look forward to the conversation we'll have in the Q&A. Thank you.

FABRICANT: So just so you know, what you say in an FDA meeting will appear in one of Cara's slides as a thought bubble in the future, so keep that in mind. Good to know. Good morning. And, thank you, Dr. Welch, Commissioner Diamantis, for focusing on this meeting, making it a priority. This is our 90th year in 2026, which is a testament to the competent professionalism of our member companies. Later today, you'll hear from some of them on a lot more specific scientific articles of the diet, from Novonesis, Lonza. And it's really important those folks really lead the way. They've invested hundreds of millions of dollars in R&D, regulatory science. You know, for an industry that still gets told they're under- or under-regulated, I think if you, when you see the science and what they're up to, it really doesn't give a lot of credibility to those remarks that they're under- or under-regulated or unscientific. We first approached the agency regarding this meeting. The focus was twofold. We wanted to discuss new techs that are growing more relevant, specifically targeted microbial fermentation, peptides, synthetic biology, enzymes, and nature-identical copies of plant constituents. That's important that they're optically pure. Second, we wanted to address regulatory definitions, as words do mean something, that are germane to these technologies, to understand the array of interpretations and flexibility going forward in how the law works. Once FDA announced the public meeting, a third discussion point came into focus: the current statutory framework to show that it works as

an amendment to the Food, Drug, and Cosmetic Act and works incredibly well. So it's achieved its goal. Every now and again, Congress does that. They do what they say they're going to do. Of promoting wide access while giving FDA the tools to safely police the marketplace. FDA has managed to get the job done, and it's a big job, as you've heard, with one of the smallest offices at the agency. That's a credit to Dr. Welch and her team and their technical capability at ODSP. Three out of four Americans take a supplement every day to promote their health and wellness. I'm encouraged by the mission of the Human Foods Program that addresses promoting and protecting health and wellness. When products are used responsibly, they're certainly a major part of contributing to making America healthy again. Unfortunately, the plane landing safely usually doesn't make the news. And despite some of the rhetoric you hear more than 30 years after DSHEA, dietary supplements remain one of the safest, if not the safest, commodity regulated at FDA. So instead of dwelling on what's wrong with DSHEA and market expansion, it's time to focus on how we can more effectively leverage authorities and how industries can support the agency in regulating, policing the marketplace. And this form of supplement modernization requires no act of Congress. And as you heard from Commissioner Diamantis, aligns with the 2026 Human Foods Program agenda. So let's pivot to the future. In 1994, no one could have anticipated this growth in scientific advances for ingredients and production methods. We know lawmakers had a bold vision to make supplements widely available to the American public because they said so. In defining a supplement, Congress intentionally covered a broad group of products, from minerals to botanicals to a category the FDA is focused on today, the 14 words that Cara said we're not going to say anymore. So with that said, the definition leads back to one of the principal reasons we requested public dialogue. What's changed the most in the last three decades is, of course, the science. So that's important, not the regulatory structure. Let's start with peptides, not explicitly called out in the definition of a dietary supplement. Recent media attention, alarmist media attention, which has us believe that peptides are only found in underground medical spas, compounding pharmacies, and court cases about weight loss, intellectual property, drugs. The truth is, we've been eating peptides our whole life. You probably ate a few this morning if you had eggs, milk, any sort of meat product. Highlights the most important term in DSHEA: dietary. Peptides are short chains of amino acids, also a category defined in DSHEA, and the building blocks of proteins. They act as messengers in the body to regulate functions like skin repair, muscle growth, and immunity. Peptides are most often broken down in smaller sequences, depending on the food matrix residues or amino acids. However, techs have emerged and are continuing to emerge to ensure that peptides stay intact through the stomach so they can be utilized at their intended targets. In a number of cases, this is no different than when vitamins were initially isolated. And vitamins come from the term "vital amines," which they aren't. Vitamin D isn't an amine,

but I digress. It's critical we explore how peptides fit into the definition of a supplement, because we're only beginning to fully appreciate what's going on at the cell signaling level for physiological health. They will need to be technical modifications, such as coding or additional functional groups to the base molecule and to, into amino acids within those groups. Some may view those modifications as establishing an active moiety or drug ingredient. We respectfully disagree. As the science evolves, we urge FDA to keep an open mind on how peptides can be delivered orally at safe doses so the substance can play a role in health and wellness. Similarly, DSHEA does not identify or define a probiotic or live microbial. The innovation in this space has been massive over the past 30 years, resulting in billions of dollars of food products, beverage products, and supplement products. Unfortunately, the pathways to market for probiotics aren't always clear. Probiotics come to the diet through a variety of sources, some through yogurts and fermented cabbage, raw fruits and vegetables. Others come from the human intestine and breast milk, not necessarily of the diet. We don't buy breast milk at the grocery store. Probiotic companies attending this public meeting are improving on existing genera, species, and strains based on physiological targets that we didn't understand 30 years ago. How do we ensure these ingredients fit within the framework of DSHEA and have a lawful pathway to market? Although the universe of live microbials added to dietary supplements cannot be unlimited, obviously, pathogens are certainly a challenge to that. How precisely or broadly should those be defined represents a source of significant new dietary notifications because of our technological advancements in understanding the microbiome? Those bright lines have not always been clearly delineated. And thus, some have termed the GRAS loophole or, is a pathway that is sometimes used for probiotics. This pattern is actually at odds with the current administration's call for overhaul of the GRAS process to ensure there's more transparency and FDA oversight of ingredients. So let's talk about the challenges the industry faces with the so-called "race to market," which is also critical to this issue between dietary supplements and drugs. The science of targeted fermentation, synthetic biology, and other advances show new physiological effects of dietary ingredients on the structure-function of the body. But advancing science to promote health and wellness does not make a dietary ingredient a drug. Also, likewise, an IND filed with FDA should not thwart research and development of new dietary ingredients. Unfortunately, the preclusion clause in DSHEA tilts heavily in the favor of pharmaceutical development. Describing the clause as a "race to market" is inaccurate because in any race, generally both participants know the starting line. FDA contends it can't disclose the date that an IND takes effect, which triggers the race to market. This creates a disincentive to innovate over concerns that an NDI could be excluded from the definition of a dietary supplement. These concerns aren't theoretical or hypothetical. Our organization has sued FDA not once, but twice in recent years over its application of this clause. Fortunately,

these cases have revealed that FDA has authorities or flexibility to allow a dietary ingredient to be sold in a supplement, even to determine that an IND predates the marketing of that supplement. For example, FDA can exercise enforcement discretion as it's done with NAC. The other option is notice-and-comment rulemaking. We look forward to the rulemaking on NAC, because this would provide an important precedent and for guidelines on this exact clause. What else can be done to overcome challenges posed by the drug preclusion clause and a secret IND date? FDA and industry should work together to ensure there's greater clarity of process over substances that may be on a dual track as investigative drugs and dietary substances. These disclosures must come to light before and not after supplement firms have invested in R&D and submitted safety dossiers to the FDA. Otherwise, innovation will be stunted. Protracted fights over the drug preclusion clause will continue to drain government and industry resources. In summary, the notion that our industry is innovating, investing in what we consider pharma-like research shouldn't be an impediment to innovation. Finally, as a former regulator at FDA, I must stress that FDA is not fundamentally broken. To the contrary, the pillars or objectives of the statute have been realized. There's a wide access to a variety of science-based dietary supplements, and FDA has ample tools to protect the public. I used many of these authorities when I sat in Cara's chair many years ago. So whatever the flavor of the ingredients we discussed are, FDA may need to either publish guidance or work with Congress on some sort of technical understanding, technical clarification of what "phony" means. Simply put, FDA does not require structural reforms to the law to protect public health and provide a regulatory pathway. So in conclusion, I'm very proud of the innovation led by our members because of their scientific research and investments to support a healthier America. We remain committed to ensuring that any new products are manufactured to FDA standards, safe for consumers, and backed by rigorous science demonstrating their health benefits. Thank you, Dr. Welch and Commissioner Diamantis.

WELCH: Can you move to the next slide? All right. So now we have an opportunity for an open Q&A of the panel. Ideally, the questions would be more focused on our panelists. But I do have a name tag, so I'll do my best. If you are interested in asking a question of the panel, please queue up at the mic. And remember, when you are asking a question, please begin with your name, name and affiliation, but at least name, to aid the transcription services. Mhm. And because I have the live mic, I get the opportunity to ask the first question. So this is actually for, for Jensen and for Daniel. I am, I am interested in hearing sort of the elevator pitch for, does "dietary substance" include substances that have never been part of the human diet? Jensen.

JOSE: I, I believe that the dietary supplement, dietary substances should be substances that are in the diet. I mean, that's, that's kind of the way to put it. You know, the adjective "dietary" goes to substances. It goes to substance. It's, you know, a

limiting, limiting word. So that's the reason why it was put into DSHEA. You look at some of the legislative intent. There's nothing that says, "Oh, it could also mean other," you know, "other things." So that's where, that's where we stand.

FABRICANT: I think the science in a lot of cases, that's, that's kind of an anti-scientific take. I think especially if you look at probiotics and you look at some of the, the microbials that are needed for development of an infant that are found on breast tissue, breast milk, that you don't have those in the diet. So, where would that innovation go? How does that promote health and wellness? I think that's largely where there's a difference. Intended use matters. Intended use is everything in the Food, Drug, and Cosmetic Act. So the notion that the intent of what's in the diet has to be considered, I think, is front and center to this discussion. Also, as the science evolves, you know, that's great that it should only be salt and pepper and things that are on your kitchen table that are allowed in products, but I don't really think that that's the case. Also, you can bring an ingredient to, it continues to perpetuate that as a food additive, it's safer than as going into a product that's a dietary supplement, dietary ingredient. I think largely, and again, I know there are some different, pretty aware of some of the different constraints in the law. But the science of the science, 90-day subacute toxicity, I mean, you're not, you're going to start there and then you've got to look at, you know, tox, you've got to look at other things. So I think if safety is assured, what are we talking about? So science number one, Center for Science in the Public Interest.

JOSE: Science doesn't change words. Science doesn't change English. I agree that as science evolves, our law should also evolve. I invite dietary supplement associations to come and come, come with me to Congress and to states to try to make the law change, the law to evolve with the science. If, and, you know, that's, that's just the way that the world, the, things, the law to say the industry is under- or under-regulated. So I don't really see that as, if that's not consistent with what's in the law now, change the law that the industry is under- or under-regulated. Again, the science, the scientific review by the FDA team versus the food additive team or GRAS team, I think are fairly comparable. While there are some differences, it's still the science. They're looking at the type of science that's required for pre-clinical ingredients to come on the market is fairly, there's a lot of, there's a lot more overlap than there's not. I think, the initial question, while simple, there is, there is a lot to dig into. I, so I do see we have a couple of questions. Christine.

AUDIENCE: I'm Christine Burdick from Farmavite. The first question I have for the panelists is, why is human breast milk not part of my diet? As a mother who had children, I have a real problem with someone telling me that the milk that I fed my child from me is not part of their diet. So I'd like to understand why that's even a viewpoint.

Dan, you're the one who said that.

FABRICANT: It's come from, I've said that from, from what we've seen, interpretations on NDI reviews and things of that nature where it's generally, you know, food, it's got to be marketed as food. And these sorts of criteria are added to the discussion. And so, and Christine, I'm not going to talk about anyone's, what they're doing in their personal lives, but I think, I think the, that's been the issue, right? Is substance in the diet generally means it has to be marketed in the diet and things like that. And that's been the response to NDI submissions is, "Hey, this wasn't marketed in the diet. This ingredient wasn't available widely in the diet." That probably isn't a GRAS substance. Or if it is, it was isolated from that tissue, right? So that's where that comes from. That interpretation. That's not my interpretation. That's what we've responded to in the past from the agency.

I do think it's, it's interesting we, we could dig into any of those 14 words. Hopefully a couple of them we could dispense with. But you know, what is the substance? What is the diet? And I think there's all types of conversations we could continue. Next question.

AUDIENCE: Hello. My name is Julie Sulak. I'm from Reliance White. I mean, my question is for Mr. Jensen, and I think it's the same way of, what Dr. Welch was saying. Like, how can we define what "diet," the word "diet," what does it mean? I've studied in Europe and then came here in the United States. There are many different diets across the globe. So how is it defined?

JOSE: Yeah, that's part of it. Usually, you know, when people say "diet," you know, they usually mean the things that are in their food. So that's, that's where their stance is. If we want to debate about, you know, does it mean things that are outside of the food, we can. At some point we have to say, what does, when, what do what do words mean, right? If you have a diet and you say it can mean any chemical out there, then what's the point of even using the word "dietary supplement substance," right? Just, they could have just used "substance," right? So I agree with you. Words do have different meanings or, you know, depending on your perspective. But at the same time, words do have meanings. And, you know, when you look through it, you see what it means. Should dietary substances be in our, in our, in our diet? And I think that it's true that that's where we're, where this is. Things are usually part of our diet.

If, okay, if I may. No, thank you for that. I just want to make the point that from where I come from, as an example, part of, like, there are certain foods that are not a part of the American diet or the United States diet. And I don't know if they are accounting for, for the entire world or for everything else that is out there.

So, yeah, there's, I mean, obviously I can't think of every single thing, for example, that's out there. But I mean, we're not, we're not saying, you know, I'm not saying at least to

say that like, "Oh, if it's not consumed somewhere else, you know, that it can't be considered a dietary substance." I would definitely want to look at each ingredient to make that determination and how it's consumed. So it's really hard to make a broad statement. And, you know, I don't really envy you too much to have to figure that one out. Sarah.

AUDIENCE: Hi, Sarah, CSPI, and full disclosure, I'm Jensen's supervisor, so I'm not going to ask him any tough questions today because it wouldn't be fair. I have a couple questions for Dan. And Dan, could you, I'm really interested in what you have to say. Can you answer these more slowly because I'm having a hard time following you? You speak very quickly. The first one is, yeah, I know, I understand for the, the time-limited remarks, but now that we're in the panel, you can slow down, slow down and walk me through it. So you've said some statements about GRAS and additives review, and it sort of seemed to presume that FDA is reviewing the GRAS dossiers. And I'm just wondering if you, what's your position on whether dietary supplements should use the sort of self-certified GRAS where FDA doesn't take a look at the safety information?

FABRICANT: Doesn't FDA, doesn't look at the safety information for self-certified GRAS. So notice, I mean, look, I think that that's part of the conversation. And it's a separate one on what the current administration is looking at. I think their, their talking point is one that makes sense to a lot of people is you look at, you know, the irony is we're up here, is the dietary supplement industry getting beat about we're not safe. The agency reviews all our new ingredient submissions. So, yes. Yeah. So, you know, so I think, look, if that's the goal of this administration, I think the devil's in the details, but the notion is that, hey, there should be some sort of at least cognizance of what was put into that review. I don't think most people would disagree with that. We certainly don't in the industry. We want to see an NDI submitted. So I think, I think where the challenge comes in in all this conversation, and this is why we're seeing so much activity in the states, is some of the, it's like this constantly moving "gotcha" game. Like we talked about, the science really drives everything here. It's driven the development of peptides, probiotics, and also the safety reviews, right? The safety reviews are largely similar, if, if I'm assuming that people are acting in good faith on the GRAS safety reviews. So I'm not going to assume they aren't. I can understand the government wanting to look at them. So I think though, again, those are, those conversations get to be a bit circular and they're not forward-looking or forward-thinking.

AUDIENCE: Sort of in properties, sort of what we call here in the advocacy community, "secret GRAS" to, to get these ingredients in. And that's, yeah. I mean, look at the companies around the room. Secret GRAS, I'm pretty sure too. And I remember, my time at the agency, if we walked into a facility, an ingredient maker, and we wanted to see something, you think they were going to tell us no?

For the fewer than 5% of the facilities, and 5% more than that get inspected. I mean, you saw us, 500 or 600 inspections.

So just to the point of today's meeting, then, you've talked about how the term "dietary substance" maybe shouldn't mean substances that are currently commonly found in that, if I'm reading it correctly, commonly found in the diet. And you have this example of breast milk, which may or may not be considered dietary for many people. What do you think "dietary substance" should mean? And should there be any limits on the definition of that term beyond just like, "Well, it's in a dietary supplement, it's supplementing the diet, so it must be a dietary substance"?

FABRICANT: I mean, I think there are other definitional aspects, but we go slice by slice. And I think I mentioned one with probiotics. Do I think that if a certain, if a genus and species are in the diet and somebody makes a modification to a strain, is that no longer part of the diet? I mean, if we're talking about pathogens, yeah, I think we all don't want pathogens, live pathogens, pathogens are pretty toxins in the diet, right? So those are like microbial. But if we're talking about, like I said, if we have a lactobacillus strain that companies are working on a new promoter region that's 99% homologous, and it's only adding additional amino acid residues that are also in the diet that may not presently be in the diet, but why wouldn't that scientifically be considered a dietary substance? The amino acid by additive, you know, additive it is, right? Because that amino acid is, and all the amino acid residues are part of the diet. But because it's a different strain, one that may not have been found directly in the food supply, it's not part of the diet. That's anti, it's really anti-scientific in a lot of ways.

So you'd still look for whether the substance was found in the diet, but you would sort of look for things that were related to substances.

I look at it at a, on a case-by-case basis. I think that's what the agency does best. Thank you.

AUDIENCE: Hi, my name is Bob Durkin and I work at Wasserman. I was formerly the Deputy Director of ODSP. So this is great, Cara, that you put this together and took this initiative. A point of clarification, and then maybe a follow-up question. Jensen, it seems pretty clear that you don't think that substances that are not in the food supply should qualify under E. And then I thought I heard you say that GRAS should be reformed to exclude things like probiotics, enzymes, and, and proteins. Is that correct?

JOSE: No. I was saying that GRAS should be reformed, should be reformed, not in terms of what substances are eligible for GRAS, but that that new dietary ingredients shouldn't be going through the secret GRAS.

AUDIENCE: So if you did that, you would eliminate a pathway to market for those ingredients. They wouldn't be in under E, and you wouldn't be able to do a GRAS determination to get them in the food supply. You'd cut them out of the market. There's no path to market then.

Yeah. So you don't want, okay. Everybody got that really clear now. All right. So you would shut down the path to market for those types of ingredients. That's fair. The other thing CSPI has been saying is that they don't like whatever a "secret GRAS dossier" is. If you opened up E and you allowed substances into E that are not in the diet, they would arguably all be new dietary ingredients. The only way a dietary ingredient can go to the market is if it's present in the food supply, in the form of chemically altered, which these wouldn't be. So these, these ingredients would have to submit NDIs to the agency, and their basis for safety would have to be reviewed. Their basis for manufacturing would be reviewed. Their identity would be reviewed. It would actually accomplish what you say your biggest concern is. And I'm just kind of curious if you've considered that as a, as a path.

JOSE: I would say that if more dietary ingredients went through the NDI process versus the secret GRAS process, there would be more safety. Yes. Things would be more safe.

AUDIENCE: Well, you should take that back and change your position then about not allowing these ingredients into E. If you allow these ingredients into E, it would basically force them into the NDI pathway.

JOSE: So what I, what I think is that FDA does have limited resources. And right now, FDA can put those resources towards expanding a market that's already pretty large. And, or it can look at, let's fix what is on the market right now.

AUDIENCE: So you want to stifle innovation. You don't want new products.

WELCH: Bob

JOSE: I want you, I want safe. So like, you know, I get it, right? There's a lot of people here that represent dietary supplement companies that want to sell dietary supplements. They want to sell more things. I get that, right? That's not my interest. My interest isn't for, for dietary supplement companies to make more money. Right? That's just not my interest. It's in safety. Right? So you can, I mean, I understand.

AUDIENCE: I just articulated how this would force them into the NDI pathway. So FDA, the folks in this room could review that basis for safety.

Sorry. Can you say that one more time?

If you force them into the new dietary ingredient notification pathway, the folks in this room on that team would review their basis for safety. It would be done by FDA.

JOSE: I would say under the circumstances where new, more new ingredients have to go through an NDI process would make things safer, right? Is my, would be my position be like, would my position be, should this be closed or should that be closed? I don't know how things are going to, are going to fall through. I don't know what reforms are going to happen. Right? If you want to have a conversation with me later on, we can talk about, hey, what's something that we can agree on? What's something that you can agree on because you want this, I want this. We're not going to agree. So like, I think that there's an opportunity here for everyone to come and to work together to figure out what is the appropriate process moving forward. And so I understand what you're, I understand you're trying to work together.

FABRICANT: What he wants you to say.

People should use the NDI because it's a safer process and more people.

JOSE: I think that that's what I've been saying is that people should use the NDI. And the answer is, should I think that that should, I think that we should expand the scope just so we can get more people into NDI? I don't know if that's, I don't think that's going to happen. I don't think if we expand the scope then all of a sudden everyone, all the, everybody here is all going to stop using the, the secret process. I just don't think that's the, that's the case, right? It's just, I mean, if everyone's going to agree on that, we're going to put it in writing and we're going to make it a law, then let's have that conversation when that comes in. But I'm not, but I just, I just don't think that's going to actually happen. Right? And that people are going to, if FDA all of a sudden says, "Hey, you know, we want to expand in the end, but we're closing the GRAS, you know, we're closing the GRAS pathway," immediate lawsuit will happen. The meetings at OMB that I've seen from the, you know, from the GRAS on the proposed GRAS, there are already threats in those letters from industry to the White House saying that we're going to sue FDA if this happens, right? So, like, let's talk about it.

WELCH: I'm going to bring us back to dietary supplements and actually bring it over to Barry.

AUDIENCE: Yeah. I mean, just to respond to that, expanding the scope will bring more ingredients through the notification process 100%. So my question is kind of like actually overlaps some of that, but just in the context of like what you set out in the beginning, like trying to get more ingredients, not in a, let's call it circuitous GRAS, notify GRAS pathway to market, as well as the opportunity to, to review more of the safety data. With that in mind, the two things I'm struggling to reconcile are, any substance can be brought into the general food supply through food additive or GRAS notification, any substance. So I have trouble reconciling that with a, with a narrower door to market if we want to see the science of dietary ingredients coming into the dietary supplement space. And the second part is if you

have a new dietary ingredient that's in the food supply unaltered, it doesn't require notification. So again, you're not, you're not seeing the data behind that market entry. So those are the two things I have trouble reconciling in this conversation.

WELCH: So I'm going to jump in on the first one because it's, it's a great callback to what I heard Kyle talking about when, when the dietary supplement program was aligned with the broader food chemicals program. I think that's an opportunity to leverage each other's work where it does overlap. But we're also separate offices. And that was distinct because it's important to retain the dietary supplement framework as it's written separately from the food framework. And we know that they intersect. Everyone in this room knows this. But, but there is, the frameworks are slightly different, for any number of reasons. And so I hear you. I think this is something that, everyone is, is thinking through. And I think it's important to give these thought-provoking questions time. I, I'm clearly working towards, we're coming up on a break. I am going to give, Jensen and then Daniel, just one last moment to answer, but, thank you.

JOSE: And, yeah, I get that if you expand the total number of chemicals that are coming into the market, you will get more NDIs. What I'm saying is, you also get more secret GRAS, right? So what you're saying, what you're saying is that that, you know, like I, that things come through the market, through the secret GRAS, through the secret...

dietary supplements to go through the, quote, secret GRAS route, though. That's my point.

Sorry. Dietary supplement substance definition today. You don't need to meet that to go through. Whether you notify or not, you don't need to, you don't need that criteria to get to.

Yeah, but if you, if you come in through and you become part of the diet, then you meet the criteria. Yeah. So that's, so I mean, that's why they're, they're the opportunity to review the safety and the science in the context of the intended use of the dietary ingredient. You've missed that chance.

Yes, I understand that. And I think that is going to exist when you expand the dietary substance. That's not going to fix it. Right? When you expand the dietary substance definition, things are still going to work as usual with, with secret GRAS, right? In fact, more things will go through with secret GRAS because we see that, you know, dietary supplement companies are using that more and more and more. The definition is not going to change that. Right? But that's just what that is, what it is.

WELCH: Thank you, Jensen.

Daniel, any final thoughts?

FABRICANT: Look, the fact you're actually giving me the last word, Cara, in the history I've known you, that's never happened. So my last word.

Fair enough. Fair enough. And since moving on from the agency, I've never gotten membership into the Secret GRAS club. So tell me, tell me how to get, tell me how to get into that. No, I think you're seeing the discussion for, for what it is. And like I said, you know, it's funny because this is part of it. When we go to Kyle, poor Kyle, Kyle, not your Kyle. It goes to state houses. He, there's a lot of confusion. I think the key in all this conversation is intended use matters if something is. And I think to Barry, he made good points like, yeah, you can put anything in the diet. Why do we have to play this game to where, hey, we want to put this in a supplement and it may not be in the diet according to someone's definition, but we've done the safety, we've done everything the right way. And like I said, using the example of probiotics. Yeah, a particular species is in the diet. The genera is in the diet, but the strain isn't. So it's, you've got to go this circuitous route versus my intent is to put this into an enteric capsule so it gets into the gut. And now I've got to play 900 million different regulatory games and hire a bunch of regulatory attorneys. No offense, Bob, you did a great job for health. How does that promote and protect health and wellness? I think it's just this is really where the definition is important because the expansion is important because this is like, okay, instead of hearing, "Hey, we got to go to the GRAS route or something else," we have a clear lane and we can develop with that lane. And I just think that overall makes for, if we start the conversation out that way, it tends to be a better conversation. So yeah.

WELCH: And so thank you. I think there's a lot that we could dig in on 14 words of this phrase. We are going to spend the rest of the day sort of digging in on the science. And I think we've already seen this weaving into sort of the policy and the legal discussion. There is, there's a lot. There's always a lot of, of review that our, our staff goes through. And I think it's important as we move forward, understanding and providing some clarity around what is meant by dietary substance that will benefit our program and our review staff. Absolutely. Our goal is that it also benefits industry to have clarity to, to understand, you know, the substance that I'm looking at, would it be a dietary substance? What are some of the attributes that were discussed? How do I package this together for, for review by the agency? I am happy to turn us out into our first break. It is 10:20. And I would like folks to gather back for a 10:30 start. Dr. Phil Yeager is kicking off the next session, and he's military, so you better know we'll start on time.

YEAGER: All right. I think I'll be calling us to order, please. And, lastly, I just want to make sure you're heading down.

Speaker.

We should have our first panelist. He was just here a moment ago, so he'll be coming in a moment. So I want to welcome everyone back from the break. As I introduce session two, I'm Phil Yeager, the Director of Research and Evaluation at the Office of Dietary Supplement

Programs. That's ODSP at the FDA. At ODSP, we understand advances in scientific innovations are for efficient production of dietary ingredients. We have a compelling session on new methods to produce existing dietary ingredients. I'm particularly excited because I feel like I'm channeling my prior experience as a patent examiner. This reminds me of the excitement I felt when I was reviewing new methods submitted in the patent applications, and sometimes we see these at the FDA. I apologize. Let me get this slide set up here. There we go.

Okay, so I have it on the screen, but you can also read the session description in your agenda. In section three, we will explore production technologies used to produce dietary ingredients and how these techniques will impact the ingredient produced, as well as how this impacts the evaluation of these ingredients. I want to focus your attention on the examples we have in there: the synthesis, the precise fermentation, the cell culture technology, and the recombinant production. There are some technical overlap in these terms, so I have a visual, provided a visual to frame this session.

Okay. This is a Venn diagram for production technologies relevant to dietary supplements. Synthesis is when you're creating a new compound through chemical reactions, and this overlaps with cell culture technology for growing cells in a controlled environment. So there's an overlap but obviously some differences. Precision fermentation and recombinant production, those two are considered the same when genetic modification of a microorganism to be a cell factory results in something that produces ingredients. This falls in that space, is completely enveloped by both categories: synthesis and cell culture technology. So our meeting, this session particularly, deals with the green and purple overlap and the red circle within that space. While there are slight or maybe even broad differences in these technologies, we're talking about creating dietary ingredients, whether chemical or microbial, from different methods. And technically we could say more broadly we're talking about creating creating ingredients because technology is used outside dietary ingredients, dietary supplements.

So in framing the approximate fit for this session, the speakers will discuss synthesis in some shape or form. Every speaker will cover this area. Doctors Glen, McKay, and Deaton will have more of a focus on cell culture technologies, while Attorney Powell and Dr. May will briefly mention them as part of a bigger picture. Dr. Deaton and Attorney Powell will discuss precise fermentation. And Dr. Glen will touch on the relationship to endogenous production. We hope this paints an informative picture about characteristics of production methods and the ingredients produced.

So I'm going to leave this up here for a minute. I'm not going to read all the questions. It's more for your perusal while I speak. We've asked our panelists some questions to guide

their presentations today. While I have them on the slide, I'm not going to go over each one. As I said, the overall theme in purple is how different methods impact the characteristics of an ingredient. And by the same token, our key question is what characteristics can equate or distinguish an ingredient made by different methods? The other questions are variants of this theme. You know, maybe the biggest departure is the regulatory question at the bottom middle, but they're all departures of a similar theme we can ask in different ways. Essentially, we can try and capture principles that might be applied beyond normal methods. Consider the impacts of these different methods and ask questions about how much production methods impact the ingredients' structure and function. So on the slide here and in your agenda, these are the expert speakers we have to address these topics. I've kept my comments concise. They can hear more from the experts in this area. I would rather frame this session to integrate it, to move it forward, and you get to hear from the experts rather than just hearing the FDA speak back. This order is provided to demonstrate the breadth of novel ingredient production methods for dietary substance, ingredients, and substance supplements, progressing from plant cell culture by Dr. Wesley Glenn, the Vice President of Innovation and Antibiotic, to industry perspectives on synthesis methods by Dr. Duffy Mackay, the Senior Vice President of Dietary Supplements at the Consumer Healthcare Products Association, to microbial and enzyme production methods, including precise fermentation by Dr. John Deaton, by Dr. John Deaton, Vice President of Science and Technology at Biome Technologies, to regulatory considerations across these production methods by Attorney Powell, a partner at Keller and Heckman, to finally manufacturing and formulation by Dr. Frank Romanski, the Global Vice President of Strategic Growth and Revenue Management at Lonza Capsules and Health Ingredients. And this session is set so that each speaker can build on the previous discussion to address characterization of ingredients, and this is to assess similarities and differences in ingredients. And with that, we will turn to the first speaker. I'll turn the microphone over to Dr. Weslie Glenn.

GLENN: If the clicker. All right. So all of the botanical supplements on the market today are produced through one of two ways. They're produced through either farming or through wildcrafting. And in either case, these plants are grown in soil. Let's take a look at saffron. Saffron is produced primarily in Iran. Over 90% of the saffron in the market today is produced in Iran. And there are a couple of considerations to take into consideration where you grow these plants. The, the, the region matters. What conditions they're exposed to absolutely matters. So in a recent study, there were several, several harvest sites that were on the eastern portion of the country. And they're all near each other, you'll notice. But they found out that when they looked at various parameters like the relative humidity, number of frost days, average annual rain, and then mapped that on to the productivity like the flower yield or the concentration of crocins, for example, that a couple of things popped out, that

there was an inverse correlation between the summer high temperature and the amount of crocins, which is typically the type of molecules that people are interested in with, with saffron. And so if you look in the blue rectangle on the top of the screen, if you scroll all the way down to where that yellow line is, the summer high temperature of 40.6 degrees, and then move over to the red rectangle, you'll see that it's about 70%, and that's an incredibly high concentration of crocins that are found in the stigma of this particular flower. Now go down just a couple of rows. You have a summer high temperature of 43°C, which is just 2.5°C higher. And then the crocin content over in the red rectangle goes down by 30%. So the conditions that these plants are exposed to absolutely matters to the phytochemical composition that comes out at the end.

And I mentioned also farmed plants and wildcrafted ones are the ways that we get these botanical ingredients. So another botanical that is both farmed and wildcrafted is ginseng. And the phytochemical composition is different depending on how you get access to the botanical ingredients. So if you grow the wildcrafted, it seems as though you get most of the ocotillo-type ginsenosides, whereas if you grow it in a cultivated region, you end up getting more of the PPD or protopanaxadiol type of ginsenosides. And the reason why this is, is because the growth conditions matter. So if you're wildcrafting it, these plants are exposed to very stressful conditions, very low levels of water, in many instances, very high or very variable levels of shade. Whereas if you're growing them on a farm, they're very pampered, so they're not producing the same types of molecules. And this is important because it depends on what these plants produce is, it determines how you have to work on them to get what you want out at the very end. So the way that the industry typically has worked on it to date is with a process known as "harvest and fix." And this is a term that Dana from Novella coined where you, it doesn't matter necessarily what you get at the beginning. You just expose it to, to solvents and heat, etc., to get to a standardized composition at the very end. And, we asked the question, along with other people in the industry, if we could control the composition from the very beginning. This makes the downstream processing a little bit easier. It also makes it a lot safer because you're not producing things that you don't want. You're producing only things that you do want. And the way that we can do or control composition is through a process known as plant cell cultivation. Plant cell cultivation is essentially us being able to take a biopsy of a plant or different plant tissue, put it onto a media, create a base cell line, expose it to a variety of conditions, scale it up, and produce the exact phytocomposition that we want. We can produce the same composition every single time, for months and years to come. This is why people often

confuse this with precision fermentation, because it's precise. You're making the same thing every single time, except we are using the endogenous machinery. We are using plant cells themselves. We are not taking the enzymes or the genetic material and putting it into a microbe like yeast or bacteria. Instead, we're using the plants themselves. The way that we have updated this technology, or brought it into the 21st century, is by using a lot of the same techniques at the very beginning. So doing the biopsy, creating the callus, and ultimately the suspension culture, but then we expose it to hundreds of different conditions. And I remember my CEO, Frank Jaques, on his first day, said, "Wesley, you don't have to guess when you can test." And I was like, "What do you mean by that?" Well, rather than guessing what the plant is making, we can expose it to hundreds of different conditions and then ultimately determine what the phytocomposition is. We can do that by looking at primary screens, like colorimetric-based assays to look for specific pigments. We can also do HPLC-based assays to look for specific molecules, as well as growth-based assays as well. From there, we can peer even deeper inside the cell. We can look at transcriptomics to see which genes are being turned on and turned off under specific conditions. We can look at metabolomics to see which molecules are turned on or turned

off under specific conditions. Each one of these datasets is interesting and informative in its own right, but together they're even more powerful and more predictive so we can control and predict what's going on inside of the cell. From that, we can revise the medium or the bioprocess condition, or pick a new cell line in general to get the exact composition that we want. We can do a quick test of productivity at the very end. And then what I'm not showing on the very far side of the screen is that we end up with a cell line, a medium, and a bioprocess combination that we can use for months and years to come to get the exact phytochemical composition that we want. This is not something that you can do with harvesting plants from the soil. Again, we use this vast array of multi-omics data, the transcriptomics and metabolomics, to be able to predict and control. So we understand what these concentration drivers are within the, within the cell. Looking at a little bit of the data that we come across on a daily basis, we can of course take these basic chromatography at the bottom and look for the concentration in a specific plant under these many, many different test conditions. We can also get more advanced machine learning type of output, such as the confusion matrix at the top left. And from there we can tell what are those concentration drivers, what allows us to boost productivity in terms of specific classes of molecules, and what breaks the productivity. So if we expose it to condition number three, we're likely to have higher concentrations of phenolics. If we expose it to condition number four, we're likely to have much lower concentrations of phenolics. And this is not just hypothetical. This is something that we have done in our lab in many different instances. And I'm just showing two cases here. On the right side you'll see sage, and on the left side you will see basil. So let's focus on the, the left side just for brevity purposes. We can show in condition two that we have very low concentrations of our terpene and much higher concentrations of our phenolics, up to over 20%. And then if we just do a slightly different condition, we can see that our terpene concentration in condition three is much higher, relatively higher, and then our concentration is much lower. We did a similar thing in basil. I won't go through this for the interest of time, but the point is that we are able to control and predict every single time. How do these technologies compare? I think this industry has a love affair with wildcrafting. I understand it has been around since humans have been on this planet, so 300,000 years. But you cannot control and predict what these plants make. I think that modern soil farming is a little bit better. It was only started in earnest in the 1890s, with the start of the Haber process to make nitrogen fertilizer, but you can't really control much with that, especially in terms of phytocomposition. I was talking to my new friend Marc, who I see back there, last night at dinner, and he was talking about how we can control the biomass and we can, we can grow plants very well, but you can't control what's inside of them as easily using modern soil farming. But with plant cell cultivation, which is only ten years younger than modern farming, I want to point that out, underscored, only ten years younger than modern farming,

you can control every aspect of it. You can control how the cells grow. You can control what the cells are making, and you can have on-demand production, meaning you can make it any time of the year. You're not confined by seasonality, and that there's a sustainability argument, that there is an accessibility argument to that, that I think should not go understated, and democratization. And with the last minute that I have, I just want to have a couple points of color commentary if I can get the slide to change. Fighting with it. But just because something's grown on the ground does not mean that it's safe. I'd even go further to say that if you grow things in tanks and you know exactly what's going in there, I agree that it's safer than what's grown on the ground. And the second piece I'll say is, really fighting today, that just because something is grown in a tank does not mean that it's actually a novel composition. You don't know what is in that saffron that's grown in Iran. You don't know what's in the saffron that's grown in Texas or any other place across the globe. And the "harvest and fix" is great for getting it normalized to a specific composition centered around one or two molecules, but not around everything else. You don't know what else is in there exactly. But what if you grow it in a tank and you know exactly what it's in there? And actually, I think it's safer and can be much more consistent. We can get the same thing every single time. And I'm getting kicked off stage. So thank you for, looking forward to all your questions.

MACKAY: Thank you, Dr. Welch, Dr. Yeager, for the opportunity for CHPA to participate in this conversation. I'm Duffy Mackay, Senior Vice President of Dietary Supplements at CHPA. And my point, I want to level-set here, is that Congress did, when it developed a definition of a dietary ingredient, it anticipated future developments and built in regulatory flexibility. The 14 words we're talking about today are a catch-all language that avoided statutory amendments as science evolved. The definition focuses on function, to supplement the diet, and purpose, to raise the total dietary intake. It does not discuss the source as being part of the usual diet or the manufacturing method. DSHEA was not intended to prohibit advances in science, including new and evolving ingredients or manufacturing changes that might enhance purity, consistency, or improve safety. And it definitely did not want to prohibit more efficient manufacturing methods or something that could be more environmentally responsible. So I was actually told to talk a little bit about synthetic synthesis, chemical and enzymatic synthesis specifically. And I want to give a couple examples. In the DSHEA, house going fine. Well, missing a slide here, but anyway. Oh, yeah. Fish oil. So think about the inherent flexibility. You think about fish oil in 1994. It was mainly fish body oil, cod liver oil, squeezed directly from the fish in the natural triglyceride form. Fast forward in time. Today we have many concentrated ethyl ester EPA products on the market. And these products, when they were developed, people submitted NDI notifications, and these notifications focused on the higher amounts of EPA and DHA they

would be consumed and the new chemical form of being ethyl ester. They did not focus on whether ethyl ester fatty acids were already in the diet. Similarly, phosphatidylserine in 1994, it was derived from the bovine cortex. And then because of prion concerns and mad cow disease, that was changed to chemical synthesis mainly from lecithin, soy and sunflower lecithin. And when no new dietary ingredient notifications were filed, but GRAS notices were submitted, and when the safety was looked at, there was the determination that despite these minor changes in fatty acids of these, they actually retained their identity, and phosphatidylserine retained its regulatory status. In fact, it retained its CAS registry number, and this is an example of an ingredient that changed its source, its manufacturing method, but it didn't change its regulatory status, and it actually became safer. So again, talking about synthesis today and regulatory consistency. So when you look at food policy and synthetic versus natural, there was a 2014 FDA guidance on changes to manufacturing methods for food additives and food contact substances. And in this document, there was a theme that a change to manufacturing alone does not change the ingredient identity, the safety, or the regulatory status, and that safety determinations are based on the finished ingredient specifications, any impurities imparted by the new manufacturing method. And because this guidance document was really developed when nanotechnology came into play, it was, you know, does the exposure to the ingredient or the metabolism of the ingredient change, as well as what is the relevant safety data? Again, not hinging on whether the ingredient is natural or a usual component of the diet. And FDA already has a long-standing acceptance of synthetic versions of botanical constituents. If you look at synthetic vitamin C, synthetic beta-carotene, and synthetic fibers all on the market, all having their natural counterparts. So the point being that source and manufacturing method can change, but that doesn't always change the identity or the safety of the ingredient. So another example, really clear example, is tartaric acid. Originally a byproduct of winemaking, GRAS affirmed. And then along comes a synthetic method of tartaric acid being made by enzyme-catalyzed synthesis, continued to be GRAS because it met the exact same identity for the Food Chemical Codex specifications. And when FDA looked at the data, they said, "We do not have any additional safety concerns with this new synthetic form, and the exposures will be the same as the traditional tartaric acid." So this was a direct substitute where the synthetic version took the place and maintained the same GRAS notification number, 21 CFR 101 84.1099. So I want to talk a second about regulatory parity. This came up early. So tartaric acid is naturally occurring in grapes as well as wine. So it is essentially a synthetic botanical constituent. And let's erase the fact that, let's pretend there were no GRAS notifications for it. Someone could have made a GRAS, an NDI notification, excuse me? Specifically, an NDI notification for synthetic tartaric acid, submitted it to the agency, and they would not have reviewed the safety data based on their opinion in the 2016 NDI draft guidance. Because in that

guidance, they say we prohibit synthetic botanical constituents. But because it, in fact, already is GRAS, so let's come back to the real world, it could be used in a dietary supplement because it's in the food supply as an article used for food. And as long as you didn't chemically alter it, you could then add it to an NDI. So this really is nonsensical. And I know that the agency is working on common sense and gold-standard science, and this would be aligned with both of those principles. Similarly, we have synthetic dietary fibers like polydextrose, polydextrose. And this is unique because it's a new-to-nature molecule. This is not a component of the diet. It's affirmed as GRAS. It's used in beverages, baked goods, as well as dietary supplements. So here is a new-to-nature synthetic compound that was established to be safe and, in this case, also effective. Because the fiber on the label, you have to show that you have the benefits of fiber. But the safety, once again, based on chemistry, exposure, composition of the final ingredient, the metabolism, and the available safety data, not hinging on whether it's natural or a customary component of the diet. So FDA regulatory principles already accept that functionally identical or, as Dr. Glenn was talking about, improved versions of bioactive compounds can be safe and lawful, and it would be erroneous and non-common sense to exclude these from an opportunity to file a new dietary ingredient notification. And in fact, there already is new dietary ingredients that have been submitted with no objection that are synthetic botanicals. In 2001, synthetic zeaxanthin with no objection. In 1999, synthetic hydroxycitric acid, no objection. So our point is the 2016 NDI draft guidance needs to be updated and corrected, and FDA must align the definition, those 14 words, with the plain language, which would not exclude synthetic constituents of botanicals or bioactives. And in fact, when you do change a manufacturing method, it should merely inform the safety assessment, but it should not preclude it from an evaluation as an NDI. In that 2014 guidance document I referred to, FDA has already addressed this issue. First, let's look at the ingredient. Did you change the ingredient identity when you did a change to the manufacturing? And we have things that help us identify ingredients: its name, any applicable ID number, its chemical formula, and more specifically, physical and chemical properties and their specifications in the combination of specifications that can make a fingerprint for that ingredient to determine, "Okay, I've changed to synthetic, but am I actually identical?" And if you're not identical, then you look at the manufacturing change as influencing the safety review. And you look at your source. Is the source safe? What manufacturing method did you use? Will that impart any impurities, contaminants, and potential byproducts? And again, to Dr. Glenn's point, the quantitative composition. You may change the quantitative composition slightly, but we know that that happens with natural compounds too, from batch to batch, from year to year, from different regions of the world. So there may be minor changes that allow you to review it safely in a fairly straightforward fashion. So in summary, opinion, and this is based on working with many people that were in the room when DSHEA was passed, but Clause E

is a catch-all for novel ingredients that were not contemplated in 1994. It's not intended as a barrier to innovation, and it's defined by function and purpose, not source or manufacturing method. So if a new compound or a novel compound is in fact intended to supplement the diet, its intended for ingestion in supplement form as defined by the statute, it is intended to affect the structure-function of the body, not treat, prevent, cure disease, and it has not been investigated as a new drug or approved as a drug. The "race to market" provision we've discussed. At that point, if it meets all those criteria, it should be evaluated as an NDI, regardless of manufacturing method or relation to traditional diet. And the GRAS process should not serve as a roundabout mechanism for establishing the safety of ingredients that are intended for dietary supplements. Thank you guys for your time. Right. Next speaker.

DEATON: Thank you, Dr. Yeager. It's a privilege to be here. Excited. My name is John Deaton. I've been in this industry, or actually, I've been doing fermentation for the last 25 years, initially in pharmaceuticals, but the last 18 years in supplements. I apologize up front for the country accent, but just briefly to go over, I've worked a lot of fermentation in terms of bacteria, fungi, bacteriophages, as well as enzymes. I'll briefly speak on enzymes in terms of your body. Your body produces many digestive enzymes. However, it does not do it alone. You actually consume, or actually your microbiome produces many enzymes to help you digest food. You also consume enzymes through fruits and vegetables and things like that. As part of the supplementation, people actually started realizing that they could, they could actually create and purify, these enzymes in nature that are coming from the organisms that naturally occur in your microbiome. Fungal amylase was one of the first ones from Dr. Takamine. And so they've been able to actually develop these, not only, basically enzymes that can break down sugars, but also proteins and many other types of enzymes so they can actually be used for supplementation. All of these can be measured by their activity. We've developed compendial methods that can actually be used to look at these. These also basically go through a very similar pathway in terms of production. They usually come from a microorganism. They are actually grown in a certain type of media to a certain level. And whether you're trying to produce the microorganism itself or you're trying to produce an enzyme or a peptide, those are monitored. And once you get up to that point, the material is then concentrated in some form, cleaned up in some form, and then it's either used as a liquid or converted to a powder. During that process, there are benefits in terms of, we've advanced quite a bit in terms of improving these areas. For instance, for media. Originally, so when you actually look at traditional versus biomass versus now precision, the original process was you're using the, the native organisms. Usually the process was in similar conditions in which they were first isolated. So a lot of times you would put this into milk protein or something like that. However, some of these actually contain allergens. And

so you could actually move that over. And they were also in anaerobic conditions, so they were slow growers, and in media that didn't always give you the best output. And we've been able to move that over. You can actually put that into, aerobic fermentation, so into organisms that grow much faster to produce the same types of enzymes or bioactives that you're looking for, as well as put it into media that actually will enhance the growth of those organisms or specific, actives that you're looking for that are not any kind of issues, such as removing allergens and things like that. Sorry. Also, don't move too far. I went the wrong way. Sorry about that. But also in terms of precision, you can actually advance that now that you can actually do, during my day, you could actually do overexpression vectors. You could actually multiply the number of genes, for your specific enzyme or, peptide in the organism. Or you could actually basically put it in an overexpression vector to get it. Obviously there's definitely much more advanced techniques now using CRISPR and basically setting up your organism to produce the materials that you need at, at sufficient, at actually much better levels and in a much better environment. Enzymes or proteins can also be, post-translationally modified. Those are also things that you can monitor and if you need it, if it takes a methylation or a phosphorylation or anything like that for the protein, the organism, you can actually choose an organism to make sure that that modification does occur. And then, of course, there are numerous techniques now for you to, Dramatic pause. Sorry. There we go. Sorry. That you can actually characterize or make sure that your proteins match exactly what the original intent was. And so you can look at the fold, the charge, the modifications, everything. There are numerous techniques that you can actually do so that the, the enzyme of interest or the protein of interest is well-characterized. So all the available, all the techniques that are available today, all of them are available for you to be able to characterize, your enzyme and making sure that, the original, endogenous, enzymes that you're actually targeting are actually what you're producing. And, just briefly, in terms of the host, you can have bacteria. As I mentioned, you can have yeast, you can have algae. Depending on the complexity of the organism. There are also other factors in terms of how quickly they grow and conditions. You can use organisms that do have some areas in which you want to make sure that there's not any negative impact in terms of the final product. If you're using yeast and molds, then you want to make sure that there are no mycotoxins. If you're using E. coli, which is common for cheese, obviously E. coli has been used for many decades. And so you just want to make sure that endotoxins aren't present. But those are actually very straightforward. Those techniques are out there. They've been around. You can actually do that. And then additionally, in terms of, like, the techniques available, the cost of full genome sequencing, it's very easy. You can actually know exactly what your organism is comprised of, what it expresses, the levels that it is expressed at, everything. And so you have all the techniques that go into your GRAS. I mean, you can put in all the characterizations that you need to

make sure that, first and foremost, that your product is safe. And so, there are numerous types of tests that you can do. You can do cell line testing all the way up to mice and, and things like that. So there are numerous advantages in terms of being able to develop exactly what you need at the levels that you're looking for with the targeted, either enzyme or microorganism or peptide, that you're desiring. And so with that, I'll thank you.

PAVEL: He was going to supervise me. Thank you, Duffy. Good morning. Thank you, FDA and all of you, for taking time to discuss these really critical and important topics where we are. My name is Tony Powell. I'm a partner at Keller and Heckman. I'm going to be expanding on some of the comments that we've heard. My conflict of interest disclosure is I am an unabashed, cheerleader for precision fermentation. I've had the good fortune of working in the industry and as an advisor to the industry, for more than 20 years, and currently serve as the executive director for the Precision Fermentation Alliance. Now, will I be able to handle the clicker? No. All right. I'm going to be talking a bit more. You know, Dr. Deaton did a great job talking about fermentation. About the framework, in terms of the regulatory and safety evaluation framework that exists and can apply across these production methods and, you know, precision fermentation or microbial fermentation. You know, one of the interesting pieces here is we're talking about it as a new method for producing existing dietary substances. This is a method that's been in use for more than 40 years. We have been producing vitamins through microbial fermentation for decades. And I would note, I did not anticipate the lively breast milk discussion when I included lactoferrin as an example of, of an ingredient produced. But perhaps we can settle that debate by noting that human milk oligosaccharides, which are produced through precision fermentation, have been on the market and commercially available for the better part of a decade, so at least some human milk is available. Now, in that context, we have had decades of developing a robust rubric and safety evaluation framework. So the question here, should the method of manufacture matter? To me is no, if and when the appropriate evaluation has been done on that ingredient and the manufacturing method. So I'm going to skip over the slide because Dr. Deaton did a great job. But this is the basic framework when you're producing a precision fermentation ingredient. And again, we're talking about an ingredient that was produced by a microorganism and then ultimately filtered out or separated from that biomass to provide, to present a final substance with defined specifications. So what does this framework look like? And this is a broad framework. And I will apologize in advance to any of my toxicologist friends if I misspeak, but I feel relatively comfortable. So the core pieces of a safety evaluation, and this is taking into account manufacturing, is that finished product identity and specification, the characterization of your substance and any other material that could be present, whether that is, you know, the typical, you know, ash, moisture, etc., or peptide fragments that are produced during the fermentation and

separation. Then an examination of the manufacturing method, what are the inputs during that manufacturing process? Are any hazards controlled? Do we understand the nature of the core components of that manufacturing method, the intended uses and dietary exposure, and then combined with your safety data, your toxicological assessment, which can be both in vitro, in vivo, and in silico, and that would cover allergens, which gives you your overall safety evaluation. So breaking this down a little bit further. A little bit further. So we've talked, and there's going to be a much more, I think a much more robust discussion around identity and characterization of substances a little later in the day. So I'm only going to touch on this and note that, you know, this is a core piece and that encompasses, encompassing specifications of that final product here. And where the manufacturing method changes, we still need to anchor around that identity of the, the, the substance itself and the overall specifications. Now, when we're talking about fermentation, you know, the production organism is the key. And there is a very well-established framework that goes back 40-plus years where the production organisms need to be demonstrated to be a safe strain lineage. Or in the EU, we have the qualified presumption of safety, which shows that these organisms are non-toxic and non-pathogenic, and there's documented safety through the lineage of those organisms and the strain. And that can be shown through use in food production or in dietary ingredient production, repeated toxicological studies. And there are established peer-reviewed approaches, including Pariza and Johnson, on this side of, of Pariza's work that have examined the factors that should be looked at in establishing that, that safe strain lineage. Now, when you understand that nature of the organism, that it's not going to be producing any secondary metabolites of concern, it's not producing any toxic substances, you can work with that organism to produce really amazing substances in a highly controlled, very safe manufacturing process.

Touching on the manufacturing. Again, when we're talking about fermentation technologies or plant, plant tissue culture technologies, these are perhaps new when applied to a particular substance. But these are very long-established methods where the, the factors are understood that must be assessed for safety. So when we're talking about fermentation, we're looking at the quality systems. We're making sure that those inputs and raw materials are food-grade, that the appropriate aseptic procedures are being used so that we're not introducing contaminants, and then evaluating that downstream processing. And there are a range of methods that can be used for downstream processing, from precipitation to filtration through ion exchange filtration that gives you your final product and specifications. The other point here is that manufacturing process and furthering on Dr. Glenn's notes, is how you ensure that you are producing the same thing over and over again. You do multiple batch analyses, non-consecutive batches, to show that you have control over that manufacturing process and the finished substance. Try this again. Okay.

Safety studies and data. Again, we have an established approach. And again, a note here for all of these, these, I'm giving a selection. There's going to be adjustment on a case-by-case basis, depending on the nature of the substance you're producing, depending on those manufacturing inputs and your exposure, etc. So nothing here is the entire, we can't boil the ocean today. But for safety evaluation, and I think it's really, I want to make sure that it's, I stress the point here that the safety evaluation looks at the, two minutes. All right. Got it. I will talk fast. Looks at the, the entire, substance and manufacturing method and consumption exposure as a whole. And that's why taking one factor, such as the manufacturing method, does not make that process unworkable in terms of looking at new methods. It just is part of that overall evaluation. So in terms of safety studies and a high level, when we're talking about, fermentation products, there are multiple sources that we can look to, including, FDA's Red Book, which lays out the basic framework. But this is a sort of typical matrix: genotoxic Ames test, chromosomal aberration, allergen and toxin screening using in silico methods, oral tox studies when warranted, and, and other data, toxigenic peptide in silico, etc. But there is a framework that will fit within the dietary, the NDI and I process in evaluating these manufacturing changes as they apply to specific substances. And lastly, okay. We can't finish without speaking about the exposure evaluation and safety margin, which are tied together to round out the final factors in our safety evaluation. Exposure is your daily consumption per person, and it should be evaluated in the context of the overall diet. And we are looking for a change at the high, high-end user, the 90th percentile user. Typically in Europe, they use a 95th percentile. And then we calculate our safety margin. This gives us our overall safety evaluation of our substance, manufacturing method. And my time is up. I will just close. I have included some references. Again, this is not complete, but I do encourage folks who are interested to, to look at some of the large body of literature that has been built up over the last 40 years that address these issues in detail and provide a robust safety framework when considering manufacturing changes. Thank you very much.

ROMANSKI: So thank you very much. And first, I want to thank all of my previous panelists today for the really excellent talks. Really insightful. I also want to thank Dr. Yeager, Dr. Welch, for inviting me to speak today. I'm going to speak just very briefly. Here's an intro to myself. I have kind of a unique perspective. I would say I am a technical person. I studied more in the formulation sciences, and I kind of straddled both lines. I work both in the pharmaceutical and the dietary supplements industry. We're also a manufacturer of what would be considered an active ingredient as part of the capsules, as well as we manufacture two demos or contract manufacturers, both one that makes dietary supplements within the United States and one that makes pharmaceuticals within the United States. And we also

have a portfolio of health ingredients that we produce and distribute, not just in the United States, but globally.

So just to give a little bit more perspective. When Phil and I were discussing this today, my perspective is really downstream of many of the manufacturers and those that are working on individual ingredients. But really, we are a manufacturer of both the health ingredients and the final dietary supplement. So we work with thousands of individual companies, some that are small, some that are large, some that are in this room, some that happen to be listening. We are a manufacturer of dietary supplements, and we get everything that comes in the front door in many cases. So sometimes we have customers that come in, and I like to describe them as a guy, a girl, a molecule, and a dream. And in many cases, they're trying to take something to market. And we as our team, we try and really help them get those types of products to market, and we try and navigate also with them through many of the novel processes with which to bring things to market. Just to give you a little bit of perspective. So some of the things that we struggle with as a manufacturer in many cases is variability within ingredients. So keep in mind, as a manufacturer, sometimes we are defining what the ingredient happens to be because we work with a couple of thousand suppliers, to be honest. And then sometimes it is our customers that are either producing and or dictating what those ingredients are. So being able to safely identify them, test them, make sure that they're up to the quality standards of our own protocols within our manufacturing facilities is indeed a challenge for us as an industrialist. The next would be the analytical methods associated with them. So we have our own suites of analytical labs, and that is one of the key challenges. And as some of the panelists described earlier today, things are made through different methodologies and they have different impurity profiles, and they have different identity profiles. And actually being able to do that in a wet chemical laboratory can be quite challenging. One example of that, we actually, one of our own dietary ingredients that we manufacture is L-carnitine. We used to make that through a synthetic process. Then we moved to a fermentation process. Then we moved to another synthetic process which happened to be cleaner, more sustainable, more high purity. And as you go through that, making sure that there's robust guidance in terms of identification and utilization of those products is important. And last but not least, it's really important that we have formulation and performance impact. So all of the ingredients that we talk about today in many cases are under siege from the body by the time they actually become ingested. And in many of those cases, we work in a lot of technologies with which to make sure that those ingredients get to where they need to go within the body. I'm going to share two quick case studies. I'm going to go very quickly through it, make sure I stay on time. So the first one is a case study related to a product that we manufacture. So this is on the ingredient side, not on the manufacturer side. This is a product that we make. It's called

UC-II. It is undenatured collagen type II. So this is a product that promotes joint mobility. This is a product that in order for it to basically do what it needs to do, it actually needs to stay in an undenatured form. And that's about 3 to, 3 to 6% of the overall collagen that is in the product. And meanwhile, to actually test that that's there, it's quite a robust testing methodology and an example of where analytics can play a very significant role. The challenges here is that we have on our specification for the product a validated ELISA methodology, which would be, we would argue, the most appropriate way to measure an undenatured collagen product. Meanwhile, there are a number of other products that are on the market that can make similar claims and ultimately are using an HPLC-based process, which is, is, I would argue, inappropriate for those types of things. So thereby you have several things that are on the market claiming the same thing, but are tested using different methodologies and thereby assuming that they're all identical or compatible or equivalent is something that is, I would argue, quite challenging. Next, I want to talk about the manufacturing side. And again, so in our case, we do a tremendous amount of research. We publish a lot of clinical studies. We publish them both in humans and animals. And also on a research side. One of the things that we were looking at, we've had some great discussions on, on enzymes and peptides and probiotics today, is actually making sure that they get to where they need to go in the body. So this is something that again, I straddled the line because I was a pharma formulator for many, many years, making sure that things can bypass the stomach in many cases because the stomach is designed to chew these things up and make sure that they do not get any further. So we've done, this is a recent publication that we did where if you were to take a standard HPMC capsule and you put an enzyme in it, this happened to be pancreatin as a model compound, it basically only a fraction of it gets to where it needs to go, where it would be effective in the gut. However, if you were to put that in a delayed-release capsule, so something that takes nominally over two hours with which to dissolve, you get to a much, more effective concentration that gets to where it needs to go. And then finally, you can actually do these more innovative technologies, like in this case, a capsule-in-capsule technology where you have a delayed-release capsule going inside of a traditional HPMC, which gives you basically the 4x efficacy that we would have for this type of product. So again, this is a model example. This is something that we do with quite honestly hundreds of formulations. And we actually are backward integrated into the capsule technology. So it allows us to take some of these probiotic peptides, enzymes and get them to different portions of the gut to make sure that they can get to their health benefits, ultimately. So last but not least, I think it's really important to share basically what I call here are considerations. And again, this is coming from somebody that's a scientist that's working primarily on the business side of things. This is a list of considerations that, that we've had from an aggregated industrial view of somebody who makes ingredients and of somebody

who receives thousands of ingredients and tries to put them into encapsulated form and help our partners get them to market. So first and foremost, I want to talk about regulatory clarity on novel production methods. So for example, a concept of, of tiered compatibility. So, and what I mean by that is when do you know when there's a meaningful change if you're going from, again, a synthetic process to a fermentation process and potentially back again, what defines "meaningful" and what are the frameworks associated with that? There's also a need for some clarity around what I would call multimodality ingredients. And to be very specific, a lot of dietary supplements contain multiple health ingredients in them. And defining that is something that I think is still an area of, of need. Next, I want to talk about analytical method considerations and expectations. So from that perspective, guidance on aligning method specificity and ingredient, ingredient complexity and production routes is something that is of particular importance. So from that perspective, I think that setting expectations in terms of the characteristics in terms of impurity profiles and residuals and byproducts is something that is still needed by industry. The next portion of that I would consider the defining what would again be adequate evidence across different supplier bases, because, again, within many of the ingredients that we have talked about today, many of these ingredients come from multiple different sources from multiple parts of the world and are tested against very different analytical specifications. So a degree of specificity there would be particularly helpful. Last but not least, I think there are gaps in the regulatory framework, one that as a manufacturer I think is really important to identify is as individual states come up with their own frameworks, it's a nightmare. As a manufacturer, I just want to be very honest with you that our customers, in many cases, these are small companies. Some of them have 10, 20, 50 people. Some of them are gigantic corporations. But being able to navigate the state-by-state variants, and that's just within the United States. So to be clear, we manufacture health ingredients and dietary supplements and they go all over the world. So we're already, it's already complicated going with exports from the US, but even within the United States is something that is particularly challenging. We've talked a lot today about the GRAS pathway, so I won't belabor that, but another one that I think is really important, and I think Dan Fabricant talked about earlier, is clarifying drug preclusion for novel bioactives is really important. And that's where something from my own personal perspective, I mean, peptides are a huge challenge right now within the industry and they're in the pharma world. We work on them within the pharma world and peptides within the nutra world as well. And yeah, in conclusion, there's a collaboration path forward on here. And once again, I want to thank all of you for the opportunity to speak today. Thank you, Phil, and I will turn it back over to you.

YEAGER: I know that clicker, right? All right. A few reminders for session two. So, we're going to move to the Q&A session. We want to remind you to keep your questions within the scope of this session, which is scientific and technical advancements in dietary ingredient production and the impact on the characteristics or attributes of these produced dietary ingredients. Please speak your remarks into the microphone and introduce yourself and your organization before your question. And as a reminder, the docket stays open for comments through April 27th, so please submit your comments there too. And so while we're waiting for people to come to the front, your main topic, how different methods impact the characteristics of an ingredient or, how they can equate or distinguish an ingredient? I think what I want to ask the panel is if you had to give your elevator pitch in one or two few sentences on what the key attributes are, characteristics to evaluate for an ingredient made by different methods, what would your one or two sentences be? So you want to start with?

GLENN: The green. I'm an opera singer, so I don't typically use a microphone, so. If I had to give my elevator pitch for plant cell cultivation technology, I would say that it allows us to predict and control the composition, the phytochemical composition of our ingredients. And that is not something that you can do with plants growing on the ground. Thank you.

MACKAY: Duffy. I would just say it's a, click, green, click, click the green. I would say that it's a case-by-case basis. And I'm kind of a cop-out. I really thought that Tony's slides really outlined those two slides where we talked about the influence on identity, the influence of the manufacturing method that provide a flexible framework that would allow you to tackle any of these manufacturing changes discussed today. Okay, John.

DEATON: I think that, I think technology's advancements and technologies and things like that just make, the product, better, safer, purer, and, you can get to the levels that are necessary for efficacy. So to me, you can get to the exact same product, that occurs naturally, endogenously, in a much more efficient, and better way. Thank you. Tony.

PAVEL: Asking a lawyer to keep it to two sentences. That's mean. And I know. And I realize that. Look, I think I would say at the end of the day, safety is our North Star. And any of these manufacturing methods that we're talking about, we have established frameworks and rubrics for doing that safety evaluation. And within that context, these should all be open for consideration as long as we are taking the steps and making sure that the products that we're putting on the market are safe. Thank you. Frank.

ROMANSKI: Thank you. Very well said, Tony. I think, I think safety being the North Star is something that's really important. And I think, as the panelists have described today, technology enables us to produce things that are more pure, that are safer for, for people,

for consumption. But there's still a need for standardization and benchmarking to know when and where those things are equivalent and or better. Thank you. Very concise. Thank you. Even Tony, thank you for being here. I'm not a lawyer. All right, Cara, you want to go ahead?

AUDIENCE: Yeah. So thank you all. What I really liked about the speeches were you were focused on some of the assessment questions that our staff is, is tackling every day. Frank, actually, this question is for you. There was something on your slide about ingredient variability altering release behavior. Didn't get complete notes, but encapsulation and impurity profiles. Which intrigued me. Clearly, I wrote it down. You also mentioned multimodality ingredients. I think I have something in mind, but I'm curious what you mean when you say a multimodality.

ROMANSKI: Yeah. So from a definition perspective, and I want to be clear, multimodality could mean a lot of different things. So the intention of the slide was really when we're working with advanced dietary supplements that contain multiple ingredients within them, how do you make sure that those are all, number one, not interacting with one another? Number two, getting to where they need to go within the body. So some of them are intended for for more, stomach release, for example, and others, as we mentioned, many of the peptide-based ingredients, they're just going to get chewed up. So they need to go a little bit further than that. So one of the areas of technology that we spend a lot of time researching is how do you build technology into the capsule itself and into the dosage form with either beads in a capsule or a singular capsule within the capsule and other things like that, so that you can, number one, segregate things that potentially could interact with one another that you might not know by just looking at a label. And then the other piece of it is making sure that they don't get chewed up by the body itself. So that's really the intention of what I was trying to explain.

AUDIENCE: Thank you. And, sort of elevator speech for the importance of NDI reviews. Indeed. Thank you. Go ahead, Sarah.

AUDIENCE: So I want to draw out what I think was a subtext to all your presentations, which is that, these, these practices, these manufacturing processes, preclude a substance from going through NDI review currently. I think that was the case, although I know that Duffy had some examples, at least one in his presentation of fish oil that did get an NDI review. So I'm wondering if you could sort of lay out what is the principle that prevents these, and maybe Cara could do it too, from getting NDI review, and then sort of how would you, how would you prefer FDA sort of identify when something that went through a novel process is a dietary substance? I'm not expecting a panel of regulatory experts on when something comes in or not, but I think answering the question about how you envision FDA could do it.

MACKAY: Yeah. Well, yeah. Let me just, let me just add, though, I think the subtext was not that they should avoid NDI review. They currently aren't allowed to. Yeah, that's the point

is. So if you, if you've changed the molecule so it's presumably no longer in the diet, you can't point to an ethyl ester fish oil in any food, that should not preclude it from being evaluated for safety. That, so when you've made a manufacturing change that's changed the identity, that it should still be looked at for safety. And we have a lot of examples of where the, the synthetic version is not exactly, exactly the same, but it may be, it still behaves the same biologically. It provides the same benefit. For example, the synthetic fiber version, it still behaves as a non-digestible fiber in the body. So it would be unfair to say that is not in any food. You don't have that polymer in any food that exists. We're not going to look at the safety data. So the point being that when you change it and you've changed identity, there still should be an appetite to evaluate the safety. Tony, you want to. I think that was well said. You know, I think the key point being is that this shouldn't be an impediment to an, to an evaluation, whether you are, when you are dealing with a substance, and there has been a new method of manufacture, as was noted a little bit earlier, there is variance in nature as well. If you're looking at any protein, there is going to be some variance in the the proteins that are produced, whether in a plant or in an animal. So I know we're getting around to your questions there. The key point being is that there are methods, there are rubrics that can be very easily applied and should be applied in the process when examining these substances. And just to add the fine point, but if it is identical, so if you change method and it is exactly identical, and you can show that in the same CAS registry number, same level of impurities and, you know, same specifications, then you should be able to avoid and that maybe that's through a pre-NDI meeting or other. But you say, "Look, we're working with the same exact thing. We don't think we need to file." Now, some might want to file in order to file a master file and get exclusivity, and that's a benefit in itself. That's something that hasn't been said is the power of a new dietary ingredient notification is also, we need enforcement and we need for the companies that go down that scientific road and make that investment to have the exclusivity until, you know, somebody else does the same. Thank you guys. Thank you.

AUDIENCE: Hi, I'm Karen Howard with the Organic and Natural Health Association. And in 2024, we presented John Fagan of HRI Labs' data relating to Bored Cow milk. So I greatly appreciate the fact that you are so sensitive to the safety issues surrounding dietary supplements. That's much more complicated than food, as we know. But I will share that there were 92 small molecules in the product previously never seen in science, that there were traces of fungicide residue. The amino acid composition was significantly different than cow's milk. And despite all claims, there was a presence of GMO residue within the, within the product. So I share that and ask, is it just that much easier to do dietary supplement evaluation safety, or is milk just an anomaly?

PAVEL: I'll go ahead and take that one. I'm familiar with your analysis that, as I understand it, analyzed a finished formulated beverage product and not the specific ingredient that which was, beta-lactoglobulin produced by precision fermentation. So your analysis did

not account for all the other components of manufacturing. And to my knowledge, you've never published that data fully, have you? It's in process right now. In final edits. Okay. And how did you separate the substance itself when you did an analytical method on a finished beverage product? I couldn't speak to that because I am not a scientist at all. Ah. Oh yes. Okay. Just sharing them. I see. So yes, I guess in short, I'm saying that it's an invalid study and it conflicts with hundreds of published peer-reviewed papers and in vitro and in vivo, in silico toxicological analysis of products of fermentation.

AUDIENCE: So your assertion is that the study is flawed. The results of the study is flawed.

PAVEL: 100%. Yes, ma'am. Thank you. All right. We can go ahead. Great.

AUDIENCE: Thank you. Graham Rigby, American Herbal Products Association. Excellent panel. Really appreciated all the insights and science that goes into making these products. The one question I had, there was a lot of very interesting slides promoting how these are different, unique, and novel. Clearly, from an identity standpoint and from a regulatory standpoint, they're meeting and going through these safety profiles. I'm curious how the panel thinks about labeling and, you know, consumer communication and letting them know about cell culture, precision fermentation, or synthetic versus sort of traditional botanicals or other products. Like how do you kind of view that going forward as an industry?

GLENN: I would love to be able to say that it's saffron, saffron, and saffron, and saffron, but I think that's in essence what people are doing today. Even we know that 99.9%, 99.3% of all saffron is clonal across the entire globe. So there's not a lot of genetic variation there, for example. And so if we're producing something that's genetically identical to what's already found in nature and, but we're just controlling the composition, I would love to just say that it's saffron. And oh, go ahead. I was going to say, but I think what I heard from your presentation was better because it wasn't subjected to 43°C. So shouldn't you be allowed to make that statement so consumers can know that yours is more consistent versus something that is cultivated or wildcrafted to your presentation? Sure, it's a differentiated product for sure.

YEAGER: And I think, I appreciate the panel's really focused on the process, right? And the question sort of about labeling. And so I guess, Frank, if we're coming to a finished product, do you have any comments about how that might cross over into, you know, what, what he's talking on the label?

ROMANSKI: It typically, as a manufacturer, we will provide some guidance to the customers that we work with, but we're not ultimately responsible for what goes on the label. And in many cases, in the example that you used, if you have something that is significantly improved upon and can allow for a claim that can go on a label that is justifiably looked through by the appropriate regulatory and legal authorities with which to

say, "Can I put this on the label and say it's three times more effective, three times more bioavailable, etc.?" And generally, what we're providing as a manufacturer is guidance from a technological perspective to say, "Yeah, I buy that study. That study was legitimate enough to, to stand up to a label claim." And Duffy is most closely related to what might be medically interesting to consumers. Go ahead. I think, you know, you have labeling, which is tightly regulated, and you have all the considerations of what you're actually going to put in your supplement facts panel. But then you have marketing, right? And some consumers might be drawn towards, "Hey, this is natural saffron, wildcrafted." And you might have some consumers that are drawn towards this, a cell culture. So I think, I think that's already accounted for in marketing, if you will. And I think you have all types of consumers that will be drawn towards these different manufacturing methods.

YEAGER: Thank you. Thank you. Okay, I guess I get moderator's privilege since the space is here. So I know, we had the elevator pitch in the beginning, but and you've really talked about how the production methods change. An ingredient may change, may change an ingredient's structure-function. I talked about quantification, but I think there are places where you talked about modifications at different stages of production that you think could actually affect the outcome. And so if we could say a few words on that, maybe starting with John, if you, Dr. Deaton, could you?

DEATON: For on the supplement side, a majority of enzymes and things that I've worked with, post-translational modification was minimal to none. There are some that are necessary. And again, you can pick the organism and the techniques to make sure that you get those modifications. And then you can test them in the end. Some enzymes and peptides, you do need the modification in order to have the activity, the effect that you're looking for. But again, all the techniques for basically up front as well as downstream are available for you to make sure that you're doing exactly what you're you're, you set a set out to do.

YEAGER: So thank you. And I think, you know, I may be asking about key stages, but I think I would ask the panel more broadly to how do you think with what's minor and what's major, what's going to make that big impact on the ingredient in the production method and that anyone can go ahead? Frank.

ROMANSKI: I'll start. So from from my perspective, also from a formulation perspective, it's really about defining an adequate specification for the product and then defining subsequently all of the analytical methods that tell you exactly what you need to know. And I know that's a very general comment, but some of the examples that I shared before show how analytical chemistry can sometimes gloss over areas that you're looking for, and using the proper tests and the proper methodology and understanding what it is that you're looking for in that specification give you the answers that you need to know to make sure that you're not. If you're changing those, the processing, for example, that you're changing the actual functionality of the product.

YEAGER: Thank you. Any other comments? Okay. And I think my last comment since we're

going to be heading into the third session after lunch, is we're talking about, you know, ingredients, how the technologies impact these ingredients. We've done plant cell culture, bacteria, yeast. We've talked about chemical ingredients. They're going to be covering a lot of those in the next session. So I'd say we can go down. Any last words before we go to the session on that. So we'll go reverse order so Frank can start first.

ROMANSKI: I don't know if I have any last words. I'm really honored to be a part of this and really engage in this public dialog. And I'm really excited to sit on a panel with some true experts in this area. So thank you.

PAVEL: echoing. Thank you all for the great discussion and appreciate the agency taking the time to work on this area. That is perhaps a little overdue. So thank you.

DEATON: I agree. So I really appreciate it. And I agree safety first. Everything else. It starts with that. And so I'm glad that, the advancements are out there, that we can actually develop a lot of different products that can be very beneficial to people, but also at the same time, make them or have them feel that they know that these products are safe to begin with. Thank you.

MACKAY: We spoke to the evolution of this industry. And if you think back to where our origins are, back with simple extracts and whey protein and fish oil and now the highly scientific and technical. I think the elephant in the room is that these are hard products to evaluate, and FDA has a small office and a small set of resources. And really, we shouldn't preclude any of these advancements from being evaluated where we need to make sure that the FDA is properly staffed and properly funded with the folks that know how to use these safety frameworks for all these different techniques to really establish the safety. And we can't. I heard, you know, we only have 75 days to review. That's important. I mean, that's hard. That's hard scientific work. But we can't let that stop the innovations that help keep Americans healthy and get the products they want. So I think it's a two way street, and FDA needs to evolve just as the industry has evolved. Thank you.

GLENN: And I don't know if I have any final words exactly, but I will just say that I'm very grateful for the opportunity to have been able to speak here. And I would also encourage anyone to talk to my CEO, Frank Jackson. Raise your hand, Frank. He's the former CEO of Chromadex, and he has been drilling safety into our entire work culture at Iona Bio. And thinking about how plant cell cultivation allows us to control and predict, as I mentioned, and also create potentially safer profiles in a democratized fashion in a way that is controllable and predictable every single time. So with that, I was like, thank you.

YEAGER: I think in wrapping up the session, I'll say, I really appreciate the speakers giving us where we can look at these differences and attributes. And I appreciate the focus on

safety, but also the focus on ingredients which should be looked at. And so what's the dietary substance back to the beginning of the meeting. So I'm very grateful. And with that I think you've given a lot of information. Obviously. Disclaimer I can't necessarily speak for the FDA unless I'm signing something for the FDA, but I think it's given some great information that our team can use to evaluate our dietary ingredients and dietary supplements. But with that, I don't want to delay. I want to get us to lunch. We're going to have session three, led by Dr. Betsy Yates and the. I want to stress she will be on time because she works for me. So we will be back at 1:00 sharp with the panelists hopefully arriving five minutes early down here. But thank you. Enjoy your lunch. Feel free to talk amongst yourselves and enjoy.

YAKES: For coming back and I hope you all had a good lunch. I have really been looking forward to this session. Oh, this is supposed to work now, if I point it at the thing they said. Oh, too far, too far. Oh, well, we'll leave it wherever it decides to be. So. Thank you for coming back today. I know it's late on a Friday. I know folks have flights, and so I want to make sure that you can catch them. And so I do want to take one moment to give a shout out to two of the team members that are in my branch. They are identity specialists and chemists and have worked a lot in this area on enzymes, proteins and microbial. And so thank you to Shontell Wright, who will be on our panel later. And then another one of our team members is in the South. And so that is Kail a Fuller. And she is online today. So I just wanted to give a shout out to those people.

And I think that's really important because as Cara said, you know, the questions were made by the team. And so to the entire team, thank you very much. I'm not going to lift everybody's names. This isn't the Oscars. And so yeah, the jokes get better I promise. So Safety First. Was said at the end of the last session. And I'm a chemist. And so like okay, I mean I can take that, right. It is all about safety, which means that maybe my team doesn't mean anything. On identity and status. I would like to say, though, that we are all here because it absolutely does matter. I think that I can argue, and I hope that most of you would agree that without identity, we don't know what it is. We don't know what's around it and how it might impact safety to public health. I think then secondly, we can't even begin to talk about identity unless we get figured out how it is a dietary ingredient. And so that's why we're here today. Right. We're talking about 201 FF, I'm not going to say it because I just I can't be bothered. And then the second thing being that we really need to figure out how we deal with novel manufacturing and novel ingredients. And so that's why we're here. My obsession, then, is on these novel ingredients. We want to explore the questions related to identity of peptides, proteins, enzymes and microbial that don't have a specific place in 201 FF. And then even building on that, we want to talk about what attributes are important and maybe conversely, what isn't important. And so to do that.

Oh my god. Okay. There's a time delay. Okay I won't I won't panic next time there's a time delay. We have a great array of panelists that will probably do better with the clicker than

me, and I'm really excited about the diversity that we have. Starting out, we have Team Protein and that is Dr. Elvira I knew I wasn't going to get it right. We'll just go with Dr. Gonzalez de Mejia and then senior VP Linda Neckmar. And they are going to present on different portions of proteins and the dietary ingredient world. And then we're going to move into a crossover talk from Dr. Andrea Wong. And then that'll lead us right into our microbes with Drs. Leyer and Smith bringing us home on those identity. And then of course we'll have questions and answers through the panel at the end. So why proteins, enzymes and microbial. And you'll notice peptides isn't on this slide. We could have added it. Clearly that's a part of the logical kind of chain of this. But we didn't. Two reasons it's a little controversial right now just to say the word peptides that was said earlier today. But that's not a reason to avoid talking about them and going through everything here. And secondly, it would make a really long title and it wouldn't fit on a nice slide and have the FDA logo in the side. I don't want to say the latter is more important, but who knows. And so we are here because right now these ingredients proteins, enzymes and microbial don't have a home in 201 FF. Okay, now that's not to say that they're homeless, but they might be a little housing insecure. And that is because they don't have a natural fit in the society of 201 FF. Now, they commonly live under the roof of 201 FF, but only when they are in human drink and is a part of our usual diet. However, with our shared goals of access and safety for dietary supplements to the public market and discussions on this trend, we want to understand how the status has or could evolve and how these then can be essential for establishing ingredients. I'm hoping to see many different viewpoints today, and even friendly criticism on the way that we have interpreted it, or the way we should interpret it. From your standpoint to my panelists. While we won't cement anything today, we can leave room for improvement, establish a great foundation, and construct a framework for these ingredients. So let's not get too floored by the details and set the stage with our framing questions. Anybody get the puns? They're house related? If you're not awake, the jokes don't get better. That was the best. There's no more. I promise. All right, so what are our questions? I'm not going to read through them all, but I'll click them as we go. Oh no, it's a clicking slide. I did this to myself. What identity attributes are important. And we want to think about them in the two realms of the proteins and enzymes, because they have their own area such as amino acid sequence, molecular weight, any modifications that may be there, and then with our bacteria, we want to think about how it works in the sequence strain. And the idea of that and maybe species versus strain difference viability, metabolic profiles, antibiotic resistance factors. And then if we want to move into the next area that's really important to think about this. It's when are we creating a new dietary ingredient. I think the last panel talked a lot about these novel methods. And in different places there we saw where at one point it was, well, they're not different. They're exactly the same. It doesn't matter how I make it. And then at another point it was said, well, but it can significantly change because of concentration or constituents or other things that may be in there, how it would fold. That's what we're getting into. We're getting into that. Once

you made it, what is it? And so the questions then for those are whoa, I had it once, I swear. Anyways, the questions for those are thinking about many of the same things. It's talking about what it is, how you identify it using science and what that means. Right. So when we talk about folding awesome it folds great. But what does that mean? What if it folds differently? And so that's what we want to talk about today. And with that, I want to remind everyone to please shut off your phones. We were just at lunch. I love your ringtone. So does your family. But it might be distracting to the people up here. So go ahead and shut those off. And with that, I will yield the floor to our first speaker. Thank you very much.

GONZALEZ DE MEJIA: Good afternoon. Thank you, Dr. Welch and Dr. Yates for the kind invitation. I bring you greetings from the University of Illinois. Okay. So today in today's session, as you can see, we'll talk about definition and sources, technology that applies to quality, potential changes in attributes that will affect safety and determine the most important quality attributes to establish identity in proteins, peptides and enzymes. So definitions As you can see here, proteins are very diverse macromolecules usually related or presented as nutrition or structural ingredients, and peptides are smaller components, more as smaller fractions, and have diverse biological activity. An enzyme is a protein. Enzymes are proteins that have certain biological activity. Okay. So the basics the basics. On your right you have the basic structure of proteins formed by 21 different amino acids linked very strongly one by one. Those bits are amino acids and they are very strongly bind. And depending on the sequence, not just the type of amino acid, but the sequence, how they are located throughout the chain, the polypeptide chain, the biological activity will depend on that. So is it going to have a secondary structure, a tertiary structure and even a quaternary structure? We have proteins of millions of molecular mass. Right. So the amino acids the physicochemical properties of amino acids. Charge molecular mass. Hydrophobicity will affect if the protein will bind or not. And that will give us the clues for biological activity. Oh, sorry. Okay. Back. This is one example just for you to see that we have the crystal structure of most proteins. Remember, like two years ago, someone won the Nobel Prize because they gave us all the crystal structure. So now it's very easy, really easy to learn about the sequence of the amino acids in proteins. And as you can see here, proteins like that crystallize a structure that is small. Crystal structure has around 571 amino acids. So sequence is important, but also type of amino acid because that's the way the protein will behave in nature. We have analyzed peptides around 43 amino acids maybe shouldn't be called a peptide, but chemically synthesized an extract from the plant extract from the grains and the activity was not the same. When we determine the secondary structure, the synthetic, the chemically synthesized one couldn't couldn't form secondary structure. So that's also important to consider. And that's just one example. So proteins have many properties. But solubility is very important if you want to isolate proteins. So you need to know that they are soluble in water albumins or soluble in salts like globulins or glutelins and prolamins that they're very hydrophobic and soluble in 70% alcohol, so that gives us a

clue on how to isolate them. Being careful not to. If you are using pH very alkaline pH, you can damage the proteins, the amino acids or the amino acids. And we have examples of amino acids that where the proteins were extracted at pH 12 for instance 11 very very high. And we found toxic amino acids within the protein. So we have to be very careful. There are not all proteins are the same are created equal. So this is the same family of grains I don't want. Well is there soybean soybean different varieties of soybean. And you can see those bands represent different proteins. And they came from the same environment. But genetically naturally genetically speaking they have different composition of proteins. So we need to know our sources. What is the source right. Do we want one soybean with more beta-conglycinin or glycinin. That's the question. If I cut each one of those bands, say 20 bands, and I analyze the sequence of the amino acids, I will find more than 300 proteins, more than 300 in each one of the wells. So again, we need to know our sources. These are just examples of crystal structures and the whole molecule. When is the hexamer or the trimer are either 350,000 daltons moles grams per mole or 150g per 1000g per mole. So just the sources we have. Right. Collagen was mentioned before. This is a very structural peptide which is a triple triple helix very resistant. I don't want to spend more time there. But why? Proteins are important. We know, right? We know that they are critical, crucial in the fundamentals of life. Enzymes. Hormones. Transporters. You can read there, but also in the industry. We can increase the amount of water. Absorb water. Water binding capacity forming emulsification many many properties in the preparation of foods and other ingredients. There are different methods, diverse methods I'm just mentioning here for others have been mentioned before. Enzymatic hydrolysis of protein is a good method because you can control it. Of course the enzymes are expensive, but you can use not necessarily very pure enzymes. And you can use germination. The grains contain enzymes, and during germination proteins get degraded or hydrolyzed and also fermentation. I want to emphasize this part because in our body we have many enzymes. Right? There has been mentioned from the body, from the mouth, the stomach, etc. so we hydrolyze the proteins. So it's important to know a raw protein. How is it going to be hydrolyzed when we eat it and then compare. We can compare the peptides that are form through gastrointestinal digest with other methods using exogenous enzymes. So here are the enzymes of course endogenous external you can use a purified enzyme is costly. But you can also know that the commercial enzymes sometimes they tell me subfamilies and contain proteases. So sometimes are really very crude preparations. So depending on the objective we want right. That will be the quality. And these are examples of where we use enzymes glucose oxidase for proteases like bases like bases. If we want to remove some fatty acids from a triglyceride. We can use some lipases as well. Types of products. Well, the hydrolysis here can be produced from several sources, different methods. When we use those methods, try to not damage the protein that you are going to use to produce the hydrolysate or peptide. Because if we use a lot of heat or pH extremes of pH, we damage the protein.

No. Okay. Okay. So this is one example of hydrolysis. No enzyme. All of these are proteins. They don't integrate during during hydrolysis time. And here you will use bromelain. And of course the higher molecular mass proteins were degraded were hydrolyzed. That doesn't mean it's bad. We're just hydrolyzed the protein. And we need to optimize. We need to optimize those conditions. Otherwise we can get some aggregates at the end. If we continue hydrolysis, we can get some aggregates. And this is the way we can characterize this is. This is an important slide because how do we determine identity molecular mass, isoelectric point. We have so many techniques nowadays HPLC chromatography methods, spectral photometric methods and mass spectrometry. We can quantify the peptides not just identify. And then there are so many databases that we can know the absorption of that peptide, the toxicity, the behavior and physicochemical properties. So there is a lot out there that we can use for free and optimize the conditions is important because there are many options, many variables that we can use and at the end determine biochemical or bioactive components of that hydrolysate or peptide. Why these hydrolysates are important. They are beneficial because good absorption, sometimes good flavor's not very good. Because we lose, we lose quality. Sometimes they oxidize and participate in other reactions. So stability, stability studies of stability are very, very important to make sure that the amino acids will not be damaged. Finally, the attributes to assess identity. You can see here the degree of purification type and length sequence. The peptide must be sequence studies, bioavailability, etc. Let's see one more I guess. Yeah. Finally, research is important. We still need to do research on these areas to determine common qualities or attributes and establish the optimum parameters for identity. Considering that this is a very complex situation. You saw the the magnitude of the proteins. Now enzymes we have to keep in mind functionality and safety. So that's that's it. I think it's very important to evaluate sources enzymes, conditions. And finally, the most important quality attributes to establish identity of the functional and structural characteristics of the hydrolysate. And finally the protein, the properties physical, chemical and biological properties of proteins and peptides. Thank you so much.

NECKMAR: Thank you so much for that good presentation and for laying the foundation for the next one. And thanks a lot also to to Cara, to Betsy, to the FDA for inviting us to speak here today. So I represent Novonesis. My name is Linda McMurray, and I'm also part of the executive committee of IPA. And I will today take a view of the industry view on the the identity of dietary ingredients. And I will go through the what, the how and why. So how we actually use those components that were so well described in the previous presentation. And up there. There we go. There we go. We'll start with this one. So Novonesis is the world's largest producer of biosolutions. We use nature's own components enzymes, proteins, microbes combined with modern technology and large scale fermentation to bring healthier lives and healthier planet. And microbiology is at the heart of everything we do, and everything is centered around fermentation. Bio solutions are used across more than 30 industries, including food and beverage where you can provide clean labels,

reducing food waste. Prolong shelf life without compromising taste and texture. Dietary supplements. Early life nutrition with focus on preventive health, animal health and agriculture. Reducing the need for antibiotics and chemical pesticides. Household care you can use enzymes washing your clothes and you use less energy, so there is a biosolution for almost everything. 2 billion people around the world are touched by a product that uses biosolutions from every single day. So biosolutions are here and they're here to stay. If we quickly move into the dietary supplement space, human health and dietary supplements are really in the intersection between food, nutrition and preventive health. And there is a really strong interest around clinically documented dietary supplement products and their impact on the microbiome and on digestive and immune health. And we work with components like probiotics, human milk oligosaccharides, enzymes, proteins, postbiotics, vitamins produced by fermentation and prebiotics. So all are part of the biosolution toolbox. And all these are produced with modern technology. Sometimes it's super sensitive.

There we go. You just got to be patient. So what is then the challenge? I mean, there is a need for biosolutions, highly effective dietary supplements at large scale. The challenge that we've discussed here today is the current interpretation of Clause E. How should Clause E be interpreted for substances that have never been part of the diet, and when is an ingredient meaningfully altered, and what parameters should then be considered? And our proposal here is as follows I mean, substances should not need to be isolated from food or be marketed as a conventional food to qualify as dietary ingredients. And regarding the alteration of the ingredient. Considering the should really be made case by case, depending on the ingredient and depending on the attribute, and here a weight of evidence scientific approach should be applied and safety needs to be the key aspect. And this clear regulatory framework that we are asking for. For now, this will really provide a greater transparency and consumer confidence in our industry. And also the focus should be on the risk factors and help prioritize safety, relevant data and a streamlined review for our colleagues and friends at FDA.

Let's take a look at history. Commercial fermentation was founded 150 years ago. We heard that already today. But we have used fermentation as the dawn of civilization. It's always been here to prevent drift, to preserve our food, and to make things tastier. So fast forward we go to 1990s. There was a lot of development from ancient time and 150 years ago into the 1990s, and the DSHEA Act was then founded. Since then, we're talking 30 plus years. Science has really accelerated recombinant strain technology, high throughput screening, bioinformatics, AI that we use a lot to predict outcome of what happens when we alter sequences and precision fermentation in large scale and highly sophisticated analytical methods. Needless to say, I think we can all look ourselves in the mirror and say, when we were back in 1994, we had no clue where we were going to be today. So I'm really happy that we are gathered to discuss what we can do to make things easier for us and for

the consumer. So back to modern times again. What are we actually doing when industry look at these components and when industry do this at large scale? And I would really like to thank both John and Tony for the previous session, because you laid a perfect foundation for the slides, this one and the next one. So thanks a lot guys. But it all starts with the DNA amino acid sequence and what kind of protein and enzymes that we would like to develop. And keep in mind, we are looking for a function. We are not just looking to develop an enzyme for fun. We are looking for a fun function that is applicable into the human health and our health and safety. So through high-throughput screening and AI driven structural modeling, we can really look at what is going to happen when we do different changes if we need to alter the enzyme or the protein. We also do assay development and we do safety testing along the way. And these assays we are actually using tons of different assays also. Those were shown in the previous session. I think I counted to 40 different analytical methods that can be used. We use all of them. We also develop totally new analytical methods and assays for the specific enzymes and proteins that we are developing. The production host is really carefully chosen. We use production hosts that are well known well-characterized and then the processes are developed, validated. They are GMP manufacturing. We follow all the rules and regulations to make sure that we have a safe and consistent process where the batch one batch equals the next batch. And finally the product is characterized. Tested both for function and for safety. So how are we then doing that. Well microbiology diversity actually comes from nature. So we always start in nature. We can use a wild type enzyme. We can use a modified enzyme if we do modify it. Again I want to call out for the use of AI technology and how we really look at what happens when we do changes. We optimize the protein, we characterize it, we do assay development, and then we do this product development. So we can produce this at scale because that is the leading word. How are we going to launch supplements around the world if we can't do it at scale with consistency, safety? As I said before, built in from the start. You can actually take it down to four different attributes. Sequence structure, function and the manufacturing process. And I know that's super simplified compared to what we've seen on screen today. But if there's something you should remember, those are the four attributes. And you can't use just one of them. Continuing on the how we spoke about manufacturing organism, we are using well known manufacturing organisms because they are characterized. We know what kind of other components that they are producing and we know that they are safe. We also know exactly the technical characteristics of these, and they've been used for a long time. We spoke about the what and we spoke about the how.

See if we can come to the next slide. Not sure. Let's speak a bit about the why. Why are we using fermentation. Well, the main driver is, of course, to create better lives and a better planet, but it's also to find a way to get access to nature's components in large scale. And a very good example is human milk oligosaccharides that are present. One of the most abundant ingredients in human milk and are really contributes to the growth of the baby

and to the development of the immune system and the microbiome. Today, it's used in commercial scale and it's used in infant formula, but also for for adults in dietary supplements. They are really hard to isolate, and they are not scalable with conventional methods like chemical and enzymatic synthesis. So here modern biotechnology has allowed us to manufacture materials that we previously were not able to do at the commercial scale. And that leads us to the summary slide. So biosolutions natural part of the food system used in dietary supplement across health systems or across health areas, and life stages and biosolutions are manufactured by fermentation, highly controlled and consistent processes by safe and known production hosts, and they are characterized to sequence and structure and function and process. I'm going to steal 10s for the new ingredients. There is a need for clarification of the regulatory pathway. We encourage a more robust and transparent FDA submission, and we also ask FDA to focus on the attributes that are most meaningful from a scientific and regulatory perspective. So for enzymes, proteins, microbial ingredients, and related biosolutions identities should evaluate using a modern and fit for purpose framework grounded in analytics, functional testing and risk based assessments. Thank you so much and looking forward to the continued discussion.

WONG: Thank you again, Cara, Betsy and all of the team here at ODSP for putting together this much needed event. I'm going to start off the brief introduction to CRN, we're a trade association representing dietary supplements and functional foods. This is an example of some of the brands and members that we represent, both at the finished product level, as well as contract manufacturers and ingredient suppliers.

So I want to take us back a little bit seven years ago to the last public meeting that was on this topic of responsible innovation and dietary supplements, in our view, responsible. And and since then, industry has continued to innovate, as you've seen some stellar examples of in the last session, as well as the previous speakers that preceded me, but we still face regulatory barriers to entry. And one of them is, of course, the interpretation of dietary substance. And our view is that innovation does not limit dietary substances only to those that are completely identical to substances in the conventional food supply. We are not meant to be frozen in time to what was innovated in 1994 and previous to that. I'll reiterate one of the thought bubbles that we had seen early on today that if dietary substances only include substances already present in foods, then nothing new can get in under this prong. And so innovation does mean that new ingredients can be considered for dietary substances, and that responsible innovation means that these new ingredients are safe for the intended use. So industry wants to do the right thing and wants to come through the front door here, and I chose a probiotic because I figured an enzyme and a protein may not be as cute as a little bug, but we're knocking at the door. We want to get in and go through the direct pathway for innovation for dietary substances. But unfortunately, we're being locked out. And the only other pathway is the indirect route of going through GRAS, introducing it into the food supply and then going into dietary supplements. And

we've heard circuitous. We've heard roundabout. Really, this is not the most effective pathway into the market. And it's also not always possible for various reasons.

Okay. So narrowing down to the topic of today's session, which is on proteins, enzymes and microbial, I've pulled a couple of examples of responses that FDA has provided to NDI notifications in previous years. The top one is related to a live microbial, and you can see there that FDA was really focused on identity to the strain level. So you provided information that there was consumption of the species. You provide some references to different strains, but no evidence that this exact strain was consumed in the food supply. And then the second example is an enzyme where you can see that we talked about post-translational modifications, folding, structure stability, enzyme activity. Again looking for sameness. So we have a question which is how did we get from the term dietary substance that plain language into DSHEA to sameness, to folding enzyme activity to the strain level. How did that interpretation come to be? And if you look beyond what's in the public record here of the NDI notifications, we also have examples of companies going into meetings with FDA wanting to introduce their new ingredients and being told, if you do submit this, we're going to we're not going to accept it. So it goes beyond what's here in the inventory.

So drilling down okay. Drilling down to microbial. This is not a new point, but I felt like it was important to raise that. We have in contrast to FDA's interpretation, other authoritative bodies have focused on species level when it comes to identity, at least for safe use. And really, our priority is for safe use in dietary supplements. And so we have the European Food Safety Authority, which has a long standing QPS or qualified presumption of safety list. And you'll see I've highlighted there that the status is granted through the assessment of species level for bacteria, yeast, etc. And then also the International Dairy Federation has a list of microbial food cultures with safety demonstration in fermented food products and in dairy products. You'll see readers will find a table inventory listing these species of microbial food cultures. So there seems to be a consensus here that identity for safety is really or history in food supply is at the species level, not down to the exact strain.

So at minimum, when we're talking for microbial, we believe that there should be a recognition that, microbial is identical to those at the in to those present in the food supply at the species level are dietary substances. And I say this at minimum because we do have a broader view of what dietary substances should encompass. And you'll hear that from my colleague later on in the comment period. But safety of the microbial for its intended use should be evaluated at the strain level as part of the NDI submission. So let us in that front door and then let us show you it's safe for its intended use through that appropriate mechanism.

And I'd be remiss if I didn't show a couple of really good examples where you can, you know, well, establish methods of establishing safety, determining safety of microbial. And the two speakers who are following me are true experts in this field. You'll see their names right there. That's intentional. You're welcome.

And so I want to close by going back to the topic of the session, which is identity attributes. All the questions that Betsy and the team have asked are are valid. They are important to address, but they are important for safety. They are not important for determining whether or not it's a dietary substance. We've talked about this is not an all encompassing list. Proteins, enzymes, microbial. All these different considerations of how they're manufactured, the source organism, the fermentation media, what happens in post-translational modifications. Those are all very important. But those are all addressed in the evaluation of safety. And when it comes to sameness, in this whole concept of being identical, that is also important if you're trying to bridge safety data to something that's already established in the food supply. And so by having a more inclusive approach to NDI notifications and removing these unnecessary, unnecessary barriers to innovation, this actually will give FDA more oversight of the dietary supplement industry and more oversight on safety, which is everybody's number one goal. Thank you.

LEYER: My name is Greg Leyer. I'm thrilled to be here and participate in the discussion. Today I have a scintillating topic today, and that's to talk about attributes of microbial identification.

Hopefully. Yeah. Let's go. Let's go. I think it's important just to recognize upfront that we're talking about unique something unique as far as dietary ingredients. We're not talking about a chemical. We're not talking about a mineral. We're talking about actively growing biological entities. And so that brings with it some uniqueness and almost a hierarchical approach in how we approach identification. Starting with genus and species and strain and etc. And so there's really multiple attributes that define identity. Of course taxonomy genomic identity, how we handle strains I'll speak about that in terms of strain lineage in the manufacturing facility and then other functional characteristics.

So how do we do this. Genomic identity for sure informs the taxonomic classification of organisms. And if you're familiar with where we have been in the last several years in Lactobacillus, there's been a taxonomic reorganization of that genus into many. Whole genome sequencing is the gold standard by which you identify the capabilities of the organism and link it to that particular strain. But I'd be remiss if I don't have manufacturing slides in my talk. But I'd be remiss if I didn't talk about strain lineage. And that's really how do we go about and use master cell banks and working cell banks to reduce any possibility of genetic drift and ensure that the strain that's produced after every fermentation is the same strain that's in our reference collection. And we do that in the industry, and there's

publications that show, Novonesis, for example, that go back 25 years to the the deposit strain. And they showed genetic identity to what's being produced today 25 years later. But it's a key component of establishing that identity. And then as important is functional and safety attributes that we could also look at metabolic traits and things like that to ensure that the strain that's being produced behaves as expected. Some of the common tools that we use in the industry to for microbial identification would start with either full gene or partial 16S ribosomal RNA sequencing. This is a quick hitter. It can be done in a matter of. Well, from a consumer perspective a couple of days, but it really just gives you genus and species information. There are some indications where MALDI-TOF is used. And that's really looking at ribosomal protein structure to identify and differentiate organisms. You can also get into genomic fingerprinting. And this really and some strain specific PCR technologies that would allow for some more strain resolution. But again I just want to emphasize that whole genome sequencing is the current industry standard, where that's the benchmark. And then that is tied back to the individual strain that's being produced. And then routine QC testing can use a variety of targeted assays, but typically we're not doing whole genome sequencing on every product that's leaving the door. We use these other more targeted assays because we have the strain lineage documentation, etc. it's an important consideration. The other thing I want to just harp on, yep, is just the whole concept of, of strain. So species versus strain. And we see a lot of analogies. I think Amy following me has some other analogies of differences, but we speak of a Lactobacillus genus acidophilus species strain. Pick your strain designator. But it's important to note that strains amongst the same species may have some genetic diversity. Clinical evidence for probiotics is typically tied to a particular strain that's been tested in that clinical study. And so the strain designation really provides a link to all the safety data that's been generated, the clinical endpoints and the clinical documentation that's been documented, as well as being controlled through that manufacturing strain lineage that I mentioned. Why does this matter? So I mentioned that strains can differ genetically and they may differ in important capacities. So they might be the same species different strains. But they could influence clinical activity. It potentially could influence safety characteristics and certainly metabolic outputs. And so the example I give on the bottom of the slide is just Lactobacillus rhamnosus, where, you know, LGG has been in the marketplace for decades. Novonesis has been on the marketplace in decades. Two different strains, same species, different clinical documentation associated with each of those strains. So it's important to consider that. This is an exceptional example because most of the time when I'm speaking about probiotics or organisms that are used for health benefits, we're not talking about those genus or species that might have potentially pathogenic cousins or strains, but an exceptional example would be E. coli. So back in 1917, so over 100 years ago, there was a strain of E. coli called Nissle. Now established to be a beneficial for probiotic uses. It's

been on the market for a very long time. But I mean, you wouldn't want a you wouldn't want to have strain Nissle be compared with a different strain of the same species being O157:H7 an enteric pathogenic E. coli. Right. So that I don't want to alarm anybody. That's a very exceptional example. But it does exist. So strain level genomic analysis is really important to identify any of those differences. What are some of the challenges. Strain specific identification. Comparative genome databases may be limited. And what I mean by that is be careful what you ask for. To say that we have a strain specific assay. What does that really compare it against? Is that compared against every reference genome of that species, you know, deposited globally, or are you just comparing it with maybe another species different strain that you're manufacturing in your manufacturing environment. So comparative genome databases may be limited to answer those questions. Bioinformatics expertise may be varies across the industry. And as I mentioned earlier, taxonomy is continuing to evolve. So that that brings with us some challenges but nothing that can't be overcome. And so perfect strain specific assays may not be feasible, but it really depends on the context of the question that you're asking. I want to just touch on this. This was brought up earlier in the day on an intentional versus incidental microbial presence. As you're aware, microorganisms are present all around us. They occur naturally in foods. But not all occurrences would represent an intentional dietary substance, right? So one example is Lactobacillus curvatus. So it is an incidental it's a non-starter lactic acid bacteria that's important and beneficial in many fermented foods kimchi, sauerkraut, sausage even some cheese flavor development. But that's an incidental contaminant. An intentional use of this strain in the food protection world is there are some strains of that species that have been shown to have anti-listeria effects. An intentional use of this could be also used as a as a probiotic. So the point is that context matters. And it needs to be context matters. Two slides I can do this in two minutes. Easily. The question of process optimization. So in the fermentation world, you heard this in session two. Fermentation. We use continual process improvement. If you have that mentality in your industrial footprint, you might be optimizing fermentation processes for that particular strain why to drive higher cell growth, improve yields, etc. but these changes don't affect well, they may affect growth in yield. They don't affect the microbial identity. An example would be if I take a corn seed and planted in where I live in Madison, Wisconsin, or I planted in South Carolina, it's still going to be corn at the end of the day. So the identity of that doesn't change. So my key takeaways key.

Is it's pretty clear microbial identity has this kind of hierarchical peel back the layers of the onion. It's different from other chemical ingredients. Strain level characterization is for sure linked to efficacy and safety. Manufacturing changes don't alter identity, but safety, as mentioned in the previous talk, is predominantly characterized at the species level, with

abbreviated conformation done at the strain level. And then I've used this phrase before, but context matters when defining dietary supplements. I appreciate your time. Thank you.

SMITH: Okay. Hi everyone. I am going to bring us home today. This is the last talk. I'd like to thank everyone for hanging with us and especially our folks online. Thank you for hanging out this long with us. So let me see if I can work this clicker. I'm here to talk to you today about the dietary substances and those 14 words. Oh, that one too far.

Oh, geez. Okay. Yes, we go back.

In full disclosure while I'm trying to get these slides. Why is it only going forward? It doesn't like me at all. Okay, so let's start again. Hopefully we stop the clock. I don't know. Okay. So in full disclosure. Wow, that's such a time delay. Full disclosure, I am senior director of medical affairs for Kerry North America within Proactive Health. We market a lot of the ingredients that have been covered today and include efficacious ingredients for probiotics, prebiotics, postbiotics, botanicals, as well as enzymes and lipids and proteins. So we cover the gamut. And I learned a lot actually today, and I thank the speakers for the earlier presentations. But I currently serve as president of IPA and have been for the past three years. I've also been a member of NPA for the past couple of years, and I really wanted to highlight these associations because they've really given us as an industry, a voice to be able to speak and meet with regulators, but also to help drive regulation. And this is a prime example of that. And I would be remiss to not thank Dr. Yakes and Dr. Welch for the invitation. Humbled to be here and to have this opportunity because we have had so many conversations over the years about these things. And you've seen it before in 2019, but we're here to give it to you again. So thank you for listening. And I thought just as a way of grounding all of us, we could just take a step back. And I really want to highlight a few things from DSHEA. So these are not my words. This is section two. This is the findings within DSHEA. And just to highlight a few things this was the intention right. So the recognition that dietary supplements can actually help us as US citizens improve our health status, the recognition of those ingredients to promote health. And I know they say disease prevention, but let's just say a reduction of risk of certain conditions. Right. And that nutritional supplements limit the incidence of these chronic diseases, and they reduce these long term health care expenses. It empowers consumers, gives them the option to proactively take care of themselves and get what they cannot get from the diet alone. It does contribute to the economy of the US. And my favorite right here. The federal government should not take any actions to impose unreasonable regulatory barriers, limiting or slowing the flow of safe products and accurate information to consumers.

So, okay, this is why we're here. And I don't want to lose sight of this. I don't want to repeat this over and over. But these 14 words. Right. This is why we're here. Maybe it's a little more

than 14, but, but we're here to talk about how probiotics and the identity of probiotics fit within E. So with that, I just need to give you a very brief history lesson, because it's important. And I only want to point out two things. So if we look at the very beginning, it is it? We all know microbes have been in the food supply. So as a category, live microbial have been in the food supply and very intentionally recognized as in the food supply document, it is in the food supply and used in the food supply. It evolved over time and again. You can read all this hopefully, but the recognition of the health benefit. So it wasn't only for cheese making and beer making, but also the recognition of the efficacious properties and the health that comes from ingesting these ingredients. But what I really want to point out is that as our microbial revolution came about in the 90s, and we really learned more, and the start of the shift was in 1994. So if we look at this, probiotics were not defined until 2001, which explains a lot. That is exactly why probiotics are not on that list. And so if I could leave you with anything, probiotics were not defined as a category of beneficial microbes within this live microorganism space until 2001. So we go to the next slide. We're really getting into what Andrea and Greg laid the groundwork for. And Andrea, I loved your picture, but it really just shows an unbalanced, uneven regulatory requirement. And so if your ingredient, as we covered over and over again today, if it falls within A through D, your burden is that of safety which is very nice. Right. And that seems appropriate. But again probiotics fall within E. And as we've talked about a lot, you must prove the presence of your strain in the food supply. Dan brought up earlier okay. What is the food supply. Is the food supply intestinal isolation. Is that the food supply? Some people eat weird things. What are we talking about? So if your strain is not exactly pulled from the food supply and intentionally present in the food supply, then you get this roadblock, right? And if you make it past that roadblock, then your burden is safety. But that's not the case. So I'm going to use a really cute analogy to further what Greg nicely explained about the strain in that, you know, when we look at the genus and species of a microorganism, there is a strain designation behind it, and it is analogous to that of domestic dogs. So if you look at the genus and species, these are dogs. But if you look at the strain it does not resonate. That's a tremendous difference. You would not, you know, use maybe you would use a French bulldog as your guard dog, but not likely. Right. So they have different behaviors, characteristics. There are different things that give them these different capabilities, just like the strains. Like LC40 is an example of a probiotic that we have that's beneficial for breastfeeding moms and also provides benefits for infants as well. But not every strain of ferment does that. And so again the strain is tied to efficacy. The species determines safety. And that species tells the characteristics of morphology metabolism and physiology. So just like Greg said, we're looking at species for safety. And there are some instances where strain information is applicable and useful. Okay I'm trying. Okay.

So when is strain information useful. Well Greg said this to manufacturing. You got to make sure that your process is controlled. The strain you start with is the strain you should end with. And it doesn't mean you test every time, but you should have a program in place to determine that. Clinical trials. We study specific strains. Those strains have specific efficacy like we just talked about. And when you have a product and you put that on your label to support structure function, language, that goes back to that strain and only that strain, no other strain within that species, unless you have clinical documentation to prove it has been shown to support those structure function benefits. Now concerning safety, when strain level information is actually useful and relevant and this is globally established antibiotic resistance profile. We need to make sure there's no transfer potential there. I wish I had more time to speak on that. This is globally acceptable. Andrea showed the the the safety publications and that's listed in there for sure. And then Greg spoke. He touched on this on the virulence factor, which is occasionally necessary, but you should screen your strains for these aspects of safety. And then of course IP.

So okay, now Andrea, you brought up QPS, which indeed species. Right. There is a recognition but it's beyond Europe. This is across the world. And there are a number of countries who recognize that at the species level, there's a number of live microbial that are recognized as appropriate for use in food and dietary supplements. Now, the point in showing you this is really to focus on what is appropriate information to be considered for use in food and dietary supplements, but in these countries they're not restricted to those lists. If you have a novel ingredient, you simply submit it as a novel food or a novel ingredient. So there is a pathway for that as well. So let's bring us back to E. I have two minutes. My gosh. So I have to move okay back to E. So there's essentially three buckets of the way that we ingest live microorganisms. The first is that that's intentionally added to the food supply. These are the probiotics that we know today. They are intentionally added to the food supply. We ingest them. They adapt to our gut environment. But they're still dietary ingredients. They are what we what we have eaten. So can we pull them from the gut and then put them in a dietary supplement? That's a question. The second, and this is why I put this publication. Oh gosh, I didn't even change this slide. I'm so sorry. The second is, this why I put this publication up here? So Berg et al. This is a great publication that establishes what plant and soil microbes we ingest. So if you eat raw fruits and vegetables, you're eating soil microbes. You're eating those microbes that live on those plants. And those are, incidentally, part of our food supply, whether we like it or not, we ingest these. And so they actually have health promoting properties. They enhance our beta diversity. And so this actually leads to health. And wouldn't it be nice to supplement the diet with these organisms that lead to health promoting properties. And then there's trillions of microbes in our gut. And quite frankly, not not all come from the food supply. And we can't trace them

back to the food supply. So with that, I also wanted to talk through beyond those three buckets, those incidental ingestion. So when you eat these microbes again, incidentally present in the soil and the raw fruits and vegetables that we're eating, our food is not sterile. They have healthful, healthy, beneficial properties. And so there's just this is from the Berg paper as well, but it really shows a nice job of how these microbes lend to overall health. And wouldn't it be nice to supplement the diet with these microbes? So I have two more slides. No. Sorry. Okay. Can I just make one point? You can read my summary slides. Okay. Yes. So the ask the ask here really honestly the ask is for dietary substance to include those substances that are appropriate for use in dietary supplements. And this would recognize subpart E as it was intended to be an innovation clause. And we've covered that today already. And the second ask is for a technical amendment to list probiotics as a recognized dietary ingredient within subpart E of 201 FF. Thank you so much. For all that.

YAKES: Yeah, I can't give extra time. My bosses are watching. Swells. My staff have to be as mean to everybody universally. So thank you all again. Oh. All right. Apparently I can't work on microphone or clicker, but that's okay. Just a reminder, there's some overlap. Please. All I really appreciate all the questions, but let's try to stick with an identity. Right. And acknowledging that status and identity are intertwined but not moving into fermentation from earlier today unless it has to do with identity. I appreciate that when you come up to the microphone name and who you are with today, and then the question, and if you have a panelist, you would like to address it to you, please do. And our other favorite thing, April 27th, is when the docket closes. Please get comments in there, especially after today. If something has really wrong with you on how you can communicate to us at the FDA what you would like to see, we would appreciate that. And so with that. Who has questions? No one. That's because we solved everything. All right, cool beans. Well, unfortunately we didn't. So I have a question. Yeah. Oh. All right, Dr. Yeager.

AUDIENCE: Yes. Okay. Okay. So in the introduction session, you covered proteins and went through some characteristics, but I don't know if you have any examples of how those differences occur in proteins.

GONZALEZ DE MEJIA: If we're comparing proteins, I mean, obviously in the last session we talked about many different ways like different expression systems and so human versus non-human. And so how can we distinguish those proteins at the protein level to see where there are differences. Well, there are many parameters. Molecular mass, the average molecular mass, the hydrophobicity through the solubility water or not. And then the, Does it contain anti-nutritional factors or not? For instance, some lectins that are present in legumes may be toxic, toxic, toxic chemicals, you know, and some are good. One amino acid of difference in those lectins can cause toxicity. One amino acid. So there are many parameters the sequence of amino acids. Does it have, essential amino acids or not? There are nine essential amino acids. Some proteins have many amino acids and

maybe are lacking lysine or tryptophan or some of the essential amino acids. So there are many ways in which way we can characterize proteins. Do they? For instance, collagen that is just has only the secondary structure versus lactoalbumin that has a more robust globular protein. So shape also is important. Thank you.

YAKES: Thank you. Linda, did you have anything you wanted to add to that or. I need to do that? I think I read your question.

NECKMAR: As you know, if you have a human protein or an animal protein of the same type, you know, an amylase that cleaves and it can come originally from a human or for from an animal. And we see use of both like bovine lactoferrin and human lactoferrin, for example. And for me, it comes down to you have to identify what you have. And you have to know what you have. And then of course, it comes down to function. And some animal proteins are actually functional also in the human body. But you have to test it. Okay.

AUDIENCE: Cara Welch, FDA. Greg, you talked about you said you would be remiss if you did not talk about strain lineage. And actually, that had come up on the previous panel as well. The documentation of stress safe strain lineage. And I'm curious if you can talk a bit more about how things. Well, how specific that is. Through the, the lifetime of production of an organism, or if you were to take a microorganism from food or from the gut, and then and then, you know, reproduce it at scale again, do you see shifts in there? And is that what you're getting at when you're talking about strain lineage?

LEYER: Yeah. When I was speaking about strain lineage, it refers specifically to the, how we handle strain collections and how we do that in an intentional way to minimize any genetic drift. So traditionally, if we isolate a strain from wherever and we've got a pure isolate, we would make a master seed collection that only gets tapped into on occasion from a master seed collection. We would create a working seed collection and that's what's used fermentation. Fermentation for, you know, when the working seed collection gets exhausted, we'd go back to the master seed collection. And so there's quality assurance and quality control ways that we can ensure that the master in this and the working seed collections are identical. And the point I made in my talk was there's obviously a dietary ingredient identification step in the process, but it might not go back to a full genome sequence, for example. You know what I mean? Because we've established all this strain lineage. And when you think about how many cell replications happened in the strain scale up process, it's a lot less than you would anticipate. And so the risk is is is quite minimal. But I'm yeah. So that's how we handle it. I don't know if that answered your question independent of where the strain is from. Yeah, Yeah.

AUDIENCE: You do Sula with your lines. Vitamin. I have a question for a professor. Professor de Mejia, my question is you mentioned something during your presentation related to the. When we have a synthetic protein and moving from, primary structure to secondary structure, and sometimes or you have seen that, synthetic proteins don't move from the primary structure to a don't create secondary structures. Is that directly correlated from

your point of view with absorption and bioavailability of of of the protein of the synthetic protein.

GONZALEZ DE MEJIA: Thank you. I'm sorry. Thank you. I was referring to a peptide that is very large for the definition of peptides is 43 amino acid three pieces of protein oligo peptide let's call it. And that one in nature can bind to a secondary structure in nature naturally extracted from the seeds. However, when it was chemically synthesized that that I could not bend could not form secondary structure. Therefore, the biological activities we were we were measuring at that time were completely different. So bending and, you know, forming secondary or tertiary or even quaternary structures, some proteins. Not all of them, of course, depend on the functionality also. And the activity is that does that answer your question. So it doesn't mean necessarily that every time that you have a protein or a peptide that cannot move from a primary to a secondary structure, that the bioavailability, decreases or increases. We don't know that. Yeah. Depending on the size, I would say if you are talking about small pieces of protein or peptides, usually they don't form a secondary structure. So then you have similar the same the same response. So it depends on the size of the molecule. Are they available as a you know primary. Oh yes very much so. And there are several mechanisms of action how they enter the body and the cell. Yes there are transporters. There are vehicles that are formed. They just move for diffusion. Yes. They are observed. Thank you.

AUDIENCE: Hi. Leslie Stein, I'm with Office of Dietary Supplements. I have a question specific to microbial ingredients. There was a lot of talk about intentional and unintentional exposure. Our interpretation of the definition is intentional because we have restrictions on contaminants. Does anybody on the panel have commentary on how we can splice that definition to allow for some unintentional but that aren't wouldn't be considered contaminants.

SMITH: Yeah. Go ahead. Amy. I'd like to comment on that because I did not have enough time to cover that in my presentation. But there was a very nice slide. That was a very nice slide.

Thank you so much. Yes. So, so we do know and that Berg paper that I did bring up from 2025 is a very nice set of data that really shows clearly how we do ingest these microbes that are, incidentally, part of our diet. So again, raw fruits and vegetables is the easiest and most straightforward, right. So those who eat a lot or, you know, at least regular consumption of raw fruits and vegetables, we do see a microbiome that is reflective of these microbes that are in the soil and often found on produce, quite frankly. So I mean, from my perspective, those are part of the diet that would qualify as a dietary substance. It's not intentionally there, but this is part of our diet. And so with that, I think it goes back to I think what every speaker essentially said today is first and foremost is it's safe, right. So for consideration to meet that criteria of subpart E, is it safe. And then, you know, make

the regulatory burden equal to that of A through D. So hopefully that answers your question. But thank you for letting me kind of talk through that slowly. Greg do you have anything additional on that? No.

AUDIENCE: Fair enough. Fair enough. All right. Bob. Bob Durkin AWG. Just a pragmatic question for when you're doing an NDI or a GRAS notification. We talked about species. We talked about strains. When you're working with two very similar bacteria. How do you distinguish whether or not they're the same strain? What's what's what. Differences matter. Don't matter. Does it have to be the whole genome sequence verbatim? Are you allowed a couple of snips or some changes? Like how do you determine what a strain is?

SMITH: I can give it a shot. There is, I think, a really nice, best practice, right, to look at the whole genome sequence. And we do alignment. So alignment to whatever that similar strain is. And you know, we've done this over the years where we do have two strains that are similar or one is derived from another. So in order to differentiate or consider them the same, you look at that whole genome sequence and you do an alignment and you find the percentage similarity on the, on the genome level. Then you look at the, translational similarity. So you would look at those amino acids and that similarity. Then, then you would look at, you know what is the difference. So is it lost genetic material. Is it gained genetic material. What are those differences and what do those equate to functionally. So can you maybe metabolize certain carbohydrates that this other strain can and are those meaningful changes. So quite frankly, I think it's a it's a slippery slope to say that one strain is the same as another strain when you do have SNPs and they may, you know, differ slightly in function. Because what you know, as a rule of thumb, the probiotic industry has studied our strains to be efficacious and offered those strains to match those benefits. But the safety aligns very well with similar strains and strains of the same species. So I don't know if you want to add to that, Greg.

LEYER: I mean, the foundational question of what differences would account for a new strain. Is it really challenging? One, I think you hit on all the different areas we can test to look for similarities and differences. And I don't know if that was your intentional question. Bob was like, how do you differentiate one strain from another? How do you say they're the same or they're not the strain? Because I think if you had a microbial taxonomist up here, they might differ a little bit. And is it one snip? Is it only a functional change? Is it? If you have additional DNA, that's probably a significant change if you lost something. So it's a really open ended question. I don't know that there's a precise answer for you, at least from this microphone.

AUDIENCE: Thank you. Dr. Yates, what do you think?

YAKES: I think they're the experts. I think it's very complicated. And I know that we've had these conversations before. How much changes is is okay to be a change? How deep do

you have to go? Do you have to sequence everything, know the exact folding and have some crystallographic structure of it? And I think that when we come back to the notifier or if we're looking outside notification and towards just an ingredient, the question is what do we know and what will we know? What gaps do we have to get to that safety. Right. So it's safety. At the end of the day, we can't get to safety unless we know what it is. And that's the identity team. And then we can't really do anything with it unless it's under our purview under E. And so in this realm. Right. And so that's what we're discussing today is kind of these things they're impossible to take apart. I think what I found really interesting was and I'm going to I'm going to say it right this time. Elvira, I got it. I'm not good with names, so I apologize. We decided I could say, Jim, that is the name that I can pronounce. Well, otherwise not so good. So you said amino acid. One amino acid change went from being nontoxic to toxic. Right. Well. Dang, that's one amino acid, right? That's just one small amino acid chemical. Right. And so when we get into these complex, how does it fold? What percentage is okay for a bacteria? Well I think it would be what is the change. Right. If it's one insertion or one deletion what does that do. Right. Did you just turn on. Oh Nissle. Was it. Nissle was your example I'm not a I'm not a microbiologist. So I'm way I'm way out of my skis here. Nissle into seven. On one. Five. Seven. Eight. Seven. I was so close. Cara's like you're not there. But you know what? What was that change I don't know. Microbiologists do. And so when we have questions our questions back to the notifier of the industry would be do you know what that change is? And if you do, tell us what it is. And if you don't, we got we got to get down to figuring that out. Own the differences and understand it from like a phenotypic expression point of view does. Does the change matter? Sure. Phenotypic genotypic. You know all the words, right? Our expectation is that the industry knows their ingredient and they know the risks. And then they come to us with that information so that we can have the same information as you do with hopefully, the goal from everyone in the room is creating something that is safe. That's a great answer.

AUDIENCE: Thanks. Again FDA. On the same vein of the conversation we're having in talking about microbes. I know there are characteristics you looked at that you mentioned, like antibiotic resistance or producing toxins, pathogenicity. But even, I guess substrate survival to be able to survive in a different place or a number of other factors. What what key factor characteristics are changing a microbe that would say, oh, well, we should evaluate it. We shouldn't evaluate it. It's it's, it's something that's characteristic that we need for identity or we only need for safety, right? For identity. What do we really need?
SMITH: Okay, that's a great question actually. And I think Andrea did a really great job of putting those two publications in her presentation. And that's been an answered question that has honestly been put out there by our industry. And I think we do a really good job of differentiating what do we need for safety and what do we need for identity. And so our best practice within our probiotics industry is to have a whole genome sequence like Greg talked about and really understanding what is your strain capable of mining the genome for different aspects of,

you know, what can it make, what can it metabolize? What are those genes do? And having a full understanding of that. But for safety, again, those publications do a really nice job of what is necessary, and especially if there is a history of use of the species, let's just say in the food supply or, you know, used in dietary supplements for sure. But but that would be an abbreviated version of safety that you would take at the strain level. And you would really look at things like that. Antimicrobial resistance, you know, are there any virulence factors. Did the strain gain any DNA to give it a new capability that would differentiate it from other strains? So so I think again, there's been published information that really sets a nice guideline. There is a consideration for a history of use though. So if it is one of these microbes that has been found in the food supply for a number of years, has been intentionally used in the food supply, that has a more abbreviated aspect of strain analysis of safety than does occur. Quite frankly. So thank you. Thank you. The only other comment I would make, and the FDA has addressed this in the past two, is that of intrinsic antimicrobial resistance. So of course, when we do a full genome sequence we're looking for any inherent virulence factors or antimicrobial resistance genes. And there are some instances where it's just the architecture of the cell wall of a bacterium that makes it resistant to a certain subtype of antibiotics. That doesn't make it a safety concern that's been addressed. But and that would be something that would always be addressed in any safety workup on a strain, because we would have to have the justification for why this isn't a concern.

YAKES: One more question. Do we have time? Yeah. Last question. I think.

AUDIENCE: Malcolm Spicer with HBW Insight, one of the award winning newsletters in the life sciences area from Citeline Publishing. This question has been forming in my mind and bouncing around since Dr. Welch's opening remarks. And Amy and Andrea, both in very diplomatic and very tactful and clear ways, addressed it. And the question is, my sense is that this space between a dietary ingredient being part of the current food supply, or a substance appropriate for the human diet, that for newly creating tension between industry and the FDA, that that there was an expectation from the industry that the flexibility that Andrea spoke of was there, that it's a substance appropriate for a human diet as opposed to the more rigid and very much more limiting human food supply, the current human food supply. So am I correct in saying that there's a new tension there, and there's concern that that if not door, that window is closing or tightening.

SMITH: So I've been visiting Cara in her office since probably 2014. Maybe it's been a long time. And Bob as well when he was there. So to new issue, I would say no. I think, you know, we as an industry have evolved in our technological advancements to help us identify strains and understand our microbes to the level that we do now. But this has been something that since, quite frankly, the NDI guidance came out, that this has been a topic of discussion. And I personally have submitted NDIs that have been rejected because the

strain was not pulled from the food supply. So I have lived that, you know, and again met with Dr. Welch for years on this topic. And that's why I'm so grateful to be here and have this conversation, because it really gives us an opportunity to maybe take a step forward. And we've not been able to do that before. Dr. Wong, do you want to close it out there?

WONG: Oh, wow. Yeah. Sorry. I'm bad. Yeah. I mean, I will echo Amy's, comments that we've had many members expressed concerns over the years about this narrow interpretation of dietary substance. And, you know, it does not reflect the innovation, the level of sophistication that has really evolved in this industry. And so we are really welcoming of this opportunity to, to broaden everybody's viewpoint. And this is an excellent first step.

YAKES: So thank you. I actually think that that's. That's. Where I want to leave everything that is the perfect like full circle moment. Because I swear that's where Kyle started this morning, right? So I'm just going to leave it there. Fortunately, unfortunately for you all and for us all, we have a wonderful time where folks can contribute. So I'm going to turn it back over to Dr. Welch.

WELCH: All right. So that was fantastic. I'm going to call down my colleagues because now we are entering into the open public comment time.

They're all three in there. I'm going to join you here in a second table. I will announce the folks who have registered to give public comment. I would just ask that you line up at whatever microphone, is easier for you to access. Thank you. You get three minutes, and then I don't have any music to play, but I am pretty good at talking over people so. I can do the jeopardy sound for you. Anyway, I appreciate the discussion. I have made a fair bit of notes, but I'll wait for my final closing remarks. For our open public comment period. I'm going to be joined at the table with Dr. Yeager. We've already heard from him. And and Dr. Yates. As well as Shontell Wright, who is a chemist in Betsy's branch. Shontell has been reviewing NDI notifications. I won't say how long, but many of you in the room are probably familiar with her work. Excellent chemist. I and I have really enjoyed working on this public meeting with her. So let's go ahead and get started. I'm going to transition down here.

Okay. All right. So first we are going to hear from, George Paraskevakos and then after George Douglas Lynch. So George, you have three minutes.

AUDIENCE: Thank you. Dr. Thank you again. So George Paraskevakos executive director of the International Probiotics Association. Basically we've been around for close to 30 years. So we felt between this and the definition, we're older than the definition on that timeline just to point it out. And basically our lane has been probiotic since three years, up until three years ago when we also took on prebiotics and post biotics. So we appreciate the opportunity to participate and bring expert experts from our membership to also present on why reframing 201 FF regarding ingredients such as probiotics to directly qualify as dietary

ingredients without having to be present in the conventional food supply is necessary. IPA's position has been based on the plain language of section 201 FF1, and in consideration of context provided by the whole section of 200 and 1FF1, and other aspects of this which Ivan Wasserman, IPA legal counsel will bring up, is that FDA's interpretation is too narrow and does not reflect the intent of Congress. IPA believes that the correct interpretation is one that provides a pathway for dietary substances that are not already present in the food supply to be appropriately utilized as dietary ingredients, as mentioned by others today. IPA believes the intent of Congress, when it included the section in the show, was to provide a pathway for innovation and biologics, that is, microbial ingredients, probiotics and all other biologics, including pre and post, are the perfect example of such dietary substances. Our goals of attending the public meeting was to seek information and to try to understand the other's views in the current scope of the section, and with a better understanding of this, IPA will move forward and will try to partner and collaborate with FDA and others in the room to assemble an administrative record that FDA can rely on in involving its interpretation of section of the section, and allow it to be utilized as the pathway to market for the innovative dietary ingredients. As Congress intended, we were encouraged to see that this discussion was facilitated, but also that FDA had the foresight to include expert panelists from our membership to discuss the implications of advancements in the manufacturing of probiotics and the characteristics that FDA believes are essential to establish their identity. So we'll hope and actively collaborate with FDA to ensure that the work started here today leads to at least three in closing, three specific outcomes that we'd like to see provide a regulatory solution to ensure the definition of dietary ingredients include microbial ingredients, probiotics, and all other biologics, regardless of what source they are isolated from. IPA's concerned about the future of innovation. Otherwise, there's no safety, efficacy, or public policy reason to treat an ingredient that's included into 201 FF1A through D differently than that of an ingredient that is not solely on the basis of whether it is in the food supply. And we should not be ascribing a legislative intent to do so. A benign ingredient should not be subject to more hurdles than a poisonous herb. This seems particularly to be the case for probiotics that were clearly marketed in the initial phase in the United States prior George. 10s. Second, we'd like to provide a regulatory solution to the unresolved clarity, recognizing that a species of like live microbial or probiotic is primary basis of determining its safety and novelty. And there's plenty of examples from global perspectives, from species level positions. And third, provide an acknowledgment that advances in manufacturing utilized for optimization innovation do not necessarily cause chemical alterations that change the identity of a live microbial or introduce unknown hazards. Thank you. Comments.

WELCH: Thank you. George. All right. Douglas Lynch. Okay. We're going to move on to Kevin Bell. Kevin Bell and then Megan Olson. Thank you Kevin.

AUDIENCE: First, I'd like to thank the FDA and of course, you, Dr. Welch, for, for the meeting today. And all in all of you, I think this has been very helpful. And I assume it works in industry as a lawyer. I truly do appreciate the work that you guys do. And so thank you. I think there's been a lot of thoughtful discussion about a lot of issues that needed to be drilled down into some of the, I mean, getting into our famous 14 words, but also the impact of that as well as, how all that plays out for the companies that have, has an economic impact for it. It affects the research and development, things like that. I was interested to hear comments about, involved in, on behalf of general counsel, the couple of lawsuits on CNN and then, that were successfully resolved. And I appreciated working with the FDA on those and getting that taken care of. And I look forward to the regulations coming out. And I truly appreciated the comments made on the in the letter, as it related to things that we can all agree that rather overlooked or or you reversed your position on and took another look at. And I think it's important for industry to know that you'll do that as soon as to advise them. It's sometimes hard when you don't know when you don't know the answer to the question. Specifically when it comes to what could be done, what should be done, what would be best for the client would be best for the government. So I do appreciate that. I'm I don't have any questions for anybody. My last comment would be is when it got to new data and get notifications, I'm always, as everyone knows, a fan of enforcement on those. So I think that what I find is really important in dealing with clients, whether they're good actors or bad actors. Compliance and enforcement has to go hand in hand because you're not going to get someone to stop speeding until you start giving them a speeding ticket. And but I will tell you this once you start handing out speeding ticket. People will slow down and drive the speed limit a lot faster. That's my opinion. Sorry. Thank you.

WELCH: Thank you. Kevin. Thank you. Megan. And then after Megan, we'll have Graham Rigby. Megan.

AUDIENCE: Hi. I'm Megan Olson, general counsel with Council for Responsible Nutrition. You heard from my colleague Andrea earlier today. And thank you for this opportunity. We're very pleased to be here having these discussions. I will say for more than a decade you've seen our comments. You know. We've been having these discussions about the fundamental question under which about what Congress intended by the term of dietary substance in the food, drug and Cosmetic Act. Our position has remained clear and consistent, grounded in the statutory text and legislative history. We're encouraged by this meeting. We're encouraged by these discussions and the FDA's interested in reexamining the meaning of dietary substances. You noted goals earlier today and we believe we can support those. We obviously very much support the goal of removing unnecessary barriers to innovation. We believe we can do this within this statutory train tracks that you mentioned earlier of the food, drug and Cosmetic Act. First, the plain language of this supports broad and flexible understanding of the term dietary substances. The statute

defines these substances. We've heard this a lot. As for use by man to supplement the diet, by increasing the total dietary intake. This language is intentionally expansive. It doesn't reference, nor does it require prior use in conventional food. Nor does it require a history of dietary consumption, so long as the substance is intended to supplement the diet. Second, the legislative history confirms this broad intent. Congress deliberately created what is often described as the catchall provision, and I know we've heard that term today throughout presentations to ensure that a wide range of dietary ingredients could be included under the DSHEA. I also want to point out that there is a shift in statutory language from nutritional substances in earlier drafts to dietary substances in the final law. This was not accidental. It reflects Congress's intent to capture a broader universe of ingredients, including those that may emerge through scientific innovation. Importantly, example cited in the Senate report during today's passage, such as coenzyme Q10, glucosamine and primrose oil, demonstrate that.

A bit of a technical malfunction. So going on noting that there are substances that were noted in DSHEA's legislative history that demonstrate Congress's intent to include ingredients that are often synthesized, are not traditionally consumed as conventional foods.

So I also want to note there was a lot of discussion here today about both industry and FDA expressing a desire. So we agree on this provision that dietary supplements should go through the NDI notification pathway to market for new ingredients. So it's incumbent that we have these discussions and that this pathway be viable for numerous ingredients. And to do that, it needs to be achieved by embracing an inclusive definition for the term dietary substances category. So in closing, I want to urge FDA to align its interpretation of dietary supplements with the statute's plain language and its legislative history. Doing so will support both regulatory clarity and the continued safety and innovation of these dietary supplements on the marketplace.

WELCH: Thank you. I gave her an extra ten minutes since the mic or 10s since the mic fell. So Graham would be next. After Graham, we'll have Ivan Wasserman. Okay.

AUDIENCE: We'll see if, if it holds. Excellent. My name is Graham Rigby, and I have the honor to serve as the president and CEO of the American Herbal Products Association, or APA. I would like to thank Deputy Commissioner Diamantis, director Dr. Welch, and the entire FDA staff associated with today's meeting for hosting an insightful day of discussion. Dietary ingredients are the foundation of our industry, and dietary ingredient innovation enhances consumer choice and addresses the evolving health needs of American consumers. Without dietary ingredients, we'd be left with excipients, and that would be a boon for the placebo effect, but not so great for human health.

In crafting DSHEA, Congress use broad language, a dietary substance for use by man to supplement the diet by increasing the total dietary intake. Stop if you've heard that before today. That wording is forward looking and functional. It asks what the substance is for to supplement the diet and increase intake, not whether the substance was traditionally eaten in foods. In other words, the diet can and does evolve. If Congress wanted to require prior presence in the food supply, it could have said so explicitly, as it has done elsewhere in the food, drug, and Cosmetic Act. Instead, DSHEA separately created the new dietary ingredient framework, which assumes that some dietary ingredients will in fact be new. That framework would make much less sense if every qualifying, every qualifying dietary substance had to already be established as part of the historic diet. AHPA supports an expansive understanding of the definition of dietary ingredient that facilitates innovation in service of consumer choice and public health.

Regulatory definitions of identity should be driven by substantive safety concerns. The associated analysis should be flexible to fit the nature and scale of ingredient type. That said, consumers have a right to understand where their dietary ingredients come from for example, ingredients not extracted from botanicals but chemically equivalent to those found in nature, must not be labeled in a manner that may mislead consumers about their source or identity. This approach promotes technology and innovation while protecting farmers and stakeholders, industry and consumers alike, who honor the millennia long traditions of cultivating, preparing, and consuming herbs. Thank you again for a productive day. We look forward to ongoing collaboration with the agency and industry on these issues to promote responsible commerce in our thriving sector for years to come.

WELCH: Thank you Graham. So next we'll hear from Ivan Wasserman. And after Ivan will be Barrett Doctor. Ivan.

AUDIENCE: Thank you. Most of you here know me as the world's only and best probiotic comedian. And I do actually have a 201 FF joke, probably the world's only 201 FF joke. And if there's time left and Dr. Welch wants me to tell it, I would be happy to. But I also am an attorney, and I'm going to be wearing my lawyer hat for this comment. I'm managing partner of the law firm at Wasserman, and I'm very proud to also represent the International Probiotics Association at its heart. And I'm going to echo some of what Graham just said. This is an issue of statutory interpretation. As a lawyer, I'm going to quote the Supreme Court in the 1995 Supreme Court decision of Gustafson v. Alloyd, Justice Anthony Kennedy wrote for the court, quote, under the canon of consistent usage and meaningful variation, a court must presume that a word or phrase bears the same meaning throughout a statute, and conversely, that a material variation in term suggests a variation in meaning. A material variation in term suggests a variation in meaning when drafting 201 FF1E whatever. The drafters chose the words a dietary substance the same people, presumably when drafting section 413 A1 of DSHEA concerning when you don't have to submit a dietary notification a

notification for new dietary ingredient chose these words. The dietary. You don't have to submit one if the dietary supplement contains only dietary ingredients which have been present in the food supply. As an article used for food in a form in which the food has not been chemically altered.

From this we know. We know that the drafters knew the phrase present in the food supply, and they chose to use it in 413, and they chose not to use it in 201, opting instead to use the phrase dietary substance. Therefore, following Justice Kennedy's guidance, reading dietary substance to have the same meaning as present in the food supply is against the canon of statutory interpretation that quote a material variation in terms. Suggests a variation in meaning. It has to have a different meaning. Thank you.

WELCH: Thank you. Ivan. So next we'll hear from Barrett. Doctor. And then after Barrett will be Duffy McCay. Thank you.

AUDIENCE: Thanks. My name is Barrett. Doctor. I'm representing the International Food Additives Council. IFAC is a global association representing manufacturers and end users of food ingredients, including live microbial dietary ingredients, cultures, probiotics that are used in dietary supplements. Thank you for the opportunity to provide comment. So in DSHEA live microbial ingredients fit within 201 FF1E, which we've talked a lot about today. Purpose definition substances should not need to originate from food in order to qualify as dietary ingredient. We support the recognition of these microbial ingredients, commonly referred to as probiotics to be considered dietary ingredients. We note, however, that there seems to be misalignment with FDA interpretation and current practices, and hence we request FDA to reconsider their interpretation, allowing for more ingredients such as live microbial dietary ingredients, heat treated microbial ingredients, and other new ingredients to be eligible to the market as dietary ingredients, whether or not they originate from food. Furthermore, to recognize the food supply, presence at the species level and to encourage innovation for both existing and novel ingredients without current categories, including new to world microbial ingredients. This does not preclude the need for adequate evidence of safety and FDA evaluation, where applicable, since other ingredients like vitamins and minerals have their own listings. It may be helpful for the industry to see a specific 201 statement from FDA naming the microbial category, since they have different considerations than other ingredients. Recognizing that changes requiring an act of Congress could be difficult. IFAC asks whether FDA can consider non-legislative changes to modify their current interpretation and practice of disqualifying live microbial, not isolated from foods per se from the dietary ingredient definition. As a final note on manufacturing, I developed a new dietary ingredient notifications or an industry guide that's available on our website, which includes a chemical alteration section. IFAC believes

the definition of chemical alteration should only encompass changes that lead to an alteration of the chromosomal genetic makeup of the microorganism, such as genetic engineering. Substituting a defined medium for a complex and variable raw material, like milk, for example, does not impact the genetic composition of a food culture when conducted in accordance with microbial food culture cGMP, such as proper cell banking and taxonomic identification, and therefore is not prima facie evidence of chemical alteration. Thanks.

WELCH: Thank you Barrett. Duffy Mackay. And that's the last for registered commenters. Duffy.

AUDIENCE: Thank you for the opportunity to offer a few closing remarks. Congress understood in 1994 that science would evolve. Rather than trying to predict every ingredient and every manufacturing method. It included a catchall provision so innovation would not be frozen in time. Over the years, FDA FDA's interpretation of that provision has at times drifted towards a narrower, narrower view one that assumes dietary supplements must be derived from botanicals or conventional foods that are historically consumed. And there's a bit of dietary supplement mythology. Here, people assume that vitamin C is just squeezed from a lemon. In reality. Most vitamin C, like many vitamins, has long been synthesized because it's purer, more consistent, and biologically the same. And even the industry's largest trade show is still called the Natural Products Expo, reflecting a 1960s return to nature origin. While the products, the science and the consumers have evolved, today, more than three quarters of Americans use dietary supplement supplements, and not all of these consumers are biased towards natural ingredients. They're biased towards safe, effective and well characterized ingredients and importantly, advances. Advances in manufacturing often reduce risk by improving purity, consistency, and controls, and excluding these definitions. These ingredients from the definition, because they are synthetic or didn't start from nature, it does not enhance safety. It simply shifts innovation elsewhere and often to the GRAS pathway, which was never intended to serve as a workaround for dietary supplement ingredients, and CHPA is advocating for innovation and safety. While we're asking FDA to review these ingredients and not to exclude them from the dietary ingredient category based on origin, manufacturing, or outdated assumptions about the diet. And finally, the much anticipated NDI final guidance presents an important opportunity for FDA to clarify its interpretation of section 201 FF and better align with congressional intent. And we see this public meeting as a constructive first step. And I want to go back to some of Kyle's comments about sort of the MAHA agenda, making people healthy and seeing supplements as part of that, and recognizing that as a $60 billion industry, we've become the size of the over-the-counter drug industry. Americans are using these products to keep themselves healthy. And I want to say to FDA leadership above you that we need to put the right resources towards evaluating these ingredients, and note that we're hoping the 2024 alignment with the food

program gives you those resources in reviewers with different types of expertise that can tackle some of the challenging problems that we've put forth. But we shouldn't shirk away from that responsibility because these are products Americans want. So thank you for your time and energy on this.

WELCH: Thank you. Duffy.

We do have time for 1 or 2 more comments. If anyone would like to give three minutes of comments. Can walk up to the microphone.

In this world of online meetings, I've gotten better at waiting uncomfortably for a minute or two. All right. Let's go ahead and close out the session, then. Thank you all. I'm going to move over to the mic for some closing comments.

I have mentioned a couple times, certainly to different people, how much I appreciate the support that this office has received in pulling together. The meeting I had was very excited to start seeing the slide decks come in and most of them last night, but we'll set that aside, including my own. But it has been I it would be remiss for me not to say a huge thank you to our experts who came to College Park. Some of them had a very long commute, put together, put their time and effort into preparing these conversations and offering us a solid ten minutes each, which is hard when you think about, you know, trying to squeeze in a very large topic into ten minutes. But that's because this is this is the beginning of the conversation. What we really hope is that the discussion today offered opportunities for for us all to go back and continue to think about it. Ideally the the.

Ideally, the attendees can just move to the next slide. Thank you so much. The ideal ideally the attendees, you know, you can take this back. And as you consider putting in comments to the docket, you can take some of this discussion away. The docket is only open for 30 days. We understand there is a memo in the docket to sort of shape some of the questions that we're really hoping to hear about. And then, of course, to today's discussion. Hopefully that will carry forward as well. I took a fair bit of notes as well. Some just fun sayings and other things that are just really interesting sort of things to take back with my team. I think a few things from my perspective. One would be talking about, you know, as we move forward, I don't I don't know what step two is. I don't know what step three is. But I do know that our goal here is to provide some clarity and some transparency around how we, how we interpret how what we consider to be the scope of dietary substance. I think that is absolutely beneficial for our audience here today and our audience online. Those who are producing these ingredients, those who are trying to figure out, you know, what type of product should they be in? We're trying to figure out the regulatory process. It would also be really helpful for our team. Right. We've talked a lot about our nine reviewers and and being able for them to have a good understanding of, of what does fit in the scope, what does not fit fit into the scope. I started the meeting by talking about, you know, what is I've

already lost my question there of you know, what is a does dietary substance include things that have not been in the human diet and got, kicked off a discussion on that? I maybe what I should have asked was more about Amy's example in the end of sort of an intentional component of the diet because it's really interesting to think about. You know, some of the microbes that are unintentionally part of the diet. And do those. Should those be considered as dietary substances? Thank you for that example. I think there's a lot to wrap my head around. I think every time I have these conversations, I come out with a more refined vision. It has taken a number of conversations over the years, but I do think, there's a lot of, Kyle mentioned this. It's an exciting time at FDA. There's a lot of things that we are undertaking. Some of them are, you know, really looking at the long standing, perspective that FDA has had some of the regulations. Right. We're looking at, you know, what regulations could we remove? What barriers could we remove? How can we strengthen the review process? I actually think this example, this topic is a great example of both of that. It is both, you know, the opportunity to ensure regulatory clarity for those who are coming to market, ensure, you know, the development of responsible innovation to go back to the 2019 meeting. But it's also an opportunity to ensure we have a strong, comprehensive, consistent review when they do come in through the NDI pathway.

You know, 75 days. We want to we want to, we want to arm our reviewers with all of the information, so that they can be giving these substances a good review and providing, you know, helpful feedback either in meetings or discussions with the NDI team or response letters. So I, I think this topic is, nicely fits into all of these categories. Thank you. I have a number of people to thank. Sorry. You're going to stick with me. So Betsy mentioned some of her reviewers, but I there's there were a number of people in ODSP who put a lot of effort into pulling this meeting together. I have to thank Helen and Gerie Voss and Caitlin Cackoski, Ada teme, and Natalie Gonzalez, who are, policy and Candra Smith, policy and comms staff for pulling together the mechanics of this meeting. We worked with some fantastic contractors, Megan Arsh Ritu. FDA's Office of External Affairs has stepped in and been really helpful. On the Division of Research and Evaluation side, you know, we have some people here at the table. Phil, Betsy and Shontell have been fantastic. Kayla, who I couldn't get to travel here, but, I know she's listening in, and she's the one who's often reviewing some of these really tricky substances that we've been talking about today. There's so many other people. Our AV staff did a fantastic job. I didn't get, like a lot of angry emails, which is I feel like a win. So thank you to the AV staff and the facility staff and the security staff at FDA for really facilitating a successful meeting. If you have any criticisms, I would offer them to Phil. You can go ahead and contact him. And you could send it to Phil Yeager. But I don't think that gets to him because he has a secret first name. So, I very much appreciate

everyone's time. I am, going to get you out early. So happy Friday to everyone, and I hope you have a lovely weekend ahead of you. Thank you.