DA/CFSAN PUBLIC MEETING

RESPONSIBLE INNOVATION IN DIETARY SUPPLEMENTS

Thursday, May 16, 2019

8:30 a.m.

US Food and Drug Administration

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College Park, MD 20740

Court Reporter: KeVon Congo

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A P P E A R A N C E S

ANDREW SHAO

ASHISH TALATI

BERIT DOCKTER

BONNIE PATTEN

CARA WELCH

CHARLES JOLLY

DANIEL FABRICANT

DANIEL WANG

DAVE SCHONEKER

FREDERICK BLAKE

GABRIEL GIANCASPARO

GEORGE PARASKEVAKOS

HARRY RICE

JAY SIROIS

KEVIN BELL

LARISA PAVLICK

LAURA MacCLEERY

MACK MITCHELL

MARK BLUMENTHAL

MARK LeDOUX

MARK MILLER

A P P E A R A N C E S - Continued

MICHAEL McGUFFIN

NANA BAFI-YEBOA

NORMAN SHARPLESS

PIETER COHEN

SANDRA ESKIN

SCOTT BASS

STEVE MISTER

STEVE TAVE

WES SIEGNER

I N D E X

I N D E X - Continued

P R O C E E D I N G S

DR. WELCH: Good morning. Good morning, everyone. Thank you for sticking with us while we get started. Welcome to FDA's public meeting on Responsible Innovation in Dietary Supplements. My name is Cara Welch from the Office of Policy, Legislation, and International Affairs in the Office of the Commissioner. And I'm so pleased to be working on today's meeting with ODSP. I have some housekeeping notes to get us started and then I'll turn it over to Dr. Sharpless.

This public meeting is being webcast and transcribed. The transcription and slide decks will be added to FDA's website once they're prepared for posting. I'm not sure on the timeline for this. It could be as much as a few weeks before they get posted. If you're interested in the transcription, I would suggest you monitor FDA's meeting page specific to today's meeting.

Wi-Fi is not available today. I'm sorry. Also please take a moment to confirm your cell phones and other devices are silenced as I do so

myself.

To ensure our webcast participants can hear, please be sure to speak your remarks or questions into the microphones. There are two mics about part way down the, the stairs and we would suggest that you use those. Also please introduce or start your comments or questions with your name and organization because of the transcription.

If, for the webcast participants, your phones sound be automatically muted. If you have a question to ask of our panelists during the Q&A sessions, please type it into the chat function. We have a few people monitoring that chat box and they can ask the questions on your behalf.

Restrooms, as you exit the auditorium at the top of the stairs, both the men's and women's restrooms are located down the corridor back towards security on your right.

Breaks and lunch. We have a couple short breaks and a lunch break scheduled. Snacks and beverages are available in the Wiley Building Cafe, which is outside of the building outside of security

to the left. Additionally, there will be food trucks available in the parking area for lunchtime. Seating is available in the café or in the courtyard area between the building and the parking lot if the weather is nice. I think it's supposed to clear.

Please use the front door to exit and enter. There is a door at the top of the auditorium. Please don’t use that. We would get in trouble. And always wear your nametag because you will need to go back through security and that just indicates that you can go directly to Donna's corridor to the public meeting.

There are also two breakrooms available for our use. They are 1A001 and 1A002 and people at the registration desk can show you where those are. There are no food or drinks allowed in this room. Again, I'm sorry.

For any media or press questions, we should have Mariana Nam and Julie Manga (ph) attending the meeting. If they're in the room right now, they will indicate. I don’t see either of them in the room right now. You can also find them at the registration

table. And then we will also have Lindsay Haik from our Office of Media Affairs available for other media questions.

The folders you were all provided when you checked in at the registration desk have some documents for the day. The agenda for today, bios for our presenters, both FDA and the panelists, and the photo register notice. July 15 is the deadline for submission of comments to the docket.

You were also able to pick up a list of persons making public comments at the end of the day. And speaking of which, the public comment session, we are having a public comment session at the end of our panels this afternoon. The list of persons who have requested an opportunity are on that sheet. We ask our commenters to target three minutes for their comments. If we have time at the end of the day, we could allow some extra unregistered people to give comments.

If you would like to have that opportunity, if we have time, please check in with Juanita Yates at the registration desk. Juanita, can

you step forward and make sure people know who you are? Very important for the meeting, Juanita Yates helps us keep moving smoothly. For questions and assistance, she is also probably your best source of information.

And with that, I am very please to welcome to the podium Dr. Ned Sharpless, Acting Commissioner of FDA. Thank you.

(APPLAUSE.)

DR. SHARPLESS: Good morning. Thank you, Cara, for that introduction. And thanks to everyone here for participating in today's meeting. Also for those of you online. The topic of today's session is of particular importance to protecting the public health and the work of the Food and Drug Administration. Although I'm relatively new to the FDA, I've been in the job about five weeks, protecting and promoting the public health has been central to my professional work and throughout my career.

As some of you may know, before coming to FDA I ran the National Cancer Institute at NIH, and before that I was a cancer researcher and a cancer

doctor treating patients with hematologic malignances for 20 years in academia. During that time I ran an NHI-funded lab studying the molecular mechanisms of cancer and aging and I was a director of a large comprehensive cancer center.

I'm thrilled to be at the FDA, to be a part of the team that uses science to develop policies and regulations that help make Americans more knowledgeable and safer. A few of FDA's responsibilities affect as many Americans on a daily basis as our work in the foods arena, which includes issues of food safety and labeling, but also issues of nutrition and diet.

As a physician, I've long seen the profound impact of diet and nutrition on human health and the importance of the food research in this area. A related aspect of this and a priority of FDA's oversight responsibilities is our subject of today's meeting, the dietary supplement market.

Today more than 75% of Americans use dietary supplements regularly. That number has grown significantly in recent years and the market and

products have changed and grown enormously as well. It's been almost 25 years since the majority of FDA's authority specific to dietary supplements were solidified in law with the passage of the Dietary Supplement Health and Education Act of 1994 or DSHEA. I think it's clear to everyone here today that the dietary supplement market does not look what it did in 1994 when DSHEA was signed into law.

In October of 1994, the industry was estimated to be worth about four billion dollars. Today it's more like 40 billion dollars. And thanks in part to science and innovation, the range of products today is far broader than was on the market in 1994, having grown from about 4,000 products to perhaps more than 80,000 products. That's really significant and amazing growth.

Added to this fact that 25 years ago we didn't have the internet. We didn't have iPhones. We didn't, you know, had this global reach that's provided to the US consumer and you get some idea of the vast changes to this growing industry.

Against this evolving backdrop, the FDA

has worked to maintain an appropriate level of oversight within the authorities granted to us by Congress. It's essential that consumers are able to make informed and healthy choices about dietary supplements they may use. And there's an important public health need to make sure the products are safe and the labels are correct, and complete information about what's in them, and there's a scientific basis for claims that are made about these products.

These elements are central to FDA's mission to protect and promote the public health. I know this is a commitment that our stakeholders share, and in fact, many of you here today have been echoing from your platforms.

We all know that there are some companies who put consumers at risk and also risk damaging the reputation of the entire industry by distributing and selling dangerous and otherwise illegal products. In my career as an oncologist, I've seen all too clearly the unfortunate consequences of marketers selling fraudulent products that make claims to treat, cure, or prevent disease and which prey on

the desperation of patients and their families.

This is an area that I know the Agency has been active in for many years, will continue to protect consumers by cracking down on false, misleading, and potentially harmful claims.

We're also committed to taking action when products contain ingredients that render the products unlawful, including many drug ingredients and when they're not manufactured according, according to standards designed to ensure quality product.

But we also understand that dietary supplements are widely used, very popular with patients, and can be safe when responsibly produced and used. FDA has an equally important role to play in allowing these products to advance public health where possible.

DSHEA was deliberately crafted to establish a careful balance of protecting consumer's rights to access safe products and accurate information while also preserving the FDA's authority to protect those same consumers against unsafe and otherwise unlawful products.

While the fundamental goals underlying DSHEA have not changed, the change, the challenge of realizing those goals has grown in magnitude far beyond what it once was. The realities of today's marketplace demand a renewed approach to this regulation and it's crucial that the FDA be nimble and adaptable as we advance our regulatory frameworks in keeping pace with this rapidly growing commodity.

Now is the time to modernize our program to ensure better alignment with the realities of today's dietary supplement market. This past February FDA announced some steps were taken to advance our regulation of dietary supplements and modernize reform, and reform our oversight in this important segment of the health economy. I want to ensure you that this work remains a top priority and will continue with me as acting FDA commissioner.

We are taking a close look at our dietary supplement program to make sure that we have the tools we need to keep consumers safe and that we are using these tools as effectively as possible. We've established an agency-wide dietary supplement

working group that is looking into our dietary supplement organizational structures, processes, practices, and procedures in identifying where we can make improvements. We've affirmed our commitment to using traditional law enforcement tools when we see products that are violative, but we also recently announced a new tool to address these potentially violative products.

Last month we announced the Dietary Supplement Ingredient Advisory List, a new rapid response tool that we'll use to alert the public when ingredients found in dietary supplements appear to be unlawful based on our preliminary determination. This is critical to protecting the public health. If an ingredient might be unlawful, consumers need to know so that they can avoid using those products with that ingredient and responsible industry participants need to know as well so they can avoid selling them.

We also recently announced a botanical safety consortium that we're kicking off with our industry, academic, and government partners to promote scientific advances in evaluating the safety of

botanical ingredients and mixtures in dietary supplements. This group, group will look at novel ways to use cutting edge toxicology tools to promote the goal of safety that we all share.

As a researcher, I'm thrilled to see these groups come together to collaborate and learn from each other while tackling these complex questions. Today's meeting is another piece of our renewed focus on dietary supplement regulation and our efforts to bring these into the 21st century.

The topic of today's meeting, Responsible Innovation in Dietary Supplements, really gets to the heart of the balance between access and safety that is the core of DSHEA. Our multipronged efforts to modernize the dietary supplement program is complicated, but so is this industry. I know that our Office of Dietary Supplements Program is looking forward to hearing your suggestions on how we might reshape our oversight of supplements.

I'm sure the conversation will be thoughtful, detailed, and productive with views from across the spectrum of stakeholders represented here

today. I'm please to see the broad interest in our efforts with participation from consumer health groups, industry trade associates, attorneys, and physicians. I know we all have representatives from our fellow regulatory agencies and other countries participating, which is very important given the global reach of these products.

Given the interest in the package that we had before, is I will turn this podium over now to Steve Tave, or director of the Office of Dietary Supplement Program and allow the conversations to begin.

Thank you for having me here today.

(APPLAUSE.)

MR. TAVE: Good morning, everyone. And thank you very much, Dr. Sharpless, for your remarks and for being here today. FDA is a big agency. They just figured to show that the Agency employs more than 15,000 people spread across headquarters here in Maryland and the field, across the United States and now the world. And our jurisdiction spans a wide range of products used every day by every American.

FDA encompasses six product centers covering commodities including foods, drugs, medical devices, biological product, veterinary products, and tobacco products. And there are a few people who now appreciate the full breadth of FDA's responsibilities, as well as Dr. Sharpless who brought a wealth of relevant experience with him to his role as acting commissioner and has since immersed himself in the full range of FDA's activities since he joined the Agency last month.

Now although dietary supplements represent a small, relatively small, discrete segment of FDA's vast regulatory portfolio, these products remain an important part of the American lifestyle. Dr. Sharpless spoke about their prevalence and about the size of this industry. He also spoke about how the market has evolved and how those changes have created a need for FDA to ensure that our regulatory framework activities are up to date and reflect the realities of today's marketplace.

Dr. Sharpless gave an excellent overview of the different steps that FDA is taking to

strengthen our oversight of dietary supplements through modernization and reform. And importantly while these steps were first announced in February before he arrived at the Agency, he also said that the intervening change in Agency leadership did not change the fact that his work, that this work remains an Agency priority.

Those words backed up by his personal presence here this morning despite the countless demands that come with leading an agency of this magnitude, including as I'm aware a telephone call that's starting any moment, send a very strong and clear message to all of our stakeholders that FDA is committed to moving our dietary supplement program forward.

So I'd like to take a moment to express my thanks to Dr. Sharpless for his continued support of our important work in the dietary supplement space and I know that you need to leave. So if, if you have other demands, this is probably an understandable time to go. Thank you.

(APPLAUSE.)

So we're already a few minutes behind schedule, but I think with so many commercial flights, we might make up time in the air and finishing on schedule by the end of the day. Since Dr. Sharpless already gave an overview of FDA's new efforts to modernize our regulation of dietary supplements, I'm not going to repeat that.

And today's meeting isn't intended to be a discussion of all of these new efforts, but it does represent an important component of these modernization efforts. So let's take a step back and talk about why we're here today and what we hope to accomplish.

FDA's authority to regulate dietary supplements was generally articulated by DSHEA, the Dietary Supplement and Health and Education Act of 1994. We've talked before and Dr. Sharpless reiterated about how DSHEA embodies two twin goals. First, ensuring the right balance between preserving consumer access to supplements that are safe, well manufactured, and accurately labeled, while second, still upholding our obligation to protect the public

from unsafe and unlawful products.

We embrace those goals and our strategic priorities for dietary supplements here at FDA, consumer safety, product integrity, and informed decision making, are in line with these twin goals. One of the critical elements of our modernization efforts is ensuring that our regulatory framework is flexible enough to allow for innovation and growth in the dietary supplement marketplace while maintaining and even strengthening our ability to efficiently and effectively evaluate product safety and protect the public health.

To be sure, DSHEA did not assume that the world would stand pat as it existed in 1994. Rather it clearly envisioned a dynamic dietary supplement market with a role for innovation. The law gave authority -- the law gave FDA authority to take action against dietary supplements on the market that are adulterated or misbranded.

Broadly speaking, though, DSHEA reflected a judgment that, and this is a quote from the congressional findings, dietary supplements are

safe within a broad range of intake and safety problems with the supplements are relatively rare. So DSHEA classified dietary supplements as foods subject to postmarket regulation by FDA, but with no premarket approval necessary before products can be introduced to the market.

As legislation goes, DSHEA is relatively short, but its provisions are there for a reason. And no one would argue that the law allows you to just stamp the words dietary supplement on any product and then market it lawfully. In fact, one way to read DSHEA is as establishing certain symbolic thresholds that must be crossed before a product is entitled to the presumption of safety that Congress bestowed on the class of dietary supplements.

Now I deliberately didn't use the term barrier there. I used threshold. Although FDA had the authority to take action when we can establish a violation by a product that is on the market, there is nothing to prevent a firm from disregarding these and introducing a product into the market anyway.

The route of administration is one such

threshold. For example, an injectable product cannot be a dietary supplement. Under the law to be a dietary supplement a product must be intended for ingestion. So while products that are swallowed like tablets, capsules, liquids, and powers can be dietary supplements, other products like products that are injected, inhaled, or applied topically cannot.

Can any ingredient be a dietary supplement? DSHEA imposes the threshold that a dietary supplement must bear or contain at least one dietary ingredient. The law then articulates six different categories of dietary ingredients. Or viewed another way, five different categories with a sixth category that captures different variations and innovations of the first five categories.

But are there limits to what these categories encompass? To take an extreme example, could you put gasoline in a six ounce bottle and sell it as a dietary supplement? Our first panel will discuss this very question. Maybe not the precise question of whether gasoline can be a dietary supplement. You never know with these folks. But the

question of how broadly the term dietary ingredient should be understood.

This is a question that has come up repeatedly in (inaudible). Synthetic copies of botanical ingredient is one. Dietary substances is another. But it also bears more generally on the question of innovation including with respect to certain classes of ingredients such as live microbials, as well as other contexts.

And as advances in technology lead to the development of novel ingredients with potential beneficial effects, the public health question of whether the safety of all dietary ingredients can be assessed equally using common criteria remains at the forefront.

Now not all dietary ingredients automatically qualify for the presumption of safety. DSHEA defines the term new dietary ingredient, which we often abbreviate as NDI, to mean a dietary ingredient that was not marketed in the United States before October 15, 1994. And like all definitions, there is a reason for this one. NDI status can

present another threshold to cross.

A dietary supplement that contains a new dietary ingredient is adulterated unless it satisfies one of two requirements. First, it contains only dietary ingredients which have been present in the food supply as an article used for food in a forum in which the food has not been chemically altered. And I apologize for reading that statute here. I'm not going to do that again. Or second -- but I think it's relevant in this case.

Second, that there is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe, and at least 75 days before being introduced into interstate commerce the manufacturer or distributor of the product provides FDA with the information that is the basis for their conclusion that the product will reasonably be expected to be safe. Pause for breath.

The second prong is the premarket

notification requirement and we'll come back to that in a minute. But let's first focus on the other prong which is at the heart of today's second panel. Our second panel will discuss exceptions to the NDI notification requirement. That is, even some new dietary ingredients may not be subject to the premarket notification requirement.

Some of you will notice that I've skipped a step in the analysis. What does it mean to be new? For example as technology advances, when, if ever, do changes to manufacturing processes alter the character of an ingredient so much that it can no longer be considered the same ingredient that was previously on the market?

Our second panel will address this question along with what it means to be present in the food supply and the related question of how evolution over the past 25 years in how we regulate the food supply has impacted what this provision means in the broader framework of DSHEA.

Now back to the NDI notification requirement. This requirement when it applies is the

final threshold. In fact, an effective NDI notification process represents FDA's only opportunity to evaluate the safety of a new dietary ingredient before it becomes available to consumers. Our goal today is not to talk about the nuts and bolts of the NDI notification process. Although as an office, we certainly remain available to work with stakeholders who are interested in preparing to participate in that process.

And our goal overall is not to maximum the number of notifications that we receive. Rather our goal is to right-size the process to see that appropriate notifications are submitted for the products for which they are required. Our fourth panel will discuss ways to promote, to promote overall compliance with this requirement including challenges and opportunities associated with ideas like economic incentives and enforcement.

I went a little bit out of order there and I skipped from the second panel to the fourth panel and I did that because of the logical flow of this discussion, but it doesn't in any way reflect the

relative importance of the panels.

As Dr. Sharpless noted earlier, one of the biggest contributors to the changing dietary supplement marketplace has been globalization and we're very fortunate that today we'll be joined by one of our international regulatory partners from Health Canada who will offer a comparative perspective on how some of these same issues that we face are being handled abroad. So there is a lot to talk about today.

A few notes. First, although we have divided the discussion into separate panels for logistical purposes, there is inherently some overlap among the topics. We've asked our panelists to focus on the subject of their panel and they very kindly agreed, but we've also told them that we're not censoring any opinions. And so they may occasionally speak about something that is the subject of another panel and that's okay.

The goal of today's meeting is to facilitate discussions. After each panel has completed its presentations, there will be an

opportunity for question and answer both among the panelists and by the audience. And at the end of the day there will be an opportunity for open public comment.

As Dr. Welch said, there's also a docket to which you can submit written comments and that docket will remain open for 60 days after the meeting. We are here to hear from you and that's my one bad joke of the day.

In terms of what we hope to accomplish, we don’t expect to walk out of here at the end of the day with all of our questions resolved. We do expect to all walk out of here. Okay, second bad joke. I'm done. I promise.

Some of these questions pertain to how the law should be interpreted. If the answers were obvious, we wouldn't need to have this meeting. The point isn't to convince one another that one view is the only correct one, but rather to articulate the parameters of the questions and then to ask on top of that what is the most desirable public health result consistent the DSHEA's twin goals of access and

safety. And then to try to identify areas of consensus about what we should do and how, and beyond that whether we currently have the authority to do it. And if not, to start to think about what it will take to achieve those desirable public health outcomes.

We have a wonderful array of panelists from a diverse range of stakeholder perspectives who have volunteered to be here to participate in today's discussion. We've also had tremendous interest in today's meeting. We reached capacity for in-person attendance here in the room and we have several hundred people participating remotely via webcast.

We've had a number of people sign up to share their thoughts during the open public comment portion of the meeting later and I expect that we'll have an active audience during the Q&A portion of our discussions today.

I want to thank you all for your interest in these topics and for your partnership in this important work. So without further ado, let's get started with our first panel and I'll invite our panelists for the first session to come gather at the

table and I'd like to invite Dr. Welch back up to podium to introduce session one. Thank you all.

(APPLAUSE.)

DR. WELCH: Good morning, everyone. Okay. So starting with our first panel. Let me get out my information here. We thought it was really important to sort of lay out FDA's definitions or working definitions of the dietary ingredients that are listed out. So the scope of dietary ingredients under DSHEA, some are more well established than others. Some less well established. And I think some of them, you know, we don't have a lot of questions from our stakeholders on.

I think the first four are pretty well accepted. You know, vitamin, a mineral, a vitamin, you know, and we're talking about the deficiency of which is, results in a clinically defined deficiency syndrome. Mineral, herb, or other botanical, for the most part we don't have questions on what an herb or other botanical is.

Amino acid, an alpha amino carboxylic acid, there, you know, some of those are fine if

they're synthetically produced versus pulled from nature. There's no such thing as a synthetic herb or botanical just in case we're, we're curious about that. Others of which, you know, we're still discussing 25 years later.

So a dietary substance, a dietary substance for use by man to supplement the diet by increasing the total dietary intake. Again, I realize I just read the statute to you all. So what do we mean by that? And I think in many instances it would be great if there was a well accepted definition. Taking it sort of on its face, what we have is a dietary substance for use by man. I'll let the man slide in today's world.

We'll go ahead and say a dietary substance for use by human. A substance that is commonly used as human food or drink. To supplement the diet by increasing the total dietary intake. As far as I'm concerned, I think this is further evidence it's intended to mean foods and food components that, that humans eat as a part of their diet. I don’t know how usual the diet must be, but, you know, evidence

that this, this is part of the diet. It's part of the total dietary intake.

I think one aspect, I don’t know if I need to clarify this, but use as a dietary supplement doesn’t necessarily make something a dietary substance. That would be a pretty big loophole if you were to put something in a supplement, put it on the market and then say, well, because it's in a dietary supplement, it is not a dietary substance. I think it has to be a dietary substance first before it goes into the supplement and on the market.

I think some additional considerations is that something in food or in the food supply might not be a dietary ingredient either. I think there's that definition of consumed in food versus consumed as food. And you know how FDA likes to pick apart every single word as part of the statutory language. So and, and the exact wording that is used is important to us.

I think consumed in food you can, yeah, you can have contaminants or toxins versus consumed as food, something that was intended to be there. And to

be clear, I think synthetics have since this can be dietary substances if the synthetic version of which is what is in the diet. So that's, that's sort of our working definition.

And then I think the next one -- my little clicker is a little touchy in that it doesn't like to click. You know what? There's always a better way to do this. There. Okay. We'll do it that way. You all may need to use the mouse.

I think the constituent of a botanical, that's another one that we're still talking about today. So we've already defined herb or other botanical, right? We have a plant algae fungus, a part of a plant algae fungus or an effector, a secretion of a plant algae fungus. Again, sort of something that is from the ground from nature.

A constituent of and, and this, these are definitions, by the way, that are directly from our NDI draft guidance, the 2016 draft guidance. So a constituent, an article that is a physical part of the whole and can be isolated from the whole. So what we're talking about of course is a constituent of a

botanical, an article that is part of the botanical and can be isolated from the botanical.

I think that's something we -- that's sort of how we've been operating. We, I hope that our panelists can offer some different viewpoints. What we want to see, of course, as the conversation sort of to set ourselves off, ideally we can get some good conversation going during the panel. I don’t want to take all of our time. I do want to turn it over to our panelists.

You know, we have, first we have Scott Bass, head of Global Life Sciences team at Sidley Austin. We were going to hear for Larisa. I'm sorry, from Loren Isrealsen at UNPA. We are, he was not able to travel. So Larisa Pavlick from United Natural Products Alliance was very, very willing to step in. So we appreciate that.

George Paraskevakos from, the executive director from the International Probiotics Association. We really wanted to have a probiotics perspective. It's just such a huge area of the industry right now and we want to make sure that we

can recognize that. George was kind enough to work with the International Food Additives Council on his presentation. So the presentation while presented by George is actually coming from IPA and IFAC. So thank you for that.

And then Pieter Cohen, associate professor at the Harvard Medical School, Internists of Cambridge Health Alliance, and well known to the dietary supplement industry. So we are very happy to have them.

I'm going to turn it over to Scott here in a moment. I forgot I was supposed to give a few more housekeeping remarks if you aren't already sick of that. So I will turn it over to Scott. We're going to ask for about ten minutes from each presenter and then we'll open it up to Q&A. We would love to have questions from our audience. And again, the webcast participants can ask questions as well. We'll be monitoring that. We, we would like to see some sort of dialog happen. You know, FDA's definition versus other working definitions and, and make sure that we understand where everyone is coming from.

With that, the couple housekeeping notices. Again, if you have mobile devices of any sort or every sort, please make sure they're silenced and I know we do have a number of people. There are, by the way, seats down in the front and in the middle, which is always fun to sit at.

It is hot in here. I recognize that as much as everyone else. We are working on cooling it down. So stick with us. Webcast participants, you are very lucky to not be in our little sauna over here. So with that, I turn it over to Scott. He will then turn it over to Larisa, George, and then Pieter.

MR. BASS: Good morning. Scott Bass. I'm heading the Global Life Science practice at Sidley Austin. So I want to first thank Steve Tave, Dr. Welch, Mr. Durkin, and Lawrence Silvus (ph) for putting this hearing on. I think it's a great, great message from FDA and I really commend the Agency. This is the first time, certainly in my career, where the Agency has reached out, acknowledging the value of dietary supplements and also seeking to allow science to lead the path forward in this very important

industry.

As many of you know, I had the honor of being asked many years ago by Sen. Hatch to lead the drafting on behalf of industry of this law and I worked with Loren Isrealsen as lead negotiators for those two-and-a-half years, and we worked with Trish Knight in Hatch's office and with Peter Reinecke in Harkin's office to produce what is the law today.

As you heard before from Steve, we're looking today to see if the regulatory framework is flexible enough to also preserve product safety. And I just want to tell you up front that I think two things in answer to that question. First, the industry has not accepted its responsibility on the safety front in growing to 4 to 40 million, billion. And second, that FDA is inhibiting innovation and actually endangering consumer safety by the way it is interpreting this provision of the law.

So starting with the beginning, the beating heart of today's issue is, of course, FF1(e) and that was written. I will be producing this testimony in more detail in written form next month.

So I'm just going to go into highlights today in the remaining eight minutes. So I'm going to make three points this morning.

Number one, none of the things we're going to talk today about, not just this panel, but the other panels, is going to work unless we have four foundations.

The first is you have to have mandatory listing of dietary supplement products. You cannot -- I am incredulous when I hear people say that they're willing to put a product on the internet or in a store, but they're not willing to tell the government they're selling it. It just makes no sense. There's no way we can have adequate enforcement, a working NDI system, or incentives for better science or for innovation unless FDA knows what's on the market.

Second, we need more enforcement money and it can't be earmarked anymore. That is a critical component. Third, we need incentives for responsible companies to innovate and spend money on science. And finally, and this is going to be another panel, other than grandfather products and foods that generally

were consumed as normal foods, everything else should go through an NDI. That was what we intended when we wrote the law and all of this talk about exceptions, which I can't wait to hear, is in my mind off the mark.

So let's get to point number two. 201(ff)(1)(E), we now call it the innovation section. We drafted that, in fact I drafted it from one product at the time, coenzyme Q10, which ironically was a synthetic botanical. And after some court decisions, we made sure we wrote into the law the innovation section, meaning we didn't know what was coming down the road, probiotics being the biggest category now, but in that time we wrote something and FDA accepted it.

So it's a dietary substance and you should know that the word nutritional, that's really key to this entire discussion, was used in an earlier law. It was brought up several times by opposition and there was a constant fight to keep it out of the (E). So the words dietary substance were in there because nutritional was not. And that's why it's

written that way.

Because nutritional is basically circular. Is it commonly used in food? Read the recent NDI guidance. Oh, yes, it's commonly used in food. So it can't be a dietary ingredient unless it's not. So it's the opposite of innovation, which is creating something new. So we had vitamins, minerals, herbs or botanicals, amino acids, and the other stuff, the CoQ10s and innovative products.

So here's how FDA a couple years after DSHEA was passed themselves describe this section. Other dietary supplements comprise a broad and diverse group of substances that are neither of plant origin or could be viewed as nutrients within the common sense meaning of the term. This is what FDA said until 10 or 12 years ago.

And that make sense because coenzyme Q10, conjugated linoleic acid, glucosamine, melatonin, various enzymes, glandulars, and now probiotics, all are covered by that section. Within ten years later, a group of people at FDA with no regulation, no hearing, and no statutory change decided they would

quietly put the word nutritional back into the act through the -- you can read it in the NDI guidance.

And now FDA has said, and I don’t think it's the ODS, by the way, Office of Dietary Supplements, that is responsible, that dietary substances now only include substances already present in foods, in food components, that humans eat as part of their usual diet. Does anybody here think that any innovative product could meet the definition? I don't.

And so here's the irony, the real irony that's caused by this distorted interpretation that's gone through no public hearing or regulation. There's actually caused the Office of Dietary Supplements now to adopt a tortured position that harms consumer safety. The very thing ODS was intended to protect is actually opening the floodgates to a bunch of products that will ever be reviewed for science.

And the reason is, here's the logic. Since nothing new can now get in under (E) under this wrong and I think ultra vires interpretation, FDA says go do a GRAS self-affirmation and without commenting -

- (inaudible) I have to be careful what I say here -- on the quality of GRAS self-affirmation, which let's just say is not consistently great -- FDA says, oh, well now that you're a food, forget the fact we said in our guidance has to be usually in the diet -- we'll ignore that for the moment -- go on the market for six months and then you don't even have to file an NDI notice because it falls within the 413 catchall.

You know why we wrote that catchall? Because if you have an orange and you extract bioflavonoids, it's a commonly consumed food, I want to take something out of it. It was not intended to let every new synthetic ingredient and every new ingredient on the market without any oversight of science.

It's a total distortion and it's precisely putting the word nutritional in (E), which is not allowed, that causes this to allow all these products in the market that are getting no FDA safety review.

That's not what Congress wrote. It's not what Congress intended. It turns the NDI process

on its head and it is dangerous for this industry's credibility and dangerous for FDA's regulation. Innovation is the key to growth and to public access and strong safety data is the only sustainable move forward.

Now Steve Tave said what about gasoline. Let me tell you the answer. No. And the reason is you can't retool (1)(ff)(1) in isolation, which is the problem here. We wrote that in conjunction with 402(f)(1), the safety provision in what's now 301(v). We gave FDA lots of safety powers that didn't exist before.

Number one, (ff)(3), if it's a drug, forget it. It's not going to be a supplement. Number two, 402(f)(1)(b), if you didn't file NDI and you were supposed to, illegal, adulterated. Number three, 301(v), you put out a product that's not safe, that didn't meet the standards of 413, illegal. FDA's never used those provisions to enforce. I'm not just looking at Dr. Frankos's here.

What we need here is to understand that we have great safe guards so you don’t look at

something and say can this be a supplement and that stops. You look at it and say can this be supplement, does it meet the other safety thresholds that Steve Tate mentioned before. That's what you have to look at. So in conclusion, do we need legislation to create innovation under (ff)(1)(3)? No, we just need to remove this unlawful interpretation FDA's put on.

Number two, do we need legislation to provide real exclusivity incentives so companies will invest? Yes, we do. We need new legislation to create incentives for responsible companies to do good science. Thank you.

(APPLAUSE)

MS. PAVLICK: Good morning. Thank you all for being here. I am here today to present for you for United Natural Products Alliance. Loren Isrealsen is, I'm honored to be supported by a ghostwriter that is a huge leader in our industry.

My name's Larisa Pavlick and I'm presenting on his behalf. And what we were asked to speak about today was the use of what has been termed synthetic botanicals. And from just this morning's

discussion, it feels as maybe there's just a terminology update that we could utilize to re-characterize these types of products that may be satisfying both sides of the industry because when we walk through this presentation together, I hope that in the end you're going to realize that innovation as Scott has mentioned, is really the key to all industries and all commodity areas. And dietary supplements is just one of those.

So as we walk through the slide presentation today, I want you to kind of reflect on where we were in 1994 and '92 when this law and DSHEA was being established and where we are today because as we have all recognized in the, the week that we've had here in Washington, DC with many supplement meetings, that there's a lot of changes in the industry.

So how can we all work together to ensure that moving forward we still maintain safe access to responsible dietary supplements that can improve the health and qualify of life for many individuals? Okay. We'll do it this way.

So within this presentation, we're going to cover a few items. We're going to talk about the FDA's goals. The FDA's goals in the public health importance of the NDI guidance, which was issued as a draft in August of 2016. As we approach August of 2019, we may approach a final form.

Dietary Supplement Health and Education Act, we're going to talk about some of the negotiation notes and regarding the synthetic ingredients that were discussed at that point. We'll also talk about the synthetic botanical ban and kind of where and when that may have taken place.

We'll look at some of the congressional and industry responses to the synthetic botanical policy, talk about current issues and market realities for the use of synthetic ingredients, and some recommendations that we have itemized for, from United Natural Products Alliance, which is our members in the industry.

So in looking at the first topic when we're talking about the FDA's goals for public health, and public health importance that was related to the

NDI guidance, the first aspect of that document was really to talk about the NDI process being the sole premarket opportunity for FDA and FDA staff to assess the safety of new dietary ingredients. And I think we all as a responsible industry agree with the intention.

We can talk about the improvement, improving the rates of NDI compliance through dietary ingredient notification and the compliance of those. And they're also looking at improving the -- the rate and the quality are two of those steps within that document.

And then we look at new dietary ingredient notifications and how it's serving as a preventive control, to borrow a term from FSMA, but to ensure that consumers are not exposed to any unnecessary public health and safety risks in the form of these new dietary ingredients with unknown safety profiles.

So as we walk through that, this term that has not been well accepted by some of the regulatory agencies and is often used in our industry,

is synthetic botanical or often referred to as synbots. And again, this is maybe where we update the terminology. If they're synthetic components, maybe there's a new terminology that we can come up and agree with and define so that all parties can agree to the functionality of these ingredients.

But synthetic botanical status is defined by its nutritional function and not by its state of matter. So as Cara mentioned, if it wasn't a plant, it was never a plant, and the component is extracted, or in this case, for a synthetic botanical, a chemically identical compound is developed, it's still not considered a dietary ingredient.

But if we look at this from other commodity groups within the FDA, we know that there's, there's drug compounds that are synthetic products and generics, which may be synthetic copies of those. And those are in the approved category.

We also have food additives that are synthetic copies, and if we want to take it to an extreme, we have, so we have food additives. We have drugs and we have chemical compounds being used in

cosmetics. They're all synthesized and the most recent and probably the most interesting to many of us in the natural products industry -- oh, and there goes the slides -- is that there's now approved synthetic meats. So if -- shazam. I didn't touch it. That's, and that's -- all right. Do you want me to switch to my own?

Now we have synthetic meat products. So if we have the ability to have approval in some of these other commodity categories, I think it's time to modernize the approach to synthetic compounds that are used in dietary supplement product regardless of their source. And I'm going to have to pose, pause a moment to pull up my own slides. You got me. Okay. And we'll continue. I'm sorry you're not going to be able to see the slides, but I'll just be working off of my copy and maybe you'll have access to them later.

A substance that has been synthesized in a lab or in a factory, has never been a part of an herb and a, or a botanical, and therefore, it's not a dietary ingredient. So that's, again, some of the rationale from FDA. Synthetic botanicals as my bullet

No. 3 are not part of the human diet, and therefore they cannot increase the total dietary intake of something that has not been part of, of the human diet.

So again, if we look at pre-DSHEA, there's many synthetic vitamins that have been on the market. It's not an orange and it's not an extract of an orange. It might be something else that was cheaper and easier to access or make. And again, making sure that the public has access to safe and affordable dietary supplements is the primary goal.

The rationale for FDA's position seems to date back to 2001 as a result of the ephedra and ephedra alkaloid synthetic products that were on the market that were causing a significant amount of illness and injury and consumer complaints, and in even some cases, death. And we can see as a responsible industry that that is a responsible step of the Agency to protect public health and safety, but it may not have been a fact of the synthetic composition of some of those alkaloids. It may be have been misuse of the product itself.

So if a synthetic botanical policy -- so then a synthetic policy was developed and in 2004 we had a regulation, which was prohibiting the use of ephedra and ephedra alkaloids in dietary supplements. But was this the right step?

So if you were able to see the slides, Loren has a great memo that was presented to Comm. Hamburg in 2011 and it was issued by two of the authors, or two of our chairs for the dietary supplement industry, our champions that were within, within government and helping us in the Agency. And this letter was addressed to Comm. Hamburg. It was dated on December 22nd of 2011 and it was in response to the initial guidance that was issued by the FDA.

And that guidance was called Dietary Supplement, New Dietary Ingredient Notifications. Excuse me. And related issues. And that document, that guidance document was published in January 2011. And within the document in paragraph number two, it states that they urge the FDA to withdraw the new guidance and to republish it. So as we know, the additional guidance was published in 2016, but have we

addressed all of the elements of, of concern and have, has the intent of DSHEA been pulled forward?

So the background of the guidance was that FSMA in 2011 asked FDA to direct, or asked the FDA to clarify the New Dietary Ingredient Notification process and to do that with means that were consistent with DSHEA. And instead what seems to have come out those guidance documents are a little bit adversarial to what we had in DSHEA.

So within this slide that you can't see, there's a quote that Loren has highlighted and the quote reads similar, similarly the draft guidance accept, accepts, attempt -- excuse me. The draft guidance attempts to assert this, that synthetic copies of botanicals can never be a dietary ingredient and an assertion that is wholly without statutory basis and in fact contradicts a longstanding FDA policy.

And again, the, kind of the punchline that you're not going to be able to see shows that this letter was signed by Tom Harkin and Orrin Hatch. So these are two of our champions in the industry that

were saying that this, the guidance and the current position of FDA regarding these synthetic compounds is opposed to the intent of DSHEA.

So what are the realities in our current industry? In 2019 if we look at the compounds and the ingredients that are being utilized, we have synthetic chemistry, we have synthetic biology, and we have -- I'm sorry, Cara -- I'll say it one more time -- synthetic botanicals. They've evolved dramatically since 1994, as has the rest of the world.

They're currently and they will continue to enter the food ingredient, spice, color, flavor, and the dietary supplement industry. And I have a great graphic that is going to show you all of the compounds that are available. This graphic is going to show you when you have access to that all of the different compounds that are currently being synthesized.

DR. WELCH: Hey, you guys, can you go to -- what is this -- slide 18, please?

MS. PAVLICK: All the compounds that are being synthesized and are available on the market

currently being processed with different yeast material. So if you look at this list and things that specifically effect our industry, you'll see caffeine, saffron, stevia, frankincense, mint. Look towards the bottom, ginseng, tumeric, all of these are being manufactured in large volumes in, and are -- well, to the market and in a much cheaper fashion. Still not moving. Oh, there we go.

So the synthetic botanical ingredients without sharing our personal opinion of our Agency, organization's opinion, but synthetic botanicals are causing an economic disruption. We have synthetic botanicals that are offering far less expensive options for buyers and if there's buyers that are not knowledgeable of the industry, it's hard to determine if it's price or if it's quality that's driving the operation.

Analytical detection is often difficult because, again, these might be chemically similar. Raw material pricing becomes skewed as the synthetic botanicals are added or replaced to ingredients and extracts and it encourages at times economic

adulteration, misbranding, mislabeling, and is a consumer deception.

So here's a couple slides from one of our MOU partners and this is talking about some examples that they've found in the market. This is from Loren Monahan (ph). He is from the trust and transparency group, but the Global Kierkenmen (ph) Association did a study to say what is the prevalence of synthetic compounds on the market.

And they purchased products off of the internet and from several brands, but they found that C14 testing was the only way to determine whether or not there was a synthetic compound. But they found that there is adulteration and it's happening pretty frequently. And typically they're not adulterating the entire product. They're only adulterating a portion of the product.

They're finding between 5 and 16% of the botanicals are including some sort of substitution or dilution by synthetic compounds, and when they looked towards the bottom in bullet No. 3, you'll see that this is affecting dramatically the prices of those

products and greater than 40% of the product that were tested online had some form of synthetic compound inside.

This is a summary of the data for some of those slides and you'll notice we don’t have time to cover most of them, but if you look at the outer column in the colors, the blue indicates those that were 100% pure, natural products, but the others in red show that there were some amount of synthetic compound present.

So in summary, the synthetic botanicals are a growing percent of the dietary supplement market. It is our reality. FDA's current synthetic botanical policy should be updated because it's currently not consistent with the intent of DSHEA.

The genesis of new current synthetic technologies -- the genesis of the current synthetic policy -- was to remove synthetic ephedra alkaloids, and again, this policy is currently based on the 2004 regulation, but in the present time if we're talking about modernization, it might not be helpful.

So UNPA has several recommendations for

the Agency, and that would be to revise the no synthetic botanicals as an NDI policy. But we're not saying that we're accepting of this as the way of the future. We're saying that let's recognize these synthetic copies as new dietary ingredients and allow it to go through the new dietary ingredient process, allow again safe access to products and consumers having the ability to make those decisions.

But with those making responsible decisions and providing public choice, we would need to have some sort of declaration on the labels -- just as you would see in a GMO or in a bioengineered product -- that you would be able to indicate that those products are synthetic and allow consumer choice.

And somebody's taking over the screen again. There we go. We want to make sure that products that have not gone through the new dietary ingredient process would have enforcement by the FDA and we would want to ensure that you were able to seek public comment regarding GRAS opportunities for these types of ingredients as Scott has suggested, that

self-affirmed GRAS may not be a strong of science as if it was reviewed otherwise.

With that, I want to thank you for your time and your patience while we got through these technical challenges.

(APPLAUSE.)

MR. PARASKEVAKOS: Well, good morning, everyone. Thank you again to Steven and Cara and the FDA for inviting us to present on probiotics. It's become quite an important category and I think it has its place in DSHEA. Today's presentation as announced earlier is a collaborative effort and on behalf of the International Probiotic Association, IPA, and the International Food Additives Council, IFAC.

So how do probiotics fit under DSHEA? So this presentation is going to underline some important aspects to show how probiotics actually do fit. Before going into the presentation, I'd like to underline and point why it's such an important category within the dietary and food supplement space.

So consumption of probiotics on a world level last year closed out at close to 44 billion US

dollars, up 6 billion from 2013. The way probiotics are consumed or the sources of consumed took was 71% was through yogurt, probiotic yogurts, 16% came from source and fermented milks, and then 13% was through dietary supplements. That's globally.

So let's look a little bit further into the dietary supplement space. Last year, 2018, the dietary supplement space closed out at 5.7 billion US dollar market value. It's projected to grow 19% by 2022 to 7 billion. Important to note here, and that's why we are here today, that 5.7 billion dollar USD number, close to half of that number was consumed here in the United States. So quite an important category.

Does an important category like probiotics have an official definition? Not necessarily. It has a few recognized and referenced definitions globally from science communities, academics, government agencies. The most referenced one I would say is the WHO definition, which was put together by an expert panel in 2001 and you can see it up here. Live organisms when administered in adequate amounts will confer a benefit to the host. What about

in the US? Under DSHEA we have some reference or terms of reference to live microbial ingredients, but no official definition per se.

So what is a dietary ingredient? How does it fall within the scope of DSHEA? We heard the previous speakers talk about their vitamins, their minerals, their herbs, so on and so forth. We've, we've questioned where do probiotics fall under in many public meetings and in different exchanges we've had with government agencies.

And specifically we have heard that the FDA say in open meetings that probiotics would fall under (E). What is (E)? Let's look at the statement. The statement says it's a dietary substance for use by man to supplement the diet by increasing the total dietary intake.

What does this statement imply? On the first part, a need to increase the intake and to supplement the diet with that particular substance, in this case probiotics, to help the maintenance, and this is important, is the maintenance of health and normal body functions. And on the second part, it is

a dietary substance.

So let's look at the first part of that statement. The need to increase intake and supplement the diet. We know the thousands of publications and articles in science that have been put out in the public domain around probiotics. We know, you know, their benefits and roles from healthy digestive support to immune. We know that humans from these publications and articles and research, we know humans are made of bacteria 10 to 100-fold more than human cells.

We know that probiotics and life organisms are beneficial to the gut. They allow for better digestion of nutrients. They allow for better uptake in nutrients and they allow for synthesizing certain nutrients. They have very multifunctional roles within the gut, but also these research articles and publications have shown that they have benefits outside of the gut. Immune support, brain-gut access, skin microbiome, so on and so forth.

At the end of the day, the aging process declines bacterial communities in our gut. So this

could possibly shift functions of the body. I can remember what I said previously; the maintenance of health is important. So it's key to understand this. The IPA is working on a meta-review and we're looking at two district databases of clinical trials that have been conducted.

We have a paper due out later this year from two databases, clinicaltrial.gov and the WHO, and we're, it's, it's quite interesting on how many clinical trials are ongoing at this point. Stay tuned for that paper.

Next, so probiotics are necessary like vitamins and minerals. So we, it begs the question, and we always ask, why did DSHEA not include a distinct line item. It would have made my life easier anyhow. So I would say a probiotic or a live microbial, they were prevalent in the US prior to DSHEA, prior to '94.

Some examples, an old dietary ingredient list which, you know, was published by a few significant associations in the US, we find genera species of probiotics. We have a food partial list

that we see for GRAS assessment and notifications. Probiotics also have prior sanctions for food manufacturing.

So they are prevalent. We have the evidence of that. And over and above that they've been also in the food supply for many, many years. One of the first papers that were written regarding probiotics was this, from the Russian scientist, Metchnikoff, who noticed Bulgarian peasants outliving royalty by a high ingestion of yogurts and cheeses.

So definitely have been around for a while. So how do probiotics fit under 20, 201 (ff)(E)? So it's a dietary substance for use in man. The second part of that particular statement, it’s a dietary substance. So a dietary substance. Let's take a look around the world how other government agencies looked at, you know, probiotics.

Clearly they exist in the food supply and there's many, many published lists or safe food lists that can be applied to be used for the, for probiotics within the food supply and in food supplements. Here's a few of the tests in Europe, the

IDS list. We have a natural health products monograph and many, many others as you see on the screen, too many to list.

So where do probiotics fall in the US? We know FDA has a partial list of organisms which have come from safety assessments from GRAS. I think the list is not comprehensive and I believe we can work on it. This is where IPA and IFAC can come into play to discuss on making a more comprehensive list or food list for live microorganisms or probiotics.

In conclusion, they fit under 201 (ff)(E) because they've been in the food supply for thousands of years. There's a health benefit like vitamins and minerals to increase the total dietary intake of probiotics beyond the foods consumed. They were prevalent in the dietary supplements based prior to DSHEA in '94.

So how can we practically look at creating maybe a comprehensive list or a way forward for probiotics within DSHEA? How to be practical? We propose grandfathered or an exempted list. We propose the list, this exempted list would include a list of

species with a safe history of use. The manufacturers of these strains within the species would have the responsibility to, to establish safety based on abbreviated criteria of safety and identity similar to other requirements that we see around the world from other global regulatory agencies.

Now it's important to note that strains within the species of this list would not need to go through notifications. They could be grandfathered, but at the some time we must also maintain we cannot forgo, we cannot forgo the establishment of the safety assessments. Safety assessments still need to happen even though there would be a grandfathering process.

The second part on how to be practical and moving forward and adding probiotics within DSHEA are master files. The master file system or dossiers would provide FDA with enough information to avoid unnecessary notifications, but also reduce the burden and resources of FDA and industry to go through notifications on strains and species that have been in the food supply for many years and have a safe history of use.

Establishing safety, I'd like to mention here that bacteria give us a very, very unique gift. Unlike chemical and innate substances, bacteria gives us a gift of a genetic code. That genetic code or its DNA allows us to look further into a bacteria organism or a probiotic so we can understand what it can or cannot do.

From there things that we can establish from what can be used within the master file system would be whole genome sequencing from, from its DNA for proper identification. Genome, genome mining to make sure there's no production of virulence factors or toxin characteristics. Additionally, we can also look for antibiotic resistance profiling and make sure that these microorganisms do not have the gene that transfers this antibiotic resistance. So all this to say there is a very practical way forward by creating this practical list for, grandfather list for probiotics.

So to finish, it's important to note that a master file system or dossiers with a grandfathered process from an exempted list is the

logical way forward for strains that have been in the food supply for many years and have a safe history of use. But at the same time, we have science which evolves and innovation continues.

So they'll definitely be new strains on the horizon and the NDI process or new dietary ingredient notification process should be reserved for these new, new strains.

I want to reiterate what was said earlier this week from Frank Yiannas, deputy commissioner. It's all about establishing consumer trust within our, and making sure that we put quality products to market. This is key for our category being probiotics.

So this is where IPA and IFAC are here to help. We like to be at the table and would like to sit with the FDA in regards to discussions within the working group and even possibly look at forming like botanicals a specific working group for probiotics. So with that, I want to thank you for your time.

(APPLAUSE.)

DR. WELCH: Can we get the screens up?

Thank you. Can you move one more slide? There we go. Whoops. Not break time yet. It is Pieter's time.

MR. COHEN: Thank you. Thanks so much for having me. It's an honor being here. Let me just share with you first what I do, which is I'm a general internist. So I see patients Monday, Wednesdays, and Fridays. And when I'm doing that I'm often -- actually yesterday I was busy encouraging my patients to restart their supplements that they have forgotten to start. Starting other patients on supplements. We had discussions about B12, calcium, vitamin D, multivitamins that I was encouraging or making sure that my patients were adhering with.

But I not only think that supplements are essential for me and all physician to practice evidence-based medicine in 2019, I also think it's essential that my patients and all consumers have access to these products without seeing me. If everything was through me for every symptom of the human body, the system obviously would break down.

So I am so thankful that so many of my patients receive their care at, at pharmacies directly

without me involved. So I'm a big advocate for access and a big advocate for safety. I got interested in supplements because of harm that my patients were experiencing. And in the last decade we've spent a lot of time and energy studying the safety of, of supplements and particularly interested in the boundaries between pharmaceutical drugs and dietary, and what's found in dietary supplements.

Now this conversation is really exciting to me because what, what we're talking about publically today is something that's been going on sort of under the radar scene, under the radar gun. And it's just wonderful to have an opportunity to discuss it.

What I think's at the core of the question is, is what's, what's the difference between a new drug and a new dietary ingredient. So for the purpose of drugs, I'm not going to be talking about any legal definition. I'm just going to use common sense definition, which is a substance which when ingested has physiological effects.

So using that definition of drug, it's

clear that some dietary supplements, many, are drugs in the sense that they're to be ingested and have physiological effects. Vitamins and minerals across the board.

So the question is not whether or not there's a clear boundary between a pharmaceutical drug and dietary supplement. There's not and that's okay, and that's what DSHEA was put in place to define, to make sure that the FDA didn't regulate these types of substances in the same way they did with pharmaceuticals.

But what I think's very interesting is how do we -- let's now move to a new drug. So a new drug being a chemical that whether or not it's extracted from a plant or synthesized, but it's placed into a pill, powder, capsule, gel, ingested for physiological effects. And the question is what are the routes in the United States to market a new drug.

So over the last 25 years what's been happening is that new drugs have been marketed as dietary supplements or dietary ingredients in dietary supplements. There's a lot of different examples of

this and different routes that these new drugs have taken. Sometimes it's a drug that was actually well known prior to 1994. Yohimbine, for example. So yohimbe is the tree. The bark of it's extracted and used as extraction. One of the most active alkaloids is yohimbine. When that's either isolated from the bark in high quantities or synthesized, it was a pharmaceutical drug well before 1994.

So this distinction that there were things that were prescribed by physicians in 1990 and things that were sold over the counter, yohimbe bark extract prescribed by physicians, Yohimbine, was a clear distinction. And there was no effort that I understand for either consumers to demand or congress to say let's move these prescription drugs, even those that might have originated in plants, directly into the store shelves and be sold directly to consumers.

So one thing that we have seen over the years is that you take a product like a food like red yeast rice, but you formulate it in a way where it becomes a drug. You have high levels, monacolin K, exactly the same chemical that's the prescription

lovastatin. Or you take yohimbe bark extract, formulate it a way that you have pharmaceutical doses of yohimbine. But there's other ways that supplements have been formulated as new drugs. And this is where we're particularly concerned because we don't have evidence about its efficacy or safety in humans.

An example of this is finding a chemical in nature or purportedly finding in nature. DMAA, the stimulant, is a great example of this. You synthesize it, place into a pill, sell as a supplement to have physiologic effects. So here we have a new drug being introduced as a dietary ingredient.

So one pathway is using that old grandfather clause, but the other pathway is the NDI pathway. Vinpocetine is a great example of this. So the vinpocetine is a drug prescribed in countries, including Russia, for neurological conditions. It's never been found in nature. However, a chemical very close to it, vincamine, is very prevalent, for example, in lesser periwinkle.

So the idea was that since it's just a tweaked version of vincamine, we can sell vinpocetine

only synthetized, only pharmaceutically synthesized in supplements. That's how vinpocetine has found itself in hundreds of supplement products.

So there's been a -- and if we follow this thinking that has been proposed by some of the industry, that we can identify chemicals in any food or botanical and then synthesize them at whatever dosages and sell them for humans, this a, that's introducing a new drug into commerce in the United States.

Now does this matter? So I would argue it does for two reasons. Number one, I agree strongly with what Scott said. We need incentives for firms to create information, especially safety information, but also access to information such that consumers, physicians, and all of us regulators can just choose for ourselves what we want to use. So consumers can decide what to use.

If we don’t have the research, a consumer can't make a wise decision for themselves. If we introduce a new drug in these pathways, there's no way that a consumer can decide if that's right,

especially when the label is not required if you mix it into a proprietary blend to include the quantity of the new drug. So I would argue that we need to have a system that insists on evidence at least of safety prior to marketing any new drug in the United States.

Now the second question is safety, consumer safety. Is this just a theoretical issue or are patients being harmed? My perspective as a physician is patients are being harmed. If you take a look at the studies, for example, the CDC's study that estimated that roughly 20,000 consumers end up in emergency rooms every year due to supplements, that more that 2,000 are hospitalized every year due to supplements, or at least the physicians caring for them believe it's from supplements, then, and you take a close look at what categories are causing the trouble, it's really categories that are doing more of this introduction of new drugs, introducing new drugs rather than nutritional categories.

Similarly, I wouldn't be surprised if we found out that the reason why ephedra led to 18,000 adverse event reports including, of course, seizures,

heart attacks, and deaths, was that, not because they were, everyone was consuming a natural extract of ephedra, but rather that the ephedra alkaloids would either be highly concentrated or synthesized at dosages that were much higher than traditionally used.

So I do think there's serious safety issues. Another recent example just of one product, which is a mixture of these kind of new drugs, basically a synthetic version of a constituent of a botanical, is the OxyELITE Pro story, which when it was introduced in early 2013 before the end of the year had already led to 69 case of hepatitis, dozens of hospitalizations, three liver transplants, and two deaths.

So, and when scientists analyzed what was actually in it, it was exactly what was on the label, which is synthetic versions of botanicals mixed together in a new way that had never been consumed before.

So where does this leave us? I think that it's very fair that we have very thoughtful lawyers on both sides of the argument. I've read the

FDA's position on interpreting DSHEA in terms of synthetics. It seems extremely reasonable to me, but I sit down and listen or talk to Scott for an hour or two, his position also sounds very reasonable.

So I, I don't think that we have a clear guidance here, but we're going to have to make a decision on how we handle this. Do we want a two-tiered system where new drugs depending on their backstory, if they've been found somewhere in nature, in a food anywhere in a world, in a botanical, they can be introduced through the NDI process? Or, and a recent example for this would be CBD, might be in this pathway. Or are we going to have a system where the courts are going to make these decisions for us?

So I'm just delighted to be at a meeting where these issues that we have known about for years are now being pubically discussed 'cause I think the, the conclusions we come to are going to be essential and I think they should be shared broadly with American consumers. Thank you very much.

(APPLAUSE.)

DR. WELCH: All right. Thank you.

Thank you, presenters. That's wonderful. I just want to note that it only took about 90 minutes for CBD to be brought up. So better than last two days ago. I intend to bring that up again. Okay. I actually would like to open it up for Q&A. I see they're turning on the mics. Thank you, guys. I appreciate that. If there are questions for our panel, I would fully encourage you to go to one of the two mics.

We do need to speak our questions into the microphone so that our webcast participants can hear, as well as our transcriber, because, again, the meeting is being transcribed. Also please begin with your name and affiliation. That will help the transcription process and so we all know who each other is. Our panelists, I, you have mics. I assume you push the button and it turns on. Great. Awesome. Thank you, George, for checking.

Also if you -- I realize there's only four of you. If you could try to remember to say who you are when you start answering the question. Our transcriber can't quite see you. So also he doesn't know who you are.

So let's go ahead and start with the audience questions. Go ahead. Thank you.

MR. GASTELU: My name's Dan Gastelu. I (inaudible). I've been working in the dietary supplement, food, and drug industry since the '80s. And can I ask a question? Like how many people were here for the dietary supplement (inaudible) Education Act (inaudible)? Anybody? All right. So very few. Because you got to really agree to have to live under that rule, FDA rule. I really appreciate the great work everybody's done with DSHEA because my life back then was, 'cause I started toward nutrition weight lose products was basically (inaudible) harassment by the FDA (inaudible) help build muscle.

So the Dietary Supplement Health and Education Act just made my life normal. Everybody's life normal. (Inaudible) big products like I was involved in, well, condition categories, (inaudible) probiotics, ultra. And there's a lot of good stuff we have right now and the great part is all in the public health business. So that's (inaudible).

So we have a (inaudible) selection of

products that are (inaudible) for health versus a lot of foods that, you know, are just snack foods and things like that that aren't necessarily made to promote people's health. I also work international and in Canada, places like that.

So one question I have is why not just adopt Canada's definition? It's a really familiar (inaudible) definition (inaudible) health products where it says bioactives of the above, which include botanicals? They also have fungi and things like that. That's question number one. Why not do that?

DR. WELCH: Do any of our panelists want to answer that? I would defer to the panel on this one. I am not --

MR. GASTELU: Reading it into the record (inaudible). (Inaudible.) I got a lot of stuff to read into the record.

DR. WELCH: George, it looks like you're going to answer Dan's question?

MR. PARASKEVAKOS: Yes.

MR. GASTELU: And also probiotics mentioned (inaudible). So (inaudible) FDA work

(inaudible). They use (inaudible). Work together closely (inaudible). I don’t know the reason, how to answer that, but what's the general consensus?

MR. PARASKEVAKOS: George Paraskevakos. And your name was?

MR. GASTELU: Daniel Gastelu.

MR. PARASKEVAKOS: Daniel. It's really common. (Inaudible) Health Canada even developing that probiotic monograph. So I think it was well, the (inaudible) was well. We're a smaller (inaudible) time. It's a simple answer, but maybe not so simple. We love to see the model be (inaudible) across the globe with (inaudible) probiotics it works well, but within each country you got to understand that there's a very specific, you know, regulatory frameworks and structure that also need to be examined.

So I, from the regulatory perspective, from the government side, I also understand that, you know, it's not easy to fit a square into a circle. So, but the model does work and (inaudible).

DR. SHARPLESS: Well, we created it. The Dietary Supplement and Education Act didn't exist.

It was created by the industry (inaudible)? (Inaudible) that's a simple solution. Now the other thing I have, well somebody else (inaudible).

DR. WELCH: Thank you, Daniel.

MR. GASTELU: (Inaudible.)

MR. PARASKEVAKOS: I would say (inaudible). One thing I struggle with is I see ingredients containing 7% (inaudible) acid and (inaudible) and pomegranate extract. I see ingredient from 90% (inaudible) claimed (inaudible) extract. When is a material, an extract, when does it become a pure compound?

MS. PAVLICK: Larisa Pavlick from United Natural Products Alliance. Looking at (inaudible) a little differently, especially with some our current market, market products. To define (inaudible) as a product transiting from an orange to an orange juice to ascorbic acid in a tablet. But the definition or the regulations have defined is that once there's chemical alterations, in that process, and it's no longer what was in (inaudible) 1994 (inaudible).

And I know that you and I share that

opinion. I think once we have that clinical alteration or manipulation for (inaudible) any one compound, that's when it needs to end of the (inaudible) ingredient pathway and goes through a notification process to unsure the safety of the product and then balancing access to innovative and modernized products and (inaudible) public health and safety.

MR. BASS: I look at it a little differently in the sense that I think it's a question of whether it's a new dietary (inaudible) or not and whether an extract or otherwise, it's something (inaudible). To determine in the first instance, but I think we really have to look at screens rather than how much (inaudible) under (E) or (f) and (inaudible) to safety and (inaudible) in terms of (inaudible).

MR. BLAKE: Rick Blake with Strategic Health Recourses. We represent (inaudible) and I, I urge the FDA and I know this is not (inaudible). I urge the FDA not to exclude patient and patient advocacy groups on the discussion because it's what we're talking about, protecting patients, patient

(inaudible).

Now, on the other hand, we also represent (inaudible) immune systems that are HIV (inaudible). So my question is it's really important in HIV (inaudible) to have supplements, dietary supplements that can help with comorbidities, co-conditions. Our patient groups are 30% more likely to have immune compromised systems, outside of just HIV. So my question to the doctors, as you see your patients and you recommend supplements, if you see HIV and AIDS patients, not just all the diabetics, or, or any, any immune compromised patients, how can we -- it's very important.

How can, how can patients be assured, not just a safe, but the efficacies of, of what they take, particularly HIV patients (inaudible) retroviral drugs?

MR. COHEN: I, I thank you for that very thoughtful question. And I just want to say that personally I'm not a big fan of structure-function claims and I think that unfortunately they might not be the intent of the law, but it has permitted

companies to advertise products as if they have (inaudible) boost your immune system, even if there's not a single study in humans demonstrating that's the case.

So in addition to what we talked about earlier, I absolutely agree with you that we should be seriously thinking about the positive and negative potential health effects of structure function.

MR. GASTELU: Yeah, that's a category that frustrates a lot of us in the industry.

DR. WELCH: Daniel, can you get a little closer to the microphone?

MR. GASTELU: (Inaudible) nutrition together with (inaudible). But in regard to your comment on structure-function, that's, to me that's the life blood of the Dietary Supplement Education Act. You have to have substantiation. And the FDA did put together guidance documents (inaudible) you know, unfortunately it's left us (inaudible) health claim (inaudible). You go to Canada, they do, they do review. They have a lot of (inaudible).

So I think, I think it's a good time to

button things up. There are good models like Canada. There's a lot of good (inaudible). They have a lot of great products. And (inaudible) products, but getting back to this one specific issue here that we brought into it, 'cause we're talking about new dietary ingredients now and (inaudible) notification process.

If I'm going to create a new product, a new ingredient, you know, it's years before you (inaudible), especially now with safety data and things. So (inaudible) do anything. So I think you just need to have a forum to communicate officially when those dietary supplement says we're going to do this product. We think it's a (inaudible) ingredient for these reasons, and then have the FDA sign off on it so when they -- you know, so this is an example here.

So when they do the 70-day notification, they have documentation that says you've accepted the fact that it's a dietary ingredient, you know. (Inaudible) now this one (inaudible) here (inaudible).

DR. WELCH: Michael, do you want to jump in while Dan's looking for his glasses?

MR. McGUFFIN: I think two quick questions. This is Michael McGuffin with the American Herbal Products Association. First to Larisa, when you say synthetic botanical, I don't think you mean somebody made a synthetic root of ginseng. I think you mean synthetic botanical constituent. Is that correct?

MS. PAVLICK: Thank you, Michael. This is Larisa, Natural Products Alliance. Yes, sir, that is a good clarification of the point. (Inaudible) compound.

MR. McGUFFIN: And that’s I think consistent (inaudible). Let's get the language really clear.

DR. WELCH: I would actually say synthetic copy of a botanical constituent.

MR. McGUFFIN: That'll work too. And then I'd like to pose to Scott. Larisa also said that UNPA's considering a policy that we would require to make a synthetic (inaudible) when you put it in your product you've identified it because (inaudible) did not come out of a plant, whether you call it a

synthetic or whatever word is used. Did I understand correctly?

MS. PAVLICK: Correct. Yes, sir.

MR. McGUFFIN: But it's also looking at a thoughtful process around that same issue. If you put an artificial flavor in your food, you call it artificial. So I'm curious, Scott. I know you advocate for the allowance for synthetic botanical constituents. Does it make sense? Would that be a service to consumers to, for companies that sell those to be required to acknowledge that it did not come out of a plant on the product label?

MR. BASS: Thank you, Mike, for putting me on the spot. Let's put it this way. Go back to Section 411 which was passed in 1973 where the congress said we're not going to distinguish between synthetic and actual sources (inaudible) minerals. So move forward from a regulatory standpoint (inaudible) matters.

So it's really a commercial standpoint and something that you would argue fairness to consumers and disclosures. So without taking a final

position on that, I would say there's a good argument on disclosure which goes to, I think, my colleagues' comments earlier that people want to know what they're getting. (Inaudible.)

MR. McGUFFIN: Thanks very much.

MR. POLINSKY: Scott Polinsky, attorney. Thank you for the great presentations. I wanted to bolster Larisa's point and Scott's as well on the distinction between synthetic and natural substances. Actually the Food and Drug Act (inaudible) regulations (inaudible) synthetic versions of vitamin and minerals equally. 21 CFR 109, subsection or paragraph K, in that section the FDA considers a food to be misbranded if it makes a label claim stating or implying that a natural vitamin is superior to a synthetic one.

And I have a, a comment on Dr. Cohen's remarks. What percentage of people who visit emergency rooms as a result of something used to have taken too much of a supplement way in excess of the labeled directions because they want to loose a lot of weight or hit a homerun? And what percentage of those ER visits and emergency situations are a result of

taking a product that is not actually a supplement? (Inaudible) that is a product masquerading as a supplement?

MR. COHEN: Those are great questions, but I think what we're getting at, especially (inaudible) because as I'm interpreting what we're hearing, we take synthetic versions of botanicals and food and place them into dietary ingredient. And the last comment that (inaudible) these are not (inaudible) masquerading as supplements. These are counter to what we've been talking about. So I'm not quite understanding that position you're taking.

MR. POLINSKY: Thank you.

MR. MILLER: Yeah, Mark Miller. INW Manufacturing. I just want to ask the panel about the (inaudible) definition of synthetic regarding a bioidentical because often what we're thinking about is something that's got the same chemical structure and you write it simply, but there are variances in it's 3D structure and (inaudible), which we've (inaudible). And if something does have the right three D structures, it's likely to have quite

different effects involved (inaudible).

DR. WELCH: I would still defer to the panel first. Sorry.

MR. COHEN: I completely agree. This is why we need, we're introducing a new chemical (inaudible) function, that we need evidence. We need data. We need to know what it actually does in the human body.

MR. MILLER: But I give a thought is some of the interesting examples. Astaxanthin is in the food supply for salmon colorant, but the natural product has a different 3D structure. All the (inaudible) chains and (inaudible) as opposed to SIS bonds makes it all bent and clearly less functional Also affects absorption.

So there are circumstances where it looks to be the same, but it's not the same. And therefore, it has a very different biological effect. Should they be treated equally?

MS. PAVLICK: Larisa with the United Natural Products Alliance. If a dietary supplement (inaudible) appropriately (inaudible) it does have

expectation of developing specifications (inaudible) and potential contaminants. And (inaudible) 111-75, you're also verifying the (inaudible) specifications are being met. So a (inaudible) is being used appropriately, it would address the system transference of a chemical compound. So within a new dietary ingredient notification application as part of the process, it should be identifying product appropriately using all examples and analytical tools available.

MR. GASTELU: I would just like to jump in (inaudible). He's talking about different chemical structures of a biological activity. I would use an example of vitamin E. It's a natural or synthetic, but our government says astaxanthin has a different chemical structure, the natural, the synthetic. So would (inaudible) what the biological activity is? Even, even natural source things like some of the omega 3 fatty acids that are reproduced are a different source. Naturally it could have different, you know, chemical structures that make the biological activity just a little different.

So even the natural depending upon the source could, could have different -- so there's the chemical side and biological activity side. I think we're trying to get at one (inaudible) biological activity side (inaudible).

MR. MILLER: Part of it is when you're looking at the chemistry, there are levels of, and I don't think in the discussions, certainly the public understands (inaudible) and things like that. So we tend to stop at a very top level and not take it all the way through. And I think that things are slipping through are inappropriate and the consumers can't tell the difference.

DR. WELCH: Thank you. So we only have about one more -- oh, Scott, you want to say something?

MR. BASS: I just want to comment it's a matter of law. You're right and the reason I said earlier that (inaudible) NDI was grandfather was common food is (inaudible) rewrote a lot of the (inaudible) to F1 safety health regs because of the tryptophan disaster in 1989. Precisely because of

that. So you can't rely upon (inaudible) structure and even if NDI is one line, it would be under the master classes (inaudible) licensing out product (inaudible) one line (inaudible). On something like you're talking (inaudible).

DR. WELCH: One quick question from Taylor.

MR. WALLACE: So we talked a lot about dietary supplements that might or might not have a direct effect in individuals. I'm really anxious to see what George has to say about this 'cause I have had the opportunity to now start the second clinical trial on a bacteria (inaudible) supplement that might not have a direct effect on human health, but if you were to have a certain maybe higher level of a problem-causing bacteria in your gut and you introduce that, there's a possibility that there could be a release of exotoxins from those bacteria that are, I guess, should say naturally present in the gut and how do you begin to incorporate that. (Inaudible) FDA (inaudible) those things in the '50s.

DR. WELCH: George?

MR. PARASKEVAKOS: So just (inaudible)?

MR. WALLACE: Well, I'm asking, you know, we talked a lot about, you know, I take ephedra that's got a direct effect on humans. If I study bacteriophages in healthy people that maybe don't have a high level of pathogen or whatever bacteria of interest, you won't have any negative health effect. There comes a (inaudible) a higher level, that bacteriophage would kill that bacteria, they would create an exotoxin and could harm the constituent. I see a lot of these hitting the market and how those, how does this go into DSHEA 2.0?

MR. PARASKEVAKOS: So (inaudible)?

MR. WALLACE: We actually make the virology behind (inaudible) specific strains of bacteriophages, but we didn't find any adverse events. Again, we were targeting inorganic (inaudible) coli which is found in very small levels to support a structured function (inaudible) healthy individuals --

DR. WELCH: I'm actually going to -- I'm sorry. I think this is a great conversation that you two may want to have in private because George is

getting all down in the details here. I don't, I just one quick editorial note and I said I wasn't going to answer the questions. But I would make the argument that DSHEA 1.0 addresses that, specifically the safety document.

So with that, I think its time to take a break. Well, we really do need to take a break. So I'm going to break, but you by all means can come up and talk to the panel. Could, could you fit it onto comments at the end of the day? We have 15 minutes for break. Fifteen minutes for break. So we'll start again at 10:40, 10-4-0, you all. Thank you.

(BREAK.)

MS. WELCH: All right. Thank you all. I'm going to ask everyone to be quiet, please. Everyone, I need you to come in and take your seats and -- thank you. Thank you. I feel like I'm corralling children here. Basically, yes. A few notes because I just can't stop giving housekeeping notes.

I feel like the temperature has really cooled down in here. So I'm sure everyone is grateful

for that and they will do their best to keep it somewhat temperate for the rest of the time. It's even hotter under these spotlights. So feel bad for your speakers.

The, this door down here is really just for FDA employees. So please continue to use the one at the top of the stairs. And I think that's it for now. We have session two beginning. This is talking about understanding exceptions to the NDIN requirement. This panel discussed issues related to when an NDI notification is not required for new dietary ingredients and whether evolution in the supplement marketplace has altered the impact of this provision.

We're going to be hearing from about three speakers about ten minutes each and then we'll open it up for a Q&A session again. Hopefully it'll be as popular as our last one was. But these speakers are between you and lunch. So I'm sure they'll keep that in mind.

First we're going to be hearing from Michael McGuffin, President of the American Herbal

Products Association, then Ashish Talati, partner, and Amin Talati Upadhye. And then Laura MacCleery, policy director at the Center for Science in the Public Interest.

I don't want to take up their time, so I'm going to turn it over the Michael right away. Thank you.

MR. McGUFFIN Thank you very much, Cara. Thank you, Steve. Thanks for the opportunity to be here today and discussing these issues that of course have been troubling us and confusing us and hopefully leading to some progress for us over the last 25 years.

And so I was asked to address this issue of the exception for filing of a notification for an article that is a new dietary ingredient, but that is also identified as an article used for food in a form in which the food has not been chemically altered. And this is the language from the law. When DSHEA amended the Food, Drug and Cosmetic Act, it clearly stated that a supplement that contains an NDI is adulterated unless it meets one of these conditions.

The first one being that it is an article used for food in a form of which the food has not been chemically altered, and the second option is submission of a new dietary ingredient notification. And the implementing regulations used exactly the same language, no reinterpretation here at all, very clearly adopted the language from the law.

And then so the first question that we have to ask I think is the first phrase, an article used for food. What is an article used for food? It's defined in the Food, Drug and Cosmetic Act in the United States Code at 321(f). Food means an article used for food or drink for man or other mammals, chewing gum, or articles used for components in any such article.

And there is another place in regulation where this is addressed on the requirements for prior notice of an imported food. FDA gives some examples of foods and I think it's good to just have this list. The Agency does not in this regulation say this is the, this is an entire list, but these are examples and this is what, there's nothing at all surprising

here. These are articles that we think of as food.

And there are many, many such articles and one thing that is, that needs to be remembered, in the, this tolerance for an article used for food, there's no geographical limit and there's no time limit. So it's not an article used for food in the United States. It's an article used for food. And it's not an article used for food prior to the passage of DSHEA. It's an article used for food.

I'm clear in conversations with the Agency over the years that there's agreement at least on that first part. The Agency's never taken a position that this means articles used for food in the United States. I'm not sure that there's been that same degree of clarity on, if it's an article introduced for food in 2018, does that grant the exception? I think industry thinks it does, but I don’t know that the discussion has ever been had.

But these are just examples of where we'll find articles used for food identified in federal regulation, and Bill Frankos brought these up at a meeting a couple of days ago that these are

clearly all old dietary ingredients. These are fairly set regulations. The Agency hasn't added to these in decades. And there are 120 botanicals in the natural flavoring. Another 80 in spices and other natural flavorings; although, there is some duplication there. Some more in essential oils. I like the one at the, at the end, 182-50. You can, if you can get your musk or your civet oil in there, which is used to make things smell good or smell like that, those are clearly articles used for food.

Now I don’t know that they would fit one of the definitions of a vitamin, a mineral, amino acid, or an herb or other botanical, but they would fit the dietary supplement for use by man to supplement the diet apparently. So I can see a musk CBD supplement coming in soon just to make the second mention.

Interesting too, so food additives and one of the things that DSHEA clarified is that dietary supplements are not food additives, but are food additives, articles used for food for the purposes of recognizing that we would have an exemption from an

NDI, from a notification if our NDI is a permitted food additive and there are a number of them, including synthetic flavoring substances and adjuvants and direct food substances affirmed as GRAS.

Well, I find it interesting that in FDA's 2016 NDI guidance, they gave us an example in asking the question, the one that I'm discussing here, is an NDI notification required for an NDI if it's an article used for food and form of food and it's not been chemically altered? No.

And then they give as an example if ingredient X is a food additive that was approved for use to sweeten baked goods in 1993, but was never marketed as a dietary, in a dietary supplement, clearly it's an NDI, but it says because it was, but it's not required to submit an NDI notification because ingredient X has been present in the food supply.

I'm not sure that the Agency intended to mean that broadly, that food additives in the food supply can be used in a, can be acknowledged as a new dietary ingredient and skip the notification. But

again, this example in the 2016 guidance, which don't forget we have rejected out of hand. So we shouldn't say, but we love this paragraph. But nonetheless, this is what was stated by the Agency at that time.

I also -- this is a place that I go. Somebody calls me and says, hey, can you find me a recipe that has schisandra in it, you bet I can. So you can see that there are 4,853 cookbooks available at archives.org. You got to love the way-back machine and all of these things are out there. Some of them you can directly download. Some of them you can borrow. But it's really a great reference for finding old recipes and new.

I organized this in two different ways, one by these thumbprints or thumbnails, and the other by just you can organize it by listing. I organize both of these from oldest to newest, but I think that was a little bit of an oversight 'cause I do want to make the point that a new food use apparently also would establish that it's an article used for food.

But again, this is a great reference if you just need to go find a recipe that establishes

that an ingredient, especially a botanical ingredient, is an article used for food. You can find plenty of recipes for hemp here. I have. I have them in a file. I can't find any recipes for CBD, though.

So then what is chemical alteration? I'm going to move to the second half of the sentence. In the, in the congressional statement of agreement was quite clear. It said that chemically altered does not include the following physical modifications, minor loss of volatile components, dehydration, lyophilization, milling, tincture, or solution, water slurry, powered, or solid in suspension. I say clear.

When you read this and you look at the placement of the commas, it gets a little hard to understand quite what a tincture or solution in water slurry, powered, or solid in suspension means or where the comma break should be, but I think the Agency grappled with this in the 2016 guidance. Again, we can take some learning from that.

What the Congress did not say is and that's the end. And so is this a list of examples or is it the list of all modifications that do not

constitute a chemical alteration? And that's another issue that we're still trying to sort out, I think.

I'm actually going to skip a couple of slides because I think it's better to start here. What, this is, again, from FDA's NDI guidance. And the balance of my presentation is not to try to sort out all of these things in the ten minutes that I was given, but to report a snapshot of where we are based on FDA's view of what constitutes chemical alteration from the 2016 guidance.

And so here are a couple of slides of what processes for manufacturing or dietary ingredient, article of food present in the food supply, do not result in chemical alteration. And you can see that first bullet point is that FDA says that they consider the list in the congressional statement of agreement to represent examples, but not necessarily a complete list. That's good.

And then if you go read the rest of them, the Agency did not add any to the list that FDA, or that was in the Congress. So even though they've conceptually stated there may be some, they didn't

offer here's, here's an example. All of the rest of these were already in that congressional statement from, from 1994.

A couple of these that I do want to comment on, I think the, not on this page, but on this page. Changing agriculture or fermentation conditions to alter the chemical, molecular, or composition, or structure. We're a little nervous about what that means.

If I'm harvesting my camomile usually in June, but I start to harvest it in May even though my yield will be a little less, but I know that the senecio hasn't germinated by then and I really don’t want the senecio in my camomile, I hope that the Agency doesn't say, oh, that's a new, a change in agricultural practice that results in a new dietary ingredient.

I think this is, these kinds of attempts in the guidance to, in my view, broaden as many ingredients as possible, but could be defined as needing an NDIN and not surprisingly industry would rather narrow that, and I think that kind of -- we, we

need to find the balance on those things. We need to still go back to these examples that we're given and, and clarify them.

Use of a botanical at a different life stage, you know, the example given here, even this one, I'm not so sure that an unripe apple or a ripe apple, I mean certainly there are some different measures of compounds in those, lesser sugars, whatever other constituents. But again, it may be a bit of a strained example. The last one on mycelium, that's actually not a, it's more of a part of the plant which we're all required to address anyway.

I'm going to move back up then to the, several slides on examples of processes that the Agency has said do constitute chemical alteration, a process that makes or breaks chemical bonds. You know, I bake bread every once in a while. There's an awful lot of chemical bonds broken there. Is that what we meant? I'm not sure there's clarity here.

Removal of some components from a tincture. So if I remove the pyrrolizidine alkaloids from my comfrey extract, is that chemical alteration

that results in, that would require a notification? I think it's hard to argue that it would not and I know that FDA has commented that that exact example probably would be an NDI.

Use of solvents other than water or aqueous ethenol. There must not have been an herbalist working on writing this guidance because they would have known that we might use vinegar. We might use oil. We might use a food grade oil. There are other solvents, food grade solvents that we would not consider that represent chemical alteration that, anymore than water or aqueous ethenol would.

There's an application of nanotechnology. I know that's one that the Agency has asked about not just in a supplement area, but also in foods and concerns about what do we know about the safety of those.

There was one other that I thought the -- but I can't find it right now. So I'll skip it and hope I've given you enough to think about.

I think kind of the takeaway is all these issues are unresolved. And, you know, we saw a

2011 guidance. We commented. We saw a 2016 guidance, we commented. There hasn't been any discussion since. I'm going to give some credit to when Bill Frankos was here and I think Susan Walker may have still been here, and we were working on the GMP rule and there was a meeting requested that we all come in and sit around tables and talk to each other a line at a time and see if we could get consensus in that kind of framework.

You know, the, the process now is it's like the doors are closed between us and we don't have a forum in which we sit and talk to each other. And I don’t mean just industry. We would invite the public health agencies, the consumer groups, but I think some of this needs to be resolved in a more, more of a dialogue than an exchange of papers with months and months or years and years between them.

Because we do need to get these things resolved if we're going to move forward in the whole issue of recognizing the new dietary ingredients that actually do require notifications. Thank you very much.

(APPLAUSE.)

MR. TALATI: Good morning. Thank you, FDA, Steve, and Cara for giving us the opportunity to provide our comments. I'm Ashish Talati, a partner at Amin Talati law firm that specializes in food and supplements. I've been working on GRAS and NDI issues for a long time. So I really appreciate the opportunity. Let me see if I can --

All right. Thank you. So I know Michael gave a good overview of these exceptions. I'll try to dig into it a little more and give my perspective. Certainly it's an important topic. You know, 2019 is, is certainly 25 years from 1994 and a lot has changed. What we're seeing in the marketplace is a line's been blurred between conventional foods and dietary supplements. Functional foods, what's called better for you, is a huge category.

We have a lot of our clients that used to be, you know, just marketing dietary supplements, but they certainly have products in the conventional foods or functional foods categories as well.

So we certainly think that the exception, you know, where a company certainly does not have to file an NDI notification, is a significant opportunity for companies that, you know, even based on their limited resources, certainly does, and can take advantage of that.

So one of the things is on the GRAS or approved food additive. In 1958 Congress passed a food additive amendment act where a company or a, you know, supplier can self-affirm GRAS or file a GRAS notification, or at that time it was an approval process with FDA, or can do without any FDA approval process, meaning they can self-affirm on their own.

Since then in 2016 FDA has finalized a GRAS rule and the independent conclusion of GRAS is certainly written in the law. So companies don’t have to file GRAS notifications with FDA.

So I'd like to walk you through a scenario. If a company works with Office of Food Additive Safety, OFAS, files a GRAS notification, has an ingredient in the food supply, they have a product, and then they would like to market also as a dietary

supplement, dietary ingredient, does that company need to file a GRAS notification? The law clearly says they can use the exception and they don't have to. And that is a huge, huge opportunity. It saves a number of resources with FDA and certainly the safety standard, which a lot of times does not get enough attention, but the GRAS safety standard is reasonable certainty of no harm. The dietary supplement, dietary ingredient standard is reasonable expectation.

I would like to get some more clarity on what the difference is with OFAS review and GRAS notification, and ODSP reviewing and NDI notification. Is there a difference in their analysis? But certainly someone doing a GRAS notification or a self-affirmed independent conclusion of GRAS, they have to meet that standard.

So right here basically the, the process, the way it should work is you have a GRAS or approved food additive ingredient or it's in the food supply for many, many years, we certainly think it should be before 1958 if you don't do a GRAS or food additive petition. And then it's available in the

food supply and then you can have it as a dietary ingredient without chemical alteration, meaning you're not making any changes to that ingredient.

So there are three bullets here. One of them I'll start that's not on here is having in the food supply. The one question we often get is, you know, if there was a, let's say, indigenous tribe in Brazil and they were using this ingredient, does that qualify as a food supply? We certainly think it needs to be very widespread and, you know, that also means, you know, if you find a cookbook that mentions it, there's no documentation of that ingredient being sold or marketed, does that qualify as food supply?

So those are some questions that, you know, certainly come up all the time. But a company can do a GRAS notification. They can do independent conclusion of GRAS or food additive petition. Those are opportunities. Those are the pathways. And then have it legally marketed anywhere in the world. And has been introduced to the food supply.

So, again, it's very important where it does not have to be in the US. It could be anywhere

in the world. The timeframe comes into the picture. You know, let's say someone does an independent conclusion of GRAS or a GRAS notification, can they simultaneously introduce a dietary supplement, have it in the food supply, and it's a dietary supplement? Is there a timeframe? No one knows. There has not been a clarity on that. So it could be six months, one year, one day, but, again, those are some of the important issues to be addressed.

And this chemical alteration issue, it does not get enough attention, but at the end of the day certainly FDA has provided a lot of details as to what they consider as chemical alteration. Certainly it involves only physical steps and it does not selectively increase the concentration of any ingredients that would modify the bonds.

We don’t see chemical alteration as, as of an issue. The bigger issue is what's in the food supply and how do you, you know, come up with, you know, what's acceptable to the FDA in terms of duration of the ingredient being in the food supply. The GRAS pathways, and either you do a GRAS

notification to FDA or do it on your own, we certainly think that the safety is paramount, but we have not seen or are aware of any ingredient that has been self-affirmed and was pulled from the market because of safety concerns. Thank you so much.

(APPLAUSE.)

MS. MacCLEERY: Hi. I'm Laura MacCleery. I'm policy director for Center for Science in the Public Interest. We're a nonprofit organization that's been around for about 50 years. I appreciate the sincere and earnest effort today to come together with all this range of stakeholders and I would enthusiastically accept any invitation from Michael or others to engage in a consistent dialogue. I agree that these sort of sporadic events are not enough to resolve the kind of issues that we're facing in this marketplace and I do think that agreement is possible.

This is an example of a recent -- well, this is last year actually. We just did one, smoking cessation, dietary supplements, and we're doing these as a repeated sort of service to FDA. We write

enforcement letters. We actually query companies that are selling products making disease treatment claims. I ask them for their evidence of efficacy and can you believe that some of them write back and admit that they don't have any?

And so we put that information in a chart with all the responses and give the particular product names to FDA as part of its enforcement, a policy which says that they're going to prioritize enforcement around disease claims. They did issue warning letters in response to this and found even more violations than we have alongside the FTC.

We think consumers are obviously entitled to a safe marketplace and there's some basic consumer protections around transparency, efficacy claims, accuracy, adulteration, and other things that are actually reflected in the law, but aren't often honored and practiced due to a number of sort of slips. And these are the kind of things we'd love to work with industry to address.

I think they're basic to any consumer product and they're a particular issue with

supplements given the size of the marketplace and the list of resources for effective regulation.

These are some of the things that we think we could accomplish working together. We see this as like sort of the low hanging, common ground fruit that we could work on including product registration and additional transparency measures. And then some safety checks where we know that there are problems with particular product categories, like weight loss and other places where we're seeing a lot of tainted supplements. We think that there's an enhanced enforcement mechanism that you could use there. And obviously improving resources for FDA and its oversight.

We've heard a little bit about GRAS. I want to talk for a minute and you'll just have to bear with me about the arcana of the way that generally recognizes safe operates as a category within the food system. In the food system, and you, many of you probably know this, there is a process for approval called a food additive petition where you have to file for that approval with FDA, and that triggers an

internal review. It's actually not a public notice and comment. But FDA publishes a notice in the federal register that they're asking these things under advisement for a food additive petition consideration.

And then there's an alternative to that and Congress in its wisdom in 1958 provided a large category that has, we think, taken over the law over time. And substances, GRAS, if it is generally recognized as safe by experts based on common knowledge. So it's not public perspective. It's expertise end scientific, and then it's supposed to be common knowledge. I'll note that no other country in the world has this category of an exemption for generally-recognized-as-safe substances. It's unusual, at least that I know of.

And the way that you establish a general, an ingredient generally recognized as safe is through scientific procedures where a safe history of use. Safety is a reasonable certainty in the minds of competent scientists that the substance is not harmful. That means that there, there should be some

body of evidence, scientific evidence. There's a book called the Redbook which lays out FDA's methodology for assuring the safety of GRAS substances. And that, you know the standard is to animal testing in different species, toxicological testing. There's also other evidence. It's a weight of the evidence approach.

You're supposed to rely on published data and the common knowledge element is really important. If it's just your own, as an industry for putting forward a GRAS substance, your own data and it's not public data, it not published data, it's not sort of a commonly known, then the general recognition element is not met. That's the idea of GRAS anyway.

This is a really boring history of, of GRAS and the precursor to the 1997 rulemaking that changed the parameters of how the industry processes GRAS notifications, but there, there has been attempts over time to put all the substances that are GRAS on a list. Those lists still exist and they still have legal force. And then before 1997, there was the GRAS affirmation process.

The takeaway here is that there were very few GRAS determinations that were made in private even though no showing this might have been a quote, unquote, voluntary process, for liability reasons they would often ask for affirmation by FDA under GAP.

And then in 1997 because of pressure on the system, there was a significant revision to the requirements for GRAS. And what happened in the 1997 notice was that FDA essentially authorized self-affirmed GRAS and laid out some additional parameters. And this stayed a draft rule for 20 years until the Center for Food Safety sued them to finalize the rule and they finalized it in 2017.

We're going to, I'm going to criticize GRAS, but I also want folks that are relying on GRAS to be aware that there is a significant amount of science that's supposed to be required for a GRAS notification or for a GRAS self-affirmation. And if you, if you look at the particulars of the '97 rule, you'll see what those are.

So GRAS now operates in a two pathway system. You can voluntarily submit safety data to

FDA. Those are called GRAS notifications, and FDA may raise questions, and then if they don't have any further questions, they may issue a no questions letter, but that actually doesn't have the status of a regulatory approval. It's just that they ran out of questions to ask you.

And those of us in the consumer community who work on this issue a lot think that FDA does a decent job of asking some questions, but also that there are key aspects of the safety standard that they don't typically ask about including around cumulative effects of something that is, is it, is it part of a chemical class of substances about which there have been raised concerns? Does it have pharmacological effects that, that should be looked at in view of other substances in the diet that have small pharmacological effects? So we don't think even the GRAS notification process is adequate for safety.

In addition, after the '97 rule it was very clear that companies can secretly self-assess the GRAS status of something. I would suggest humbly to you that it is not a system, the secret GRAS

affirmation process, that can be defended publically with a straight face. It doesn't provide any adequate assurances that an ingredient is safe. It's so conflicted that if you look at any guidance on addressing conflicts of interest and scientific determination from the national academies, anything, that you cannot view the process of a, a paid consultant or employee of a company that has a direct financial stake in the outcome of a decision assessing the science as being a process that's free of conflicts of interest.

So what happened after '97 was that, and this is not secret GRAS. This is just GRAS notifications versus food additive petitions. You can see the, the, the GRAF notification sort of take over the whole game. And this is another failure that we think is, is a part of FDA's approach to this. We think that part of what's going on is that FDA's allowing things to proceed as GRAF notification when they're really deserving of a food additive petition and possible Burger might be an example of that.

They went through the GRAS process.

Really that science was proprietary to their particular heme-protein that they were developing and putting in their meat substitute product. That's a food additive petition. Any novel substance that doesn't have a public, published record of safety that's available and cognizable to experts is a food additive petition, not a GRAS process substance.

So this was a report in JAMA that showed the conflicts. And again, these are just what we, we know that we know. We can't look at the unknowns, which are the secret GRAS. This is notifications to FDA who makes these decisions, 22% were made by an employee of the additive manufacturer, 13% by employee of the consulting firm to the manufacturer, and 64% by an expert panel selected by the manufacturer. There were ten experts that were on 27 or more panels and one expert who was very busy was on 128. Very well compensated, I'm sure.

So is the opposite of what the law intended, said Mike Taylor. He was very interested in this when he was deputy FDA commissioner. He said, you know, this really is supposed to be about general

recognition, not about private science.

So we sued. We joined Earthjustice and a whole cadre of other organizations. We're in the 2nd Circuit. We survived the motion to dismiss. This is a case against that FDA's final rule on GRAS. It makes the argument that it illegally sub-delegates to private companies the safety of the food supply. And that is still pending.

So how does this apply to dietary supplements? Well, as we saw from Michael's slide, FDA's answer is that you can apply a GRAS designation to be an exemption from the NDI requirements. There was a bit of a shift that was sort of subtle in the way the Agency positioned this issue. In the 2016 guidance, they dropped the reference that was in the 2011 guidance to food self-affirmed as GRAS.

So that suggests to me that the position of the Agency is that a self-affirmation for GRAS is actually not adequate, that you're supposed to go through notification. If you look at the question for 2016, it has been listed or affirmed. So we know things can be GRAS listed or affirmed. Affirmed is

not quite the right language. It should be notified under the notification process because FDA doesn't actually approve substances.

But, you know, that suggests to me that there's some shift here going on and that there's some discomfort at FDA around self-affirmed GRAS. I think that should, that's an area where we could look at additional clarification that would be very useful.

I would say also that even our speakers today have acknowledged that GRAS self-affirmations are not what was the best science, right? We think it's far worse than that obviously. But, but I do think it provides the kind of assurances of safety that, that the law had in mind. And Scott's comments earlier suggested that when they were thinking about the exemption to the NDI requirement for DSHEA, they were not contemplating that it would be an end-run around the NDA requirements to have things go through this GRAS process.

And I would -- if you think about the legislative calendar, you have DSHEA in '94, the regulations changes to GRAS don't happen 'til '97. So

it's really not conceivable that it would, would have been part of the legislative design in '94 to think about self-affirmed GRAS as the main pathway.

Here's some differences just from a regulatory compliance perspective between GRAS and NDI. We know that GRAS is being used by the industry. Our colleague, Loren, at the last public meeting said it's six to seven times more GRAS affirmations than there are NDI notifications. This is from the transcript of that meeting.

And I would suggest to you a GRAS self-affirmation or even GRAS more generally is not an adequate substitute for an NDI. It certainly, I think based on the changes to the guidance FDA put and should clarify that, that an NDI is required if you are relying on self-affirmed GRAS as opposed to a GRAS notification. That seems to be to me, to be sort of a de minimus clarification.

Also we're concerned about the fact that it could be legally marketed but not actually used in food. We think that if not accurate, that, you know, we've heard stories of people short of putting things

into marketing for food abroad and not actually using it in food. That's a clear end-run around the NDI requirement. And same for outside the US.

GRAS also critically fails to address the safety of mixtures. And I actually think the DSHEA language is a little bit better about the NDI review process which contemplates that people will submit safety information on combinations of ingredients. GRAS really looks at each ingredient in isolation, which has been one of its major issues.

GRAS, the GRAS notification is also for the food use typically, right? It's not going to consider the application of the conditions of use for dietary supplements. So it actually is totally inappropriate on the face of the document to then turn around and say we've got, we've got a GRAS notification, submitted GRAS notification based on this particular condition of use in food and we're going to cross-apply that to a different condition of use.

DSHEA also recognizes the need to have conditions of use specified as to the NDI. And then I

do think that the GRAS notification is supposed to take into account exposures and typically would not, because you're filing it for food to put it into presence in the food supply, it's not going to take into account the exposures that might be part of the picture from a supplement perspective.

So you have an application for a GRAS notice that doesn't take into account adequate exposures or conditions of use for the supplement context. That, for that reason I don’t think it's actually appropriate.

So we do know that substances that are withdrawn from the FDA GRAS notification process show up in foods and supplements anyway. This is a report by an NRDC. These were substances that had been put as part of a GRAS notification, FDA raised questions, the substances were withdrawn from the notification process and, you know, they had serious safety issues. And then they showed up in products anyway and a lot of the products that they showed up in were dietary supplements or functional foods.

In addition, we think GRAS is just

generally broken. That's why we're in court and we don't think that it should be expanded or used to also undermine the safety of dietary supplements. There's a lot of things that are sort of wrong at the level of the, what's required for a GRAS notification.

Here's also a kind of cautionary tale. So here we have percumin, is going through the GRAS notification process at this moment. There's an example of supplements that are already selling the substance. And then we looked at the effectiveness data for our nutrition action health news letter and we found that there isn't really any. There's, there's a, one study that has some equivocal data, but really the stuff is being marketed all over the place.

And so, you know, I think we're focused on GRAS and NDIs and the pure safety of it, but there's a whole host of other issues around efficacy and claims that we could also usefully talk about. That's my presentation. Again, I'm very happy that --

(APPLAUSE.)

DR. WELCH: All right. So Q&A. Again, if you want to ask a question, please go to the mics

on either side. I will ask that we just have one question per questioner until everyone has sort of cycled through. I, I appreciated the robust discussion last time, but I want to make sure everyone has a chance. And Adrian might be coming down to turn the mics on. So thank you for that. Quite quickly, in fact. All right. So first question for our panel.

MR. GASTELU: At it again. I just want to get my money's worth. This is a rare opportunity (inaudible - off mic).

DR. WELCH: Right. I would remind you to speak your name and affiliation into the mic before your question and answer, please.

MR. GASTELU: Daniel Gastelu (inaudible - off mic). So anyway, only one question now?

DR. WELCH: Please.

MR. GASTELU: Will it rotate like it did before?

DR. WELCH: Mm-hm, yeah.

MR. GASTELU: The first one is (laughter). There's companies selling synthetic isoflavone. So that would be a synthetic of a

botanical bioactive. So did that go around in the GRAS process somehow? Are you familiar with that whole --

DR. WELCH: Push the button right there. Thank you.

MR. McGUFFIN: The question is isoflavone being sold --

MR. GASTELU: It did --

MR. McGUFFIN: So then the question would be was synthetic isoflavone being sold as a dietary ingredient prior to 1994, if yes, then it's not a new dietary ingredient? If no, then it is? And and then the next question is, is synthetic isoflavones being sold in foods or are we finding it in --

MR. GASTELU: Well, how would it qualify to be a food ingredient to begin with if you wanted to go that route. It's (crosstalk). But you're saying wait a minute. I just picked up on something there. So if I have proof on what a manufacturer is doing, 'cause I work with companies that are manufacturing, obviously synthetic isoflavone like beta-sitosterol,

that that was before 1994, that basis, you go use a synthetic? It's a basis to use a synthetic bioactive?

MR. McGUFFIN: Well, again, the test is was it a lawful ingredient at the time? So (crosstalk).

MR. GASTELU: (Crosstalk) that's another one. So around that loophole, how do you (inaudible) if somebody (inaudible) GRAS and it's not being used, how does that whole thing, that puzzle work? Do you have any -- I gave you a specific example of an ingredient I know about. Does it make sense to you that that's a legal dietary ingredient?

MR. McGUFFIN I, I couldn't comment on that from here (inaudible), but I think the, (inaudible) our comments is if it's a synthetic constituent, you have to assume that it's a new dietary ingredient unless you have a history of use of that exact synthetic prior to '94. And then you probably have to file a notification unless it's already used in food and that's, those are all discoverable facts.

MR. GASTELU: So you just correspond

(inaudible) dietary supplements (inaudible) question probably?

DR. WELCH: I would encourage you to correspond with her, yes.

MR. JAKSCH: Frank Jaksch, ChromaDex. I guess can we (inaudible) as an industry maybe start to agree to not overcomplicate the NDI process and, in the sense that it's actually pretty easy to navigate the process and understand what you're having. A lot of it starts with understanding what it is that you're introducing to commerce itself.

So if you understand the chemistry of the ingredient that you're introducing to commerce, then you know where you stand in terms of what you need to file in terms of NDI. I don’t care if it's a synthetic, is that you understand that chemistry. It goes back (inaudible) exception as well. Three dimensional chemical structures, understand ingredient isomers, yeah, of course. You, you owe it to understand the chemistry of what you're introducing to commerce.

If you're introducing something that is

noticeably different, notably different than what is natural, which is easy to understand by knowing the chemistry of it, then you should understand whether or not you need to file an NDI (cross noise). And, so I just wanted to make sure that, you know, label or anything you guys want to comment on can we, you know, potentially stop over-complicating that process.

If the goal is to get the Agency to define down to every possible combination and detail or nuance of what is, what they mean by the guidance, it's actually fairly simple to understand where it fits.

MR. TALATI: No, I agree. We certainly think the GRAS issue is not the bigger issue. The issue is enforcement. There are a lot of TGIs (ph) in the marketplace. The FDA had enough resources and tolerance enforcement, is probably the bigger issue.

MR. JAKSCH: One other comment on the GRAS as well as that. The case (inaudible) use of self-affirmation process is definitely there, but in reality the one major fail point if you look at the GRAS self-affirmations that are, the data underlying,

they aren't going to know the chemistry or the substance or whatever it is that they have, so it fails right out of the gate. And the same thing again in understanding whether or not you need an NDI or not.

MR. McGUFFIN: You know, that issue on that identification of the ingredient, you try to keep, probably notice is the single most observation by FDA in NDI notifications where the Agency says they have significant concerns, the most common identified significant concern is that you did not clearly identify the ingredient. And it's got to be (inaudible) GRAS what are we talking about. You know, there are two words in the statute that are not hard to understand. I don’t think we need, you know -- these are not complicated. It's ingredient and an (inaudible), and if you don’t know exactly what that ingredient is, then I don’t know how to go forward.

MS. OESTERLING: This is Janet Oesterling from Novozymes. My question is for Laura. You mentioned in the GRAS requirements that you have, have a limit on how much you consume and there has to

be safety evidence to provide for that consumption. And in the NDI guidance they talk about the adulteration standard and that you must also consider the addition of consumption and also chronic use when you look at your GRAS assessment as compared to NDI. And I'm just wondering what your thoughts are on that.

MS. MacCLEERY: I'm not sure I follow. Are you saying that the NDI application process accounts for the consumption as a food item?

MS. OESTERLING: What it does is there is an adulteration standard in the guidance that talks about the level of use in the GRAS assessment and whether or not that level of use is consistent with your NDI consumption and pattern of use. You have to make adjustments for that if it does not.

MS. MacCLEERY: So you're, you're saying if you're filing an NDI, you have to account for the GRAS uses of that same substance.

MS. OESTERLING: What I'm saying is that the, the use of your substance as affirmed as GRAS, the level of use and the consumption pattern must be taken into consideration when you're using it in an

NDI as a dietary supplement. You have to make adjustments for that consumption pattern, chronic use, and level. So you have to increase your safety assessment?

MS. MacCLEERY: Yeah. So that would be true if you're filing an NDI, but if you just file, if you've just gone through GRAS and you see, viewing that as an exception to the NDI requirement, then you wouldn't taken that step. So my point was for, the, the assumptions in the GRAS notification are around the conditions of use in food typically. I haven't gone to look at some of the details of some of the supplements like GRAS notifications, but --

MS. OESTERLING: It's already an exception. It's number three in the exceptions, the rule?

MS. MacCLEERY: Yeah. So those food uses are what's the subject of the safety analysis for the GRAS status and there, if you're using the GRAS exemption to bypass the NDI process, there wouldn't be a place where you actually account for the conditions of use of the, of the supplement in addition to

whatever food uses there may be. So they're not good substitutes for one another. They're actually looking at different conditions of use. One is looking at conditions of use in food and the other one is looking at applications of use in supplements, plus any additional uses that may be in a food environment, in food.

MS. OESTERLING: Thank you.

MR. POLINSKY: Scott Polinsky, attorney. Thank you again for your comments. So I have a brief discussion on the use of foreign data for self-determination of GRAS. FDA's clearly leery of independent conclusions of GRAS in addition to requiring the level of data on par with GRAS with notifications. For those seeking an independent conclusion for GRAS, the final rule of 2, 2016 includes more stringent requirements for evidence of use outside the United States.

So for the example of indigenous populations in Brazil or adherence of higher data in India, the outside use must be corroborated by qualified US experts in addition to foreign sources.

Number two, FDA states that a person who concludes that a substance is GRAS based on use in food outside the United States should notify FDA of that view. And this seems to contradict or eviscerate the notion that an independent conclusion is truly independent.

So I'd like to ask the FDA of their current view of the foreign source requirement and the, the notion that an independent GRAS determination is truly independent.

DR. WELCH: So I'd, I'd rather not address that right now. Kind of puts me on the spot there. I, does anyone on the panel have a response while I formulate my thoughts?

MR. TALATI: I can add that it can certainly be GRAS notification or independent conclusion on the standard safety (inaudible - room noise), i.e., the same amount of data, need the same amount of (inaudible) GRAS dossier over (inaudible).

MS. MacCLEERY: I would think that the, the information required for a GRAS notification would be potentially more than is required for an NDI, but

actually put them side-by-side and look. I, I do think that obviously the global marketplace is a great business source of ingredients and to find ingredients that are of interest to consumers on a global health perspective. I worry that some of the additional requirements that FDA's put in place are inadequate to really ensure that merely having a food be present for long term use in a, in a food environment like India or Brazil where it hasn't been well characterized or well studied in terms of is effects on human health, may not be an adequate basis for ensuring it's safety for US consumers.

And so I think some additional actual safety data would be important, not just data on the, the history of use of an ingredient. There are lots of ingredients and, you know, that have been used for a very long time but that are still poorly understood from a scientific perspective.

MR. McGUFFIN I can't answer Scott's question directly but just in bringing up this issue of different regulatory approaches around the word and as we find ourselves in a global marketplace,

certainly a move towards greater harmonization would be of value on issues.

For example, like CGMP, there's an awfully good regulation in Australia. But if I make my target in Australia, going to be inspected under 111 if I try to sell it in the United States, is that necessary? Is it a pride of ownership in every country? Are the regulations any good?

I would encourage some further discussion of harmonization of the regulations where it would work, including safety evaluations. Of course by that I don't mean how about (inaudible) the question (inaudible). But some further discussion of working globally since the marketplace already is global would be a benefit for all.

DR. WELCH: And I would just add a few thoughts. I think this panel is focused on the exceptions to the NDIN requirements. So, and getting back to the questions from Novozymes, whether a notification is required is, is one aspect, and then whether it's, the ingredient as it's being used in a supplement is, is a different aspect. And so the, the

premarket notification and the NDI guidance does address this question which I think is what you were referencing.

So the, the notification, the premarket notification to FDA for use of an ingredient in a supplement might not be required, but you still have to know that conditions of use of your ingredient in your product are safe. Just whether or not you proactively premarket, tell FDA that information. So some of that is ensuring that the, the, the marketers, the manufacturers, and distributors know that information.

It's really nice when FDA knows that information. So sometimes we are playing a bit of catchup. So, and if, this has come up a couple times. So I would just sort of put in a plug for, for greater communication with FDA. And I know our, our Office of Dietary Supplement programs has put a lot of effort into this and we do want to be open to communicate with folks that are thinking about an NDI notification, thinking about an ingredient even before they realize if it's new or old.

There's, there's a lot of questions that come up as you're formulating a new product I can only imagine. And, and so we do want to make sure we have those open lines of communication. I think it helps everyone. Manufacturers, distributors understand the requirements, but also FDA understands the safety of the products that are being out there.

It is hard just from personal experience when you find a product and you turn it over and you read the label, what are we dealing with. What is the actual ingredient, again a concept that has come up a couple times already, and then is it, is it safe in the levels.

And so I think those are great aspects to mull over as we break for lunch here shortly. A thank you to our panel. I appreciate that. Thank you to the Q&A. It's, I appreciate folks coming up to the mic. It's wonderful. We are going to break for lunch now and we are going to reconvene at one o'clock.

Our session three, before everyone runs out of the room, our session 3, we will be hearing from Health Canada. So I think that's a great

opportunity to hear one of our counterparts. Again, we are starting at 1 p.m. sharp. We have a big afternoon ahead of us. So thank you and we'll see you soon.

MR. TAVE: Good afternoon, everyone. If we could begin to come back to order, please. I never quite reached the pinnacle of where I'm being a judge, but I can call the room to order and maybe I'll get a gavel for the next session. Wow. That was more effective than I thought it would be.

So for those, for those online, one thing I've observed is that the Wiley Auditorium can function something like a theater before we come back from intermission in that the lights went down and then up, and went back down again, which I think is why everybody is so neatly shuffling to their seats so we can get back on track with our schedule.

One administrative note and then we'll, we'll move right into the important fun stuff. For those who are participating remotely via webcast, we understand that you had some questions that came through during the earlier sessions and we didn't do a

very good job of responding to those in a timely manner. We have been going through those questions. We are going to be a little bit more attentive to that as we get through the next sessions in the afternoon, but we're also going to go back and try to address some of those questions that came in later on either during the open public comment session or otherwise as we have time.

So we appreciate your attention. We know it's always a challenge to participate when you're not in the room, but we are going to continue doing what we can to make it a little bit easier for all of you.

Okay. I hope everybody enjoyed their lunch. Thank you all. The next session is a bit of a departure from the rest of today's agenda and I'm particularly excited for it because I think it might be the only time all day where nobody talks about how wrong FDA is on one of those positions; although, maybe I shouldn't speak too soon. We'll see.

In all seriousness, I think that, that this next session is going to be particularly

informative as well as interesting. We talked about it this, this morning, but globalization has been one of the biggest forces driving change in the dietary supplement marketplace, as well as probably every commodity that's in commerce over the past 25 years.

American firms regularly source raw materials and other ingredients from abroad and just as many firms sell their finished products overseas to foreign jurisdictions. So as regulators we are very fortunate to enjoy a really wonderful working relationship with our neighbors to the north from Health Canada.

And during the course of some of our discussions, we realized that we grapple with many of the same issues and we face many of the same challenges. And even though we operate under different regulatory schemes, there's still a lot of relevance to the differences, as well as to the similarities.

And so in light of that we thought it would be useful for today's proceedings to introduce a comparative perspective to this discussion and to hear

how some of these issues are being addressed in Canada, as well as what has worked successfully for them and what has not.

Our next speaker is Manon Bombardier. She's the Director General of Natural and Non-prescription Health Products, directorate health products and food branch of Health Canada. It's a role she's held since October 2016.

Manon has years of experience as a regulator including as the Chief Compliance and Enforcement Officer at the Canadian Radio, Television, and Telecommunications Commission and before that at Environment and Climate Change Canada. She holds an MBA and a PhD in environmental toxicology.

Manon will be speaking. She's got a presentation that will take about 10 or 15 minutes, I think, and then she has very nicely agreed to be available for Q&A. She has a colleague, Nana, here who much like I don't answer technical questions without my staff using a normal heart rhythm. I think Manon is relying on expertise as well to complement what she brings to the table.

So after her presentation, Manon and I will -- or Nana and I will, will go to the table. We'll go through the Q&A and then we will continue on with the rest of the afternoon. So we are very grateful that Manon has agreed along with Nana to travel here today from Ottawa to share Health Canada's experience and perspective with us. It's my pleasure to introduce Manon Bombardier.

(APPLAUSE.)

MS. BOMBARDIER: Thank you very much, Steve. Good afternoon, everyone. Pleasure to be here on behalf of Health Canada, and as Steve mentioned, I'm here with a manager in our Product Evaluation Bureau, Nana Bafi-Yeboa, who will join me after for questions.

So as Steve mentioned, we do have a regime in, in Canada for, for dietary supplements and I'm very happy to provide the highlights of what the, the, the regime looks like and provide the regulator's perspective. I know there are some companies have sort of industry stakeholders in the room. Probably some of you do business in Canada and have experience

with our regime. So the, I think if, if you want to bring some insight from an industry perspective at the end, that would be helpful as well. I'll try to move the slides. Oh, that works. Okay.

So what I want to provide is first the regulatory context. So how, how we regulate them with the regime that governs dietary supplements in Canada, talk to what we do on the pre-market review and some of the work we're doing on the post-market review.

As with the US FDA, we do have a good size of our regime, but there's also other areas that have not evolved as quickly as the market in terms of policy development. So we're doing some work to improve in those regards. I want to say a few words in, on those as well at, at the end.

So in terms of the regulatory context, dietary supplements fit under a category of drugs under the Food and Drugs Act. In Canada the Food and Drugs Act govern all foods and all drugs and those include natural health products and within the natural health products we have dietary supplements.

So there's three sets of regulations

under the Food and Drugs Act. Dietary supplements like vitamins, minerals can fit under any of the, of the three regimes. It could be used in cosmetics; it could be used in natural health products; it could be used in drugs.

Depending on what the intended use is and whether it requires prescription or medical oversight, depending on what other ingredients are in there, the requirements would change and the regulatory framework would, would change as well. But it's all under the Food and Drugs Act. So three sets of regulations that govern cosmetics, natural health products, drugs, other drugs, and food.

The natural health product regulations were put in place in 2004 and they came into effect in 2004, but actually came into force in 2014. So ten years after, ten years of transition for the industry to bring their products legally to market. And so the -- what was the impetus for the regulations was a report that was provided to Senate Committee on Health, one of the cabinet committees, the government of Canada, because of the routine use of natural

health products in the daily diet of Canadians. Three out of four Canadians use natural health products on a daily basis and that is on the rise.

Given the propensity of the use of these products, there was definitely a call for having the proper regime to regulate them in, in Canada. So they're considered as drugs, but they're subject to requirements that are not as stringent as what exists for prescription drugs for instance or non-prescription drugs. So, so we have a, a level of oversight that's properly to address, to address the level of risk of natural health products with are, which are considered lower risk.

Under the Food and Drugs Act there's three main outcomes that we're trying to achieve, safety, efficacy, and quality. So natural health products including dietary supplements are subject to requirements and we want to make sure that they're safe, they do what they say on, on their labels, and they're manufactured consistently in accordance with the quality standards that apply to them.

So those three elements apply to all

food and drugs products including dietary supplements. And the purpose of the regulations is to make sure we apply the right balance of oversight while maintaining access to these products for Canadians.

So the, the scope of the products is, is quite large under, in the natural health products, and the actual groups of products that are acceptable to be regulated and, and regulated under the natural health product regulations are listed in our regulations. So probiotics are in there, vitamins, minerals. So we have all, all the, the, the product types which you see here on, on the list. Homeopathic products as well, and traditional Chinese medicines are also covered by our regulations.

All product must be assessed for safety, quality, and efficacy prior to reaching the market. All products need a market authorization from Health Canada and that market authorization is notified to Canadians on the labels by an NPN number, which you see in the picture at the bottom left. So there's an NPN number that says Health Canada has approved this product. It's a natural product number.

Similar to what exists for drugs, we have a DIN, drug identification number. So NPN is for dietary supplements and other natural health products. There's over 150,000 products that have been approved for market in, in Canada to date.

I, I know that there was some interest into synthetic duplicates. So synthetic duplicates of natural ingredients including vitamins and, and minerals are actually listed as acceptable ingredients in natural health products. So as long as the activity of the synthetic substance is the exact same as, as the natural substance, but those are allowed to be used in natural health product and therefore are regulated under the natural health product regulations. Vitamin C is, is a great, is a common example.

We also, probiotics is also part of the scope. We have what we call a monograph. Basically it's a standard that Health Canada has established. It's published on our website and it specifies all the conditions under which a probiotic can come in for an application. If it meets all the requirements of the

monographs, and we do verify those, so the proper name, the common name, the, the source material, the conditions of use, the dosage form, the dose, risk information if any applies.

If all the requirements of the monograph are met and appear on the label as such, the company receives a, a license for that product. So monographs have been -- they love to facilitate more timely and efficient processing of applications that come in and it's based on established standards that we've reviewed, like as an organization and we've deemed to be acceptable. So we have one for probiotics and I have the link at the bottom of the slide which I understand will be made available so you can access it.

There's, there's three pathways for product licensing under the natural health product regulations and I know what is of most interest here would be captured under the modern natural health products. So vitamins, fish oils, for example. The level of evidence that's required to support the safety and efficacy of these products is based on

risk. So we have lower risk, medium, and high risk, depending on the level of risk of the ingredients, the intended use, if, if it requires some assistance from a health professional, for instance. All of those are taken into considerations when assessing the level of, of, of risk and then the, the level of evidence that's required. And in some cases it could be clinical trials. In other cases such as homeopathic product, it could be a reference, a pharmacopeia reference as long as it meets all the requirements of, of the monograph and there's only specific, very specific claims that can be used.

So we have a three class system and it's based on the use of, of monographs that I mentioned. So a product, for instance, that comes in an application and all the requirements of the monograph, it's a single monograph -- let's say it's, it's a probiotic -- and all the requirements of the monograph are met, it could come in as a Class I and in 60 days the company would get the license for market authorization.

If the product is supported by two or

more monographs, entirely monograph supported, it is still reviewed and the timeline there is 90 calendar days. If anything goes beyond the monograph, it's a new ingredient or it's a new condition of use that we've not seen before, we don't have the data so it has to be provided by the applicant, it requires a full review by our scientists including members of Nana's team. It's a 210 day to get the license.

So we have the classification system which allows flexibility to the companies and you can come in and if you meet all the pre-established standards, your product can go quickly on the market as long as your label meets all the requirements as well, and if it's a new ingredient, then there's a review and there's, and there's -- we have a lot of policies on our website that describe what's required in terms of level of evidence to support a particular product and condition of use.

The other element that's key in our process is we have an NHP ID which is the natural health product identification database. It's a list of medicinal ingredients and non-medicinal ingredients

that are deemed to be acceptable in natural health products. So no application will be accepted unless the ingredients are listed in that database.

Listing does not mean that the ingredient is safe and effective. It still needs to be reviewed, but it is acceptable to submit an application. So it's a key tool and it's available. It's very transparent for applicants to use.

So I spoke a lot about safety and, and efficacy. The other key element, of course, is the quality. So applicants must provide to us a product specification form that describes the quantity, the, the identification, the quantity of the ingredients, their level of purity, and the testing methods that, that were used with the level of sensitivity of that method. So we have a product specification form, again, that's available on our website and, and that comes in with the application.

What I, I want to talk about just for a few minutes is some of the challenges that we've had with safety, efficacy, and, and quality to date. We had been relying on attestation forms from companies.

So when the regulations came into force 2014, we had about 60,000 products on the market, natural health products that were already on the market that needed an NPN to be legally on the market. So we've introduced what we call an attestation model where companies would come in and provide us an application with an attestation form that the product met all the requirements of the monograph, and in ten days they would get, they would get their license.

In 2017, we did an audit of a number of files that we had received applications for and that we had licensed, and we found out that 70%, 7-0 percent of the applications actually did not meet the requirements for safety and efficacy. So we adjusted our approach and we said that doesn't work. We need to review these diligently line by line and make sure that all the requirements are met.

Ultimately it's our obligation to make sure that products that reach the market are safe for Canadians and we were not doing this. So we changed our approach and now we have a pre-market review. So the applications come in and we review everything

that's in the application.

On quality, we're not there yet. We're going there. So right now we're doing a similar audit on product specification forms and other material that were provided us for applications for quality and we're finding similar results.

So, so far we've reviewed a number of applications and, and we've identified gaps on specification forms, information that's missing. Stability, no indication that the product has been tested for shelf life, instability over a certain period of time, and gaps in terms of quality assurance having a QA person in place, having the proper training, proper methodologies and, and procedures in place to make sure that the quality standards is met on a consistent basis.

So given those gaps, we are going to reintroduce a quality review in the coming months, but we're still looking at the results to figure out where exactly we're going to focus our, our assessment.

We've also started a proactive inspection regime which is fairly new for NHPs. In

the previous years the, the approach to compliance verification was very reactive and complaint based. We've moving into a more proactive approach which I'll, I'll give you a bit more details. But some of the findings were particularly concerning based on 46 inspections that have been done to date, which represents about 6% of the, the market, the sites that had received a license, 'cause we do issue site licenses. For any site that produces or imports NHPs in Canada, they need a site license and there's a review process in place for those.

And when our colleagues from our enforcement branch inspected, they found problems at all the sites and some of which were quite concerning, again, no specifications, unavailable or incomplete, no data on stability, QA person was not there or was (inaudible) person who had no training, cracks in the walls, contamination fungus. You name it; we found it.

So with those results we said we need to adjust our approach to pre-market and, and post-market. So we're making significant changes. The

results of the compliance verification are available in that report at the link at the bottom of the, the slide there if you're interested.

In terms of processing -- so I spoke about the ten day standard and the, the lack of pre-market review prior to 2017. So we've made some changes as a result of the findings of our audits on applications and the gaps that we found. And we've updated our policy in April of 2019 with new performance standards. So instead of 10, 30, 210 for Class I, II, III, it's now 60, 90, and 210. So for a Class I and II we're taking the time that we need to do a proper review of those applications.

Also we have provided the industry with a web form that instead of sending us a pdf and we would get five or six different forms. Companies were even creating their own form and sending that to us. And we had to stop and had to manually enter the data, which is totally unsustainable. So we've created a web form and, and as of June 2019 it will be mandatory for companies to submit us that form for their application.

We also have provided more clarity on criteria for refusals. If an application is deficient in certain areas, it's going to be automatically refused; whereas, before we would help the, the company develop their application to be compliant. With the volumes that we get, we get about 7,000 per year applications, there's no way we can do that. We can't continue to do that. So we are refusing if there's substantiative gaps. If the form is not complete, it's, it's refused.

So with those changes we hope to be more efficient and to get to the market the products that meet the requirements in, in the most efficient way possible.

On the post-markets I said we, we have been quite reactive. An area where we need to continue to be reactive is when we get adverse reaction reports from patients or from hospitals or health professionals. So when we get those, of course, we review, we have colleagues in our market health products directorate that can help us do safety assessment of the signals that we get. And then if we

find that there's enough evidence to suggest that there's a high, a risk that outweighs the benefit of the product, then we take action. It could be a recall. It could be labeling changes. We've done that recently on green tea where we found we had a lot of signals of liver toxicity.

We did a safety assessment. We published a report on our website and we're now working with companies to adjust their labels to make it very clear and prominent in the warning section that if you have jaundice or symptoms of liver toxicity, you need to consult your health practitioner or doctor right away.

So those activities will continue, but we're moving more and more into proactive monitoring and we're focusing not only on site inspections, but also on false and misleading advertising. So we have a prohibition in the act against false, misleading advertising. We've been quite reactive to date, but we're moving into a more proactive approach, again with our colleagues and we're working with pre-clearance agencies.

We have agencies in Canada like the Advertising Standards Council who help industry make sure that their labels don't provide misleading claims and that comply with our regulations. So we do work very closely with them to indicate and promote compliance with that provision of the legislation.

In terms of modernization efforts, so we -- for natural health products, the area that we're working on now from a regulatory change perspective is on the labeling. We have on the non-prescription drug side, we've just implemented changes to require plain English labeling with a drug facts table, product facts table for drugs. And so we're looking at implementing a similar approach for the labeling of natural health products similar to what exists for dietary supplements in the US. We've looked at that model and borrowed quite a bit from it as well.

And the approach that we're -- so NHPs, as part of our modernization effort, NHP is there, but we're also looking at non-prescription drugs in cosmetics and bringing improvements there as well. Non-prescription drug side -- I know this is not the

focus here, but just to say that we have non-prescription drugs that are cosmetics like toothpaste with triclosan in it. It's considered a non-prescription drug and it's held to the same standard right now as prescription drugs and companies are saying it doesn't make sense and we agree with them. We need to make sure the regulatory burden and oversight is appropriate for the level of risk. So that's what we're doing right now for non-prescription drugs.

So for labeling for NHP, so we're looking at three key requirements for all labels of NHPs. I will go in the regulatory proposal that will be consulted on in the spring 2020. First is minimum font size. So size six for non-medicinal ingredients we're looking at, at font size five point five and we're allowing condensing. Minimum contrast, meaning black on white is, is also something that we're going to require and standardization. So a product fact table with the headings in bold and the, the, the text, again, making sure that the text is in font size six and proper contrast and, and in the same order.

We have some exemptions for a very small package. We're about to publish proposed guidance for labeling of natural health products in May. I could share the link if you're interested when it comes out. And our proposal will lay out some of the flexibilities that we're proposing to industry to implement those changes.

In Canada we have French and English and a lot of companies are telling us both languages won't fit. So what flexibilities can you give us to make sure we don't have to resize our packages or resort to innovative labels? So we're working on flexibilities and that includes an exemption for small, very small packages. Anything less than 12 square inches would be exempted from the product fact label. And that's what it would look like. So very similar to what exists on the dietary supplement side in the US.

For questions we're providing, you know, a phone number or an e-mail address, and we're also allowing some information to go on a URL. So for very, very low risk products, one of the flexibility that we've introduced is for point of views warnings

such as if, if you get a rash when you apply it, stop using it. Those types of warnings would be able to be moved to a URL, again, to save space on the label. So we're consulting on that proposal. The policy will go up for consultation in, in the month of May, near the end of the month, with a regulatory proposal in 2020. That's it.

MR. TAVE: So now we have an opportunity for questions and just like this morning anybody who wants to come down to the microphone, please feel free, and I think we have somebody monitoring remote questions through the broadcast and we'll have (inaudible) monitor, please tell us your name and affiliation before your questions.

MR. FRANKOS: Hi, there. Is this on? Okay. Thank you for your presentation. My name's Bill Frankos of Herbalife and my question has to do with whether there is any propriety given to a manufacturer who has developed the data, the safety data of that ingredient they submitted, and can other people use that information that's, that was submitted by another company to support their adding that

ingredient to their product?

MR. BAFI-YEBOA: Nana Bafi-Yeboa. Thank you for the question. Part of that really comes down to what an ingredient is because by our regulations the medicinal ingredients, the source won't have to appear on the label. So in terms of the provisions around it, you're in a space where you have to declare enough to the regulator for them to know exactly what that ingredient is and to then provide the evidence that supports the safety and efficacy of that ingredient. There is no provision of use of a master file, which can keep certain pieces of information confidential and, and not in the public domain. But there isn't a way to mask the identity of your ingredients on the label.

MR. FRANKOS: But as far as, for instance, the manufacturing specifications, the let's say all of the steps that go into manufacturing, is that protected?

MR. BAFI-YEBOA: So if it's within the context of the master file, that is confidential. The issue then in practical terms is whether someone else

can represent the ingredients in a way that appears to be similar to yours and have enough publically available information to substantiate the safety and efficacy of your ingredients.

Now whether indeed it is a, a sort of a certain trademark issue that you may have, that would be the role of the, I guess, manufacturer to enforce that, that piece. In terms of our role as the regulators strictly looking at do we have enough information regarding the ingredients and then enough information concerning its safety, efficacy, and volume to issue a license.

MR. FRANKOS: Okay. Thank you.

MR. TALATI: Hi. It's Ashish Talati from Upadhye. Thank you so much. Are you able to share with us the number of employees in your office and your, your budget?

MS. BOMBARDIER: Number of employees and --

MR. TALATI: Budget size.

MS. BOMBARDIER: Oh. The number of employees is about 150 people and the budget is about

17 million. (Inaudible) responsible for pre-market (inaudible) other programs that are involved in the post market (inaudible).

MR. TALATI: Thank you.

MS. MCENROE: Hi. It's Diane McEnroe from Sidley Austin. In terms of what we call structure function claims here, the claims are C claims, what does it look like in, in, you know, my own decision of what is an appropriate structure function claim? If you look at the science, if you come up with something that is solid for a company to rely upon and then look at is as is it something that we can model here in the United States, would that be a, a particularly long process?

MR. BAFI-YEBOA: I think there's two parts to it. I think the experience basically had the benefit of what had happened with respect to DSHEA in 1994 because our regulations came into effect in 2004. So we had that ten years to really look at what was working and what was, could be improved and perhaps use that model.

In terms of also structure function

claims, it would be very similar to what you have for vitamins and minerals and these type base claims. You're, you can also have some structure function claims that you see in with the probiotics where you have source of probiotics with probiotics to help wt, you know, promote, you know, like a favorable (inaudible).

So it really depends on the type of ingredients and the evidence that's available. What we do is we publish monographs so we're satisfied that there is sufficient information regarding some of those claims and our monographs do not only relate back to the structure function claims, they will have full range of claims.

Granted there are certain conditions and diseases that products intended for self-care should not really go forth. So our monographs do not speak to those whatsoever. It, it's, it's just a way of understanding that it's always based on what the evidence is and what that ingredient is, that we then use to leverage to label for safety, efficacy, and then what the quality standards are. So that also

takes into account the nature of the ingredients.

MR. TAVE: I don't see anyone at the microphone. So are there any questions coming through the webcast?

MR. BOLAR: Paul Bolar of Pharmavite. My question is, well, twofold. First of all, I'm wondering how effective are these, the regulatory schemes that you have with respect to products sold over the internet? Does it effectively -- are products sold over the internet effectively controlled and do they comply with the requirements?

MS. BOMBARDIER: So any product that's sold on the internet, I mean it's a challenge for an individual organization to make sure they comply because the reach outside of jurisdiction is always challenging because it's no different and health products are no different. So we, we do work with our colleagues in order as it is CSA (ph) Agency. So (inaudible) agency to verify and monitor (inaudible). When we see claims that are egregious (inaudible) product with the disease claim that's illegal in Canada and we do take action. We do take those things

seriously (inaudible).

MR. BOLAR: And the, the second question is I'm, I'm wondering with respect to the system that requires numbers and every product needs to be submitted. How effective is that system in preventing drug adulterated products or tainted products from entering the market, which is a huge problem here in the US?

MR. BAFI-YEBOA: That, that really is a post-market type of issue and it really goes back to what is the circumstance, the intensity of activities related to both proactive and random verification of standards. Because as much as you can introduce certain things on the pre-market side, unless you have the ability to balance that out and verify on the post-market side, you, you really do not have the type of (inaudible - sneezing) in my opinion to kind of make a difference.

MR. TAVE: We have time for one more question and looks like we have one ready to go.

MR. MACKAY: So this is Doug MacKay from CV Sciences. I'm just curious from both your

perspectives. The arbitrary line that we have here in the United States that products can only support normal health, and then you guys were able to venture into this area with natural products can actually have a therapeutic benefit. That seems to translate a lot of the issues that we talk about, even getting the right king of evidence to make a claim becomes difficult if we can't talk about lowering cholesterol or changing hemoglobin A1C.

So just philosophically, how much does that shape the regulatory paradigm and what advice would you give to the United States on that topic?

MS. BOMBARDIER: Well, one of the, the key elements for health regime for drugs to ensure that claims are well-supported and well supported by a level of evidence, scientific evidence. While we do have traditional Chinese medicine, homeopathic medicines as well, that's for the purpose of maintaining a process of ingredients and proper balance (inaudible - room noise) allowed to have general claims without the scientific evidence especially monographs and establish (inaudible) these

health claims are adequate in, in Canada.

What is most important for these products is the safety and any other operation we do look at safety and, and, and adulteration. So we do look at safety and quality more than anything else for these (inaudible). For high risk ingredients, then there's, we have what we call a pathway for licensing, which is our policy that establish what evidence that's required. It can be on the level of the claim.

And if the claim doesn't work (inaudible) we do think (inaudible) and the functions of use and it requires (inaudible). So those are all factors that are considered. And that's everything. You want to add?

MR. BAFI-YEBOA: I would just add on the philosophical aspects I think regardless of where you stand, there will be a line that you'll have to draw and that may seem arbitrary at times. The more important pieces that you have safety for who have a say speaking to where that line should be. And agreement that once that line is established, you have the tools in place to move it as the evidence changes

or the assumption that led to that establishment also changes.

I think these type of forms are very, very important because at the end of the day the markets do not exist unless they can meet a consumer need. And when we talk about innovation, you know, innovation is the meet what consumers want or consumers need. That's, that's an ability to meet than need, but it's also an ability to impact the health of, of consumers. Obviously the health of communities, but the health of Americans.

And that's, that's a very, very important thing and the more you can engage in these type of forums, I think that you do actually start making progress and landing where you really want to be.

So it's -- thank you for the opportunity to speak at this type of, you know, meeting, and to really hear all of the voices that are, you know, have an interest in improving where we currently are.

MR. TAVE: And I want to say thank you. I know that the session after lunch from this morning

was (inaudible) I can tell you with certainty today (inaudible). This has been incredibly informative. We, we are (inaudible) to both of you. So we do not have (inaudible).

(APPLAUSE.)

ADRIAN FROM AUDIO DEPARTMENT: One question from online.

MR. TAVE: Okay. We have one question from online.

UNIDENTIFIED FEMALE SPEAKER: Hi. I hope everyone can hear me. We have one question online. Can you please share information about the percentage of products so that an NPN in Canada are registered with Health Canada and have an NPN number?

MS. BOMBARDIER: So the question is, is the question whether there is any actual (inaudible) products on the market in Canada without an NPN number?

UNIDENTIFIED SPEAKER FROM AUDIO: I'm having trouble hearing you.

MS. BOMBARDIER: So --

UNIDENTIFIED SPEAKER FROM AUDIO: I, I

want to say, yes, that's the question. Okay.

MS. BOMBARDIER: So products that don't have an NPN first are illegal in Canada. So there needs to be an NPN which says that Health Canada has approved this product. If there's any point that comes to our attention that a product is on the market without an NPN, we take action. So if you have any examples you can provide them.

MR. TAVE: Okay. Thank you again. I think we can have our, our panelists come down. Okay. So, so as our panelists find their seats, I'm going to start talking to encourage everybody to, to keep things moving. Place on mute in the background as we switch off. All right. I'm going to get started.

So we've now reached the last panel of the day, but certainly not the least, and the topic of this panel is promoting compliance with the NDI notification requirement. And the title sort of begs the question and maybe it's obvious to some people, but why do we think that there isn't already adequate compliance with the requirement? I've got to ask. The answer is twofold.

First we hear it anecdotally and I'm sure we'll hear it anecdotally later during Q&A and public comment, but it's not at all uncommon for stakeholders to say to us that FDA, and to others, that FDA needs to do a better job of enforcing the NDI notification requirement. And we hear complaints from firms, typically those firms who have successfully navigated the notification process who feel that their competitors are getting a free pass.

And like I said, I think we're going to hear a few pretty compelling examples before the end of the day of firms that have made significant investments in being transparent and coming through the front door and complying with their understanding of the law and, you know, there's, there's a degree of sympathy to that view.

All right, but second, we can look to the data and this is somewhat challenging because we don't know what we don't know. Specifically, we, we don't really have any way of measuring how many firms are marketing products for which an NDI notification should have been required, or should have been

submitted, but it wasn't.

So we can start with what we do know. And what we do know is that in 1994 when DSHEA was enacted, there were approximately 4,000 dietary supplement products on the market. And we don't know exactly how many products are on the market today, but the prevailing estimates range from 50,000 to 80,000 different products.

So for purposes of this exercise, let's take the most conservative assumptions and let's use the low end of that range and suppose that there are 50,000 products on the market today. If you subtract out the 4,000 that were on the market when DSHEA was enacted in 1994, that means that approximately 46,000 new products have been introduced to the market in the past 25 years.

Now clearly not all of those new products contain new dietary ingredients as it's defined in the statute that are subject to the notification requirement. Some of them might be new brands of old ingredients, some might be new combinations of old ingredients like a reformulated

multivitamin, and some might be exempt from the notification requirement because of presence in the food supply or otherwise.

So let's take a conservative assumption again and let's suppose that 90% of the new dietary supplements that have been introduced to the market in the past 25 years were not subject to the notification requirement. So let's say 90% of these products did not require notification. That still leaves 10% of the products that did require notification and 10% of the 46,000 new products is 4,600.

So by that math we should have received approximately 4,600 new dietary ingredient notifications since 1994. In fact, the number that we've received is quite a bit lower. To date we've received just over 1,100 notifications. So in other words, even using the low end of the estimate for the number of products on the market today, and even assuming, assuming that 90% of the new products that have been introduced were not subject to the requirement for notification, we still find that the number of notifications submitted is less than 25% of

where we expect it should be. And you can quibble with the math, but I think the orders of magnitude are probably fairly accurate. The point is that compliance clearly needs to improve.

So this panel initially began as two separate panels and if you look back at the federal registry notice announcing the meeting, and there's no reason you should do this, but if you do look back you'll see that we listed four separate topics for discussion.

And as we started planning out the agenda and talking to speakers and thinking through the flow of the day, we realized that two of the topics, potential commercial or marketing advantages to incentivize responsible innovation, as well as promoting overall compliance with the pre-market notification requirement through enforcement we're really opposite sides of the same coin.

Effective enforcement by itself provides something of a marketing advantage for products that have successfully gone through the notification process and at the same time commercial incentives

won't really be worth anything if there isn't effective enforcement to prevent non-compliant copycat products from free riding. So you can't really discuss one without the other.

Now as it turns out these companion issues are particularly challenging. We've heard stakeholder calls for economic incentives and marketing advantages, but unlike with some other FDA regulated commodities, there is no statutory intellectual property protection in play. So we're open to the concept, but we want to hear ideas about whether this is something that can be done under existing authorities, and if so, how.

Similarly, it's easy to call for more enforcement and it's certainly fair to do so. But even in a straightforward case, unfortunately it can be time consuming and resource intensive. That doesn't mean it's not worthwhile. But these cases present some unique challenges. For one thing, a competitor product might not have submitted an NDI notification, but as you heard in session two before lunch, it might be on the market by virtue of the GRAS

loophole via self-affirmation. And because DSHEA places the burden on FDA to show that a dietary supplement is adulterated under Section 402(f), we wouldn't necessarily know that until we had travelled well down the path of an enforcement action.

Well let's suppose that the competitor product hasn't even done that much. The case is still far from a slam dunk. Recall that we're typically being asked to bring enforcement action to protect a product or an ingredient that has successfully gone through the notification process. That means that when we reviewed their data, we had no objections to the notifier conclusion that the product is reasonably expected to be safe. So it follows that a knockoff product that is identical or very similar to that product is probably at the very least not clearly unsafe.

So even assuming that we can satisfy our burden of proving a product is technically adulterated under DSHEA, there's still a practical question of resources. And to make the best use of our finite resources, we've established three strategic

priorities. I mentioned them this morning: consumer safety, product integrity, and informed decision making would always be consistent with those priorities to investing an enforcement action against a product that is closely similar if not identical to one that is expected to be safe.

Now there is a lot of value to upholding the integrity of the regulatory process and you can say that that's part of promoting consumer safety. So let's, let's say that a case like this is consistent with our strategic priorities. When we issue warning letters, which some call for us to do and we have done, it's important for us to be able to follow them up with judicial action if we don't achieve compliance. We can't be a paper tiger. But FDI, FDA can't bring cases in court on our own.

We have to rely on the Department of Justice to bring them for us. And they have limited resources and competing priorities. Would DOJ be willing to take on a case that faces all of the obstacles that I just mentioned?

And I haven't even mentioned one of the

bigger obstacles. As you'll hear in a few minutes during this panel, there's a legal argument that once one firm has submitted a notification for a new dietary ingredient, anyone can freely market that ingredient.

I'm not saying that I agree with this position, but it's one that we have to acknowledge and recognize, and it's one of that we have to respect at least as a potential defense that we'd encounter in any enforcement action.

So there's no doubt that the public health is best served when we have a robust effective NDI notification system working as DSHEA intended. And we know and we'll hear it today that it's possible for firms to use this process to introduce innovative new ingredients that are reasonably expected to be safe. So the question becomes what can we do to get firms to see the value and to realize the value in this process rather than having firms exploiting it through loopholes or, or ignoring the requirement altogether.

And for those easy questions we'll turn

to our panel. And so before we begin, I'm going to introduce each of our panelists and we've got a pre-established order of presentation. So I will introduce them all and then we'll, we'll call up our first panelist to speak.

So we'll start with Dan Fabricant, President and CEO of the Natural Products Association. He'll be followed by Andrew Shao, Interim Senior Vice-President of Scientific and Regulatory Affairs from the Council for Responsible Nutrition. Then we'll hear from Wes Siegner, Senior Counsel at Hyman, Phelps & McNamara. Then Jay Sirois, Senior Director of Regulatory and Scientific Affairs Consumer Healthcare Products Association. And finally Sandra Eskin, Project Director of Food and Dietary Supplement Safety at The Pew Charitable Trust.

So with that, let me turn the mic over to Dan.

MR. FABRICANT: Steve, you're kind of a low talker. I was worried I was going to end up wearing a puffy shirt or something, but -- and the only thing people -- the last time we were in this

room we were talking about old dietary ingredient lists and the only thing that the ODSP staff remembers was that I was talking about a claims question. They said it's like porn, you know it when you see it and they just liked seeing that up there on the, on the board. So there it is again for, for -- we aim to please.

Daniel Fabricant, President and CEO of Natural Product Association. And this is an interesting topic; though, it's not that interesting in some ways 'cause you're, you're talking about a statute that's in existence for 20, 25 years and in the crux of -- and there's a lot of NDI topics that are unresolved and we'll touch some of them here. I think IP ties in. Steve did a really nice tease up to kind of where, where these issues are, but it really comes down to -- and these meetings are, are kind of formulated on getting the guidance out and we'll talk more about that later this afternoon.

But that's kind of the, the basis of these meetings, is the Agency wants to get the guidance out and this is a, you know, everyone feels

good. We had meetings and let's get the guidance out and everyone will hate the guidance again. That's that.

But more importantly is I think the, is the lack of enforcement. You have, you really have a disconnect I think in terms of -- and I understand people may make a legal argument that, okay, if one person submits an NDI, then everyone can ride on that, but I don't think that's how the statute reads at all. And I heard Scott, you know, the, the framer of the constitution down there. What was Patrick Henry like, Scott?

Anyway, but I think that important, it's important that it's, it, you know, the law is pretty clear and, and, you know, and then you hear about resources and there's also ways that the Agency's enforce using a very low resource burn and I think we'll touch on that right now 'cause what does it buy you? And this is the key thing. By notifying the Agency it's on the, the burden is then on the Agency.

But by not notifying the Agency, who's the burden on? The burden's on the company to say,

hey, this was either -- and they may not have to necessarily provide that information to the Agency. They either have to have it in their back pocket saying it was on the market pre-94 or some other basis for which they're exempt from filing an NDI.

So without notifying the Agency, and the law was clear on this and introduced a new adulteration clause, that if the product is in fact adulterated, the ingredient is in fact adulterated for not notifying the Agency. That simple.

And, you know, not getting into the safety data part of it, 'cause while you may be able to, and I heard Steve say, you may be able to reasonably conclude that if someone says it's the same, it's safe. Okay, but someone says it the same, says it's the same doesn't provide the Agency or anyone else specifications that the product is exactly the same, that it's made the same, that it doesn't have solvents that could be a problem, impurities that could be a problem, etc. and so forth.

So I think this is really the biggest challenge when we talk about NDIs is, are the

knockoffs. There's 900 NDIs filed and, Steve, I think, you know, I, I like the mathematical exercise. I don't know that I agree with it, that 4,600 that should have filed, but okay, the bottom line is this, I don't think that people are going to file unless there's a strong enforcement component.

And it's really simple. These are all enforcement components the Agency has. Some of them are actually NDIs. The claim on kratom, it's not that it's unsafe. It's actually, it's actually held because it doesn't have an NDI, under 402(f)(1)(B). Sorry. I hate, I like to walk. This mic doesn't walk with me.

These are all import alerts that the Agency has in place that, again, there's, there's really -- this is on firms to show they're compliant with the law, not for the Agency to show that firms are noncompliant with the law. This can be done. It has been done already in NDIs, but not specific NDIs, not in kind of a bolus or broad fashion on anyone who has an NDI. If there is someone knocking them off, why aren't they held up until they show the Agency

that it is the same?

Simple. Not a big resource burden and for the life of us we can't understand why this isn't being done on a frequent manner. I understand there may be some legal arguments, but if someone has the product, the product is the same as what's been submitted, it should be relatively easy import to show the Agency that it is the same. That shouldn't be a big ask on routine in other parts of the Agency too. So, and again, these are all import alerts that are currently proffered that, again, very little resource burn on the Agency.

So, and if we go through them, so 5411 import alert references NDIs, androstenedione, and again they never filed androstenedione. So it gets held up, 350(b)(A)2 and 21 CFR 190.6. So this is, again, there's precedent there. It's just not being done in a more routine fashion to other NDIs.

Dietary supplements as well. You know, this is where I think there should be some concern because if it's not a priority of the Agency they go, well, wait a second, it's adulterated, but it's not

adulterated. Well, it's a technical adulteration. Failing to file is a technical adulteration. Not meeting GMPs is also a technical adulteration. So there's an import alert for all products that don't meet GMPs. It seems that there's somewhat of a picking favorites of which part of the statute people choose to enforce or not enforce and I think that that should cause some concern here. And there's Mitragynine speciose, and again, kratom, and again the kratom charge is failing to file an NDI. While there is information on the safety, it is that they didn't file an NDI.

So -- and I'm very lucky. We've got a very good board chair, Mark LeDoux, and he's going to make some comments later, but I think certainly when you're hearing from groups in the industry that feel like this is the appropriate time, while Mark is the leading provider of this particular amino acid, there are others out there making it, bringing it into the country routinely, and we don't know what's in it. And yet it comes in the country freely and no one seems to mind. Kind of a problem. Knockoff

ingredients may purport to be the same, but there's no way of knowing until they provide the Agency with that sort of information.

So we'd like to and certainly look forward to working with the Agency on submitting some other NDIs or a bolus import alert for NDI so this happens in a matter of course routinely. We think it's important and we think it's really the only way you get at some of these issues that are present as it pertains to the guidance, and more importantly what's in the statute.

So with that I will shut up and turn it over to Andrew.

MR. SHAO: Let's see. Is this working? There we go. All right. Good afternoon, everyone. How's everyone doing? Good? All right. Well, I'm Andrew Shao with the Council for Responsible Nutrition. Grateful for the opportunity to have CRN provide some perspective on the topic here in this session. I'll be talking about three areas, three main areas you see here up on the slide to improve compliance with the notification requirement. One is

providing intellectual property protection, then reducing the NDI notification burden, and then finally conducting meaningful and effective enforcement.

So first is the challenges in this area, which I think is no secret to anybody, a lack of data protection, and previous speaker I think alluded to this a little bit. Past commenters have as well.

It's a disincentive for companies that do actually invest in generating science behind their ingredient, but the lack of protection of that data is a disincentive for them to participate in this process for the fear of having their ingredient get knocked off or the data that they use they've invested in generation of to be pirated by other ingredients that have no assurance of safety or maybe very little and not relate to the actual ingredient at all that was subject of a lot of research on safety. They get the benefit of pirating, pirating their data.

Another thing I'd like to bring up is the fact that it seems that FDA sees itself first and foremost as a protector of public safety, but not a protector of intellectual property. But these don't

have to be mutually exclusive. Incentivizing more NDI notifications fosters better assurance that these new ingredients and the products that contain them are safe. So actually ultimately public safety can be served by protecting the investments that ingredient manufacturers make in generating safety data.

So as an opportunity here you see the concept of the master file, which maybe is not so much of a concept anymore. So the opportunity is incentivizing ingredient manufacturers by vigorously protecting their investment in the generation of safety data. So the master file is a means of collecting and protecting data investments made by ingredient manufacturers specific to their products, and the master file can be used or cited by subsequent filers with permission or with licensing agreement as opposed to just showing up at the dock unannounced and claiming to be the same thing.

Another thing we might recommend is allow companies to reference NDI notification numbers of successful ones on labeling any marketing materials, that this may provide an incentive for

compliance with this provision. But really the most important thing is to vigorously defend and enforce the proper use of the master file to maintain its integrity and utility.

And I do also want to point out that when we talk about IP protection, it's not the same as exclusivity. It's protecting the investment that's made in the generation of safety data. It's not giving exclusivity on the ingredient itself. That's not what we're talking about with this concept.

Okay, next. Reducing the burden of NDI submissions, NDI and submissions. So I think, Steve, you addressed this in your opening remarks, so maybe this isn't so relevant now, but there I, I would say has been a misperception that every new dietary supplement contains an NDI and requires a separate notification. We just heard that that's really not FDA's view.

So we've seen some of these statistics before of the mast, vast majority of the growth that we've witnessed here in the industry, it doesn't come from new dietary ingredients and for those that do

contain NDIs, duplicative finished products should not have to be notified if a valid notification already exists on file. So it provides little additional public protection and it's another thing that creates a barrier to participation in this process.

Another thing that's a barrier is industry is not clear when a, a notification is required and also what exactly needs to go into a notification. There's a number of notifications that are filed that are woefully incomplete. So for opportunities is permit ingredient manufacturers to determine the scope of their new dietary ingredient notification, establish a reasonable expectation of safety of the new dietary ingredient under a range of conditions of use that would cover different finished products.

There's also a confusion here between the, the NDI notification process and the GRAS process. We heard a little bit about it earlier today where foods that come under the market that contain a GRAS ingredient don't have to be notified, so there's a little disconnect there between these two processes.

Finally is to provide clarity in the guidance addressing requirements for new dietary ingredients to reduce objections due to lack of completeness. So some sort of template that walks the submitter through the specific areas of information that are needed to be included so that we avoid situations where there are objections due to incomplete notifications.

Okay. Finally is meaningful and effective enforcement. So there's a lack of perceived consequences for those who fail to comply with the provision, the NDI provision. That creates a disincentive for others to participate and contributes to a lot of confusion as we've already heard.

So another challenge is that FDA has limited resources. So if something doesn't pose a safety concern, it's unlikely to be addressed. I think that's a, a challenge we'll have to continue to work on, also mentioned earlier by Steve.

Another thing is discovery of a, of a, an API in a product results in referral to that product over to CDER because it's not a food and it's

not a supplement. It's an unapproved drug and so it goes over to CDER and then CFSAN seems to lose control, lose continuity of the enforcement process.

And then there's the perceived stakes in, of pursuing full investigation, prosecution. It discourages FDA legal action beyond some basic steps because it's resource-intensive. So the first opportunity, consider using mandatory recall might be a stretch. FDA has mandatory recall authority under FSMA. Products containing NDIs as we just heard from Dan that have not been notified are adulterated, may be considered adulterated.

There is a second requirement for a mandatory recall and that's establishing, the acronym is SAHCODHA or a serious adverse health consequence. That could be challenging for certain new dietary ingredients.

The next opportunity, mandatory product listing. So this is not a cure all, it's not a catch all, it's not a, a complete solution in and of itself, but it would in concept allow for easier identification of noncompliant products. But there

have to be consequences. If there is a mandatory listing there have to be consequences for lack of participation. So a voluntary system that everyone knows about of course, supplement OWL, certainly a worthy effort, but not very effective without consequences for failure to list. So this is a very important thing that we all have to keep in mind. FDA has to be prepared with the resources and the resolve to address violators if a mandatory product listing is, requirement is created.

Finally, wrapping up with meaningful effective enforcement. FDA should utilize its other enforcement tools including, but not limited to warning letters such as untitled letters, seizure, authority to initiate misdemeanor proceedings, administrative detention, fines, disgorgement of profits. That should, that's a typo. That should be debarment, not disbarment; although, maybe there are some attorneys that should be disbarred for advising their clients not to file notifications. But that should be debarment, not disbarment, and then injunction.

FDA should enforce through CFSAN all products that are represented to be dietary supplements. So even if they are products masquerading as dietary supplements because they have unapproved drugs in them, they shouldn't be kicked over to CDER. If they represent themselves with a supplement facts panel, we should treat them accordingly and CFSAN should retain control over that for more consistent enforcement.

Work with state partners such as attorneys general to increase enforcement activity. And FDA itself should, the Agency overall should be requesting additional funding to the Office of Dietary Supplement programs.

So with that I thank you for your attention and thank you very much, Steve.

MR. SIEGNER: Well it's an honor, an honor to be here and I'd like to thank Cara and Steve for organizing this meeting. I began practicing in the food and drug area in 1986 and primarily spent my first four or five years litigating cases against FDA on, on GRAS food additive issues and that was mainly

surrounding evening primrose oil which it's, it's a longer story I won't get into here, but led to the black currant oil decisions that helped kind of lead to DSHEA. And I'm, I'm just curious, how many people here, show of hands, had some input into the drafting of DSHEA? Maybe paying legal bills as this business person or writing? So we, we have a fair number.

A couple of people that haven't been mentioned here I would like to mention. One is Peter Reinecke, who is with us today, was the point person on Harkin, Harkin's staff during this whole exciting time. The other I would mention is Steve McNamara, my partner, who is, when he was practicing one of the giants in, in food and drug area. He's a great man.

So my assignment here today is pretty narrow and I've already heard four people who I would view as experts, either agree or disagree with the position I'm about to take. So it's interesting that we're still 25 years out debating some of these kind of basic concepts within DSHEA and what is an NDI and what isn't an NDI and when do you need to notify, so.

Okay. Let's see. Which button am I

supposed to push here? Okay. So I put this -- I, I originally drafted a long answer to this question. I said, well, okay, everybody knows lawyers can give long answers. Why don't you just put a short answer in. So my job here today is to explain whether I view that there is a, some type of market exclusivity provided under DSHEA, specifically in the present in the food supply exemption to notification filing and I'd say, no; although, being a lawyer I, I would put an asterisk there and I'll explain where, what the asterisk means later.

So a little, a little bit of history. I, I, I say here that FDA has struggled with how best to address dietary supplements. The other way you could frame that is FDA is truly in kind of an uncomfortable position. With respect to supplements if you have a, as a continuum a pre-market here, and pre-market approval here I'm getting, you know, it just easier for FDA to talk about products and, and agree with products and to support products that are pre-market approved.

Well, we're somewhere in the middle

here. Okay? We're expecting FDA to assure safety of the products without pre-market approval and that obviously has led over decades up to some difficulties for FDA and some attempts to kind of say, well, how can we get a better grip on this.

Congress has a couple of times pushed back with the Proxmire Amendments. Back in the '70s FDA came up with the idea that dietary supplements over, or vitamins and minerals over a certain dosage amount should be drugs. And basically Congress said no.

And then it was actually a, a partner of mine who before being a partner was a commissioner at FDA -- I'm sorry, general counsel at FDA, Tom Scarlett, who came up with the idea, well, we could use the food additive amendments to better confine the industry and declare some of these ingredients that are coming out that are new as unapproved food additives, which led to the whole GRAS food additive litigation and, and eventually to DSHEA.

And if I, I have a link to our blog and there's a post on here that kind of goes more into the

depth of that history. So, you know, it's -- given where we are, and we're kind of in this continuum with FDA pushing toward approval and industry and others may be pushing toward more of a free market, we're still debating a lot of these issues.

So it's important to understand when we're talking about this concept of market protection or exclusivity to understand where did, where did the -- you know, DSHEA did evolve from something and it really did evolve from the whole concept of GRAS affirmations, GRAS, GRAS self-affirmations, FDA affirmations, food additive approvals, and that these are ingredient-based ideas, okay?

So what we're trying to assure here is the safety of an ingredient and the identity of the ingredient is very important. Now sometimes the identity is very easy, albeit there may be SIS transformations and I think those are important, but when we're dealing with herbal extracts it, it can be much more difficult. But ,nonetheless it's still an ingredient-based concept and in my view that leads us into this presence of the food supply, it's the

ingredient that is the issue here.

So what is -- just, quickly, this slide just quotes the exemption. So you do not need to file a notification for a dietary supplement that contains only the dietary ingredients which have been present in the food supply as an article that is used for food in the form -- okay. The rest of that deals with chemical alteration and I don't want to get into that.

But there's, this -- you could base a whole legal career on this one sentence. I mean there's so many ways that I can be creative with this. But I think one way that I, I don't need to be creative is the question when we talk about food supply and we talk about used for food, what does that mean because the Food, Drug, and Cosmetic Act defines the term food as a dietary -- sorry. Defines the -- states that a dietary supplement shall be deemed to be a food within the meaning of this act.

So in my view this is actually part of the simple part of this definition or this sentence. When we're talking about foods and food supply, we don't just mean conventional foods. We mean both

conventional foods and dietary supplements and dietary, dietary ingredients in dietary supplements.

Now I, and I'm not going to go into at length what FDA has said about this, but briefly they've said that this is not, that the case -- sorry. The slide -- I am ahead of myself here. That basically it's just conventional foods. Food supply is conventional foods. In this -- if you follow that interpretation it would provide some market incentive. You go ahead and file an NDI for your ingredient and you go on the market, then the subsequent manufacturer making the same ingredient would need to also file a notification.

Now there's ways to make that easier. It's not a great protection to the market, but in my view it's actually no protection because in my view the subsequent manufacturer can go onto the market as long as the ingredient is identical to the ingredient that's already been notified. So again, once an ingredient's been notified, in my interpretation you can go ahead and market.

And I'd like to point out that this is,

it's not a novel concept. This is how the GRAS process works. This is how the food additive process works. The importance, again, is ingredient safety and it's not an exclusivity issue.

So I, I, I do want to say kind of in closing that we're talking here about promoting a compliance overall and the important thing to me in promoting compliance is to try to simplify what the NDI process is and what is and is not an NDI and how to go through notification, what you need to, to submit to FDA and when you need to submit it.

Unfortunately, what we're seeing here is there's so much confusion surrounding these draft guidances that it is forcing companies seeking alternative routes to go through the GRAS process. And ironically DSHEA was intended to cure that process and to avoid having to, people to go through the GRAS process.

I, I have different view of the GRAS process than some other speakers here. I actually think it's a very good process. I think it works well. I think as one speaker noted even through the

kind of secret GRAS affirmation, self-affirmation process, we've had very few instances of safety issues. I think, you know, PHOs are maybe the only exemption section I can think of where ingredients have gone through self-GRAS and then subsequently been determined by FDA to be something that should be pulled back. And with that, thank you.

MR. SIROIS: So good afternoon, everyone. I'm Jay Sirois with the Consumer Healthcare Products Association, one of our five major trade associations in the dietary supplement space. I'd like to thank the FDA for holding this important public forum today to discuss responsible innovation and also for providing me an opportunity to present.

CHPA is a 138-year-old member-based association representing companies that market OTC drugs, some of whom are also involved in the dietary supplement space. We have a very active dietary supplements committee comprised of companies committed to manufacturing high quality products and marketing them in a responsible manner.

We appreciate the Agency's efforts in

looking at potential new pathways to strengthen regulation and perhaps develop new pathways for innovation. We share the commitment frequently espoused by the Agency that consumer safety, product integrity, and informed decision making by consumers are paramount.

I'd like to briefly share with you some of the items our supplement committee has been discussing over the past year and I will note first that these are topics of discussion within our association, and again, I'll note that we share the Agency's commitment to, to safety, integrity, and informed decision making. We have initiated outreach efforts to other stakeholders in the supplement industry to discuss these items as the industry seeks to chart a path of responsible growth while ensuring that consumers have access to appropriately labeled quality products marketed in a responsible fashion.

In the spirit of the statement issued by Dr. Gottlieb back in February and, and, and reiterated this morning by Dr. Sharpless, we believe an appropriate balance can be struck between fostering

the development of innovative products while maintaining the, the commitment to FDA's three priorities.

So mandatory product listing, of course, as you've heard, has been a hot topic of discussion in the industry and FDA is noted that they are unable to determine what products are sold in the US market hampering their ability to act against dangerous and/or illegal products. Listing could provide greater transparency into the marketplace and perhaps FDA allow them to better enforce against violative products.

FDA has estimated that there are over 9,000 dietary supplement facilities worldwide and in fiscal year '18, 2018 inspected less than 10% of those. Poor quality or adulterated products can lead to greater consumer safety risk, a black eye for the whole category, and a significant increase of FDA inspections through authorization of, FDA authorization of third party GMP inspectors could perhaps increase the number of inspections and make certain of the retailer requirements that have

proliferated become unnecessary.

We know that FDA devotes approximately 5 million dollars to regulate the 40 billion dollar dietary supplement industry and we know that insufficient FDA oversight due to a lack of funds can diminish consumer confidence in the industry. So I think there's widespread support for increased funding for the Agency throughout the associations.

Innovation. We know that that is hampered by the current NDI process since companies are reluctant to take on the expense of testing as Andrew described, that it's required for an NDI application as the data subsequently become public. FDA has also expressed concern as you just heard that the number of NDI submissions is far below what they would expect.

So one proposed fix to both of these issues is for FDA to implement the master file process whereby FDA would hold data submitted in support of an NDI notification confidential and require subsequent companies wishing to market that ingredient to either submit their own data in support of, of an NDI or to

obtain permission from the innovator company and submit a one page NDI, or NDI notification informing FDA that they have permission from the innovator company to rely on that information.

This would foster innovation and occur as a development of conduct of high quality safety studies and provide an innovation incentive as the initial company would have early entry into the market. It would also address FDA's stated desire for all companies submitting an NDI to submit notification. And I'll speak more on this in a bit.

The definition of a dietary ingredient, or excuse me, a dietary supplement, includes a dietary substance for use by man to supplement the diet by increasing the dietary intake. We know that Congress removed the term nutritional substance from the definition in order to not restrict ingredients to those substances with nutritional value where they were naturally occurring, and you heard Scott Bass speak of this, this morning.

FDA's restrictive interpretation of what constitute a dietary substance, to mean a substance

that's commonly used as food or drink, limits innovation and requires clarification.

Structured function claims right now we know comprise the majority of, of the claims that are found on supplement products. However, many dietary supplement products are used to help manage conditions and their symptoms without direct claims. Product innovation and the public health would be better served if claims for these specific benefits were permitted, of course, with the appropriate level of substantiation and the demonstration of safety.

And lastly, we encourage the FDA to finalize the authorization of an old list, or the list of old dietary ingredients and to consider moving the date for inclusion on the list to perhaps a more recent time for those ingredients with a demonstrated history of safety.

So at the risk of sounding repetitive, and I promise that Andrew and I did not copy term papers, I'm going to, I'm going to talk about the NDI master file process.

So we're convened here today to discuss

possible ways to foster innovation while increasing compliance with the notification requirement, and again we know the cost associated with preparing and submitting an NDI notification including the cost of safety studies can be hundreds of thousands of dollars and companies are often reluctant to incur these as subsequent entrance to the market can basically market the ingredient without having to incur the costs.

So one possible mechanism to encourage innovative safety studies and to enhance NDI notifications submitted was to -- this was described in the 2016 NDI guidance on NDIs. Under this master file concept the innovator company would conduct the appropriate safety studies, submit the notification, and the FDA would keep the data and information confidential in a quote, unquote, “master file.”

Following the receipt of a good day letter by the innovator company, subsequent companies wishing to enter the market and to market the new ingredient in a supplement would have to do one of two things. Either perform their own safety studies on the ingredient, defining the conditions of safe use,

followed by the subsequent submission of a notification, or alternatively they could obtain a right of reference from the innovator company. And in the latter case that company would submit a one page notification to FDA signifying that they had been granted access to the master file from the innovator. This would reduce the burden on industry in terms of submitting duplicative NDI notifications, but it would also satisfy the FDA's call for increased numbers of, of notifications.

The NDI master file process would also provide for a de facto marketing advantage for those companies filing a, a, a, an innovator NDIN and would ensure that any responsibility for companies marketing an NDI to submit notification could potentially not be too onerous.

To implement the NDI master file process FDA would need to ensure that the safety information contained in the master file is treated as confidential and trade secret beyond the 90 day pre-market filing period so that it is only relied upon by those who are authorized, and as you've heard, needs

to take enforcement action as authorized under the Food, Drug, and Cosmetic Act against any entity marketing an NDI without a notification on file. Full implementation of the NDI master file would result in a de facto marketing advantage for the innovative company filing the initial notification.

We believe the NDI master file would allow for efficient filing of notifications and would also provide transparency into the NDI marketplace allowing FDA to better identify industry outliers. Similar to master files for other FDA regulated products, an NDI master file could contain information such as the owner's name, as well as composition and manufacturing information, and any unpublished safety studies on the NDI. Again, FDA would be responsible for protecting all of this confidential information.

Okay. There we go. Lastly, we believe this type of process would encourage the development and conduct of high quality safety studies supporting the marketing of the innovative products, but importantly there would be no lessening of the current requirement for demonstration of a reasonable

expectation of safety. Of course as with all the topics we've discussed here today, the devil's in the details, and in this case perhaps the most important devil would be how to prevent companies from marketing the me-too ingredients without either relying on the innovator company master file or through the performance of their own appropriate safety studies and subsequent submission of a notification. We believe that FDA and industry must work together to find solutions to this.

To conclude, by implementing the previously described NDI master file concept, FDA could allow for the development of responsible innovation by the industry while ensuring that notifications were submitted for all products containing a new dietary ingredient. To do this FDA would need to ensure that the contents of our master file are treated as confidential trade secret information including unpublished safety studies, and would need to commit to a robust enforcement action against entities marketing dietary supplements containing NDIs that have not been a subject of a

notification. Thank you.

(APPLAUSE.)

MS. ESKIN: You're just going to have to stare at the slide 'cause I don't have any. Good afternoon. I, too, would like to begin by thanking FDA for holding this meeting and for inviting Pew to participate.

I'm often asked what is The Pew Charitable Trusts. It is a public charity. The funding came from the children and grandchildren of the founder of Sun Oil or Sunoco. We focus on evidence-based solutions to today's greatest challenges, and maybe not the greatest, but important ones like how to figure out NDI compliance and incentives.

So our focus on food safety on -- I do food safety too. Our focus on supplements is on safety, which has to be an essential component of innovation. It will be the focus of my comments and it has been raised by many other speakers today.

So consumers who use dietary supplements should have assurances that the products they buy are

safe, high quality, and accurately labeled. I will focus on three points today. Again, there's been a lot of, of common points raised and so you've probably heard some if not all of these before.

One is the general concept of marketing advantage in this context. The importance of effective enforcement and one thing that I think began the discussion this morning thanks to Scott's presentation, mandatory product listing.

So again, first, regarding market advantages, if FDA comes up with a way to create a marketing advantage whether it's a master file or some other concept to incentivize compliance with the NDI system, we ask that along with it, the, the Agency explore ways to incentivize research related to ingredient safety. It is absolutely critical that that be encouraged.

At the very least any marketing advantage should in no way dilute the safety standard in the NDI notification process. We've heard what that standard is. The product should be, it should reasonably expect it to be safe under the supplement's

labeled conditions of use.

And I think Larisa mentioned it this morning in her presentation. Only the NDI safety standard, which is provided in the NDI process, right, provides FDA with pre-market authority to stop the sale of a supplement that includes a potentially unsafe new dietary ingredient. All the other safety provisions, and there are numerous, are all post-market.

Second, regarding enforcement and its role in promoting compliance, I think everybody believes that it needs to be strengthened and I'm going to mention two things that have been mentioned before, but they bear repeating, please finalize the August 2016 guidance on NDIs. This will give needed clarity and it will make, it will hopefully enable companies to meet the requirements of the law easy, more easily.

Number two, you need to have more resources. Not endless resources, but more resources than the Agency has currently provided to ODSP. And Pew has been working with other advocacy groups like

CSPI. We've been working with CRN and other trade associations and CHPA to work to get FDA's supplement program more money. I think we've had some success in the last year and I think we have to continue to do that because that is the only way you will see anything that looks more robust than what you're able to do in the current resource environment.

Okay. So third, mandatory product listing. A number of the panelists here this afternoon have mentioned it. To do its job, FDA needs to have a comprehensive picture of what's on the market. As we've heard, we've gone from 4,000 or so products in 1994 to as many as 80,000 products. The tool that will enable FDA to effectively carry out its existing authorities -- again, it's not greater authority, it's just a tool that let's it exercise what the law currently provides it -- is a listing requirement.

Every manufacturer would be required to provide the Agency with basic information such as the product name, the ingredients, and the labels for every product that is sold. This tool is a win-win

for almost everyone. It will enable FDA to determine compliance probably pretty quickly with NDI notification process and other requirements. Consumers would be able to identify reputable supplement products, and retailers would have an assurance with being able to only sell products that are produced by companies that are on FDA's radar screen and that are compliant with the law. Thank you.

(APPLAUSE.)

MR. TAVE: Thank you to each of our panelists for the (inaudible) and for taking part in Q&A. (Inaudible.) So that is before we (inaudible) and I will pay attention (inaudible) questions that are (inaudible). So we can start with Mr. Bass. And again, just a reminder, please, give name and location (inaudible).

MR. BASS: Scott Bass, Sidney Austin. It's a kind of question; though I would say it's rhetorical, but can I ask you all. We all agree that Section 413 -- is there anybody in the room who disagrees it's a horribly written section? Nobody.

That was the subject of so much (inaudible), but when I hear people say that nobody else has to file, I just want you to understand today the responses I hear.

This section came about because a year earlier there was a version that said everything was grandfathered before '93. Everything after it had to have (inaudible) approval. This was the compromise, but the word everything is the key and the one word that tells you why everybody has to file an NDI is L-tryptophan.

Are you going to relay upon a sleazy second comer and say, oh, it's identical? No. FDA has to know the manufacturing method because if it's different from the first product that got an NDI, we could have another L-tryptophan episode. If the FDA does not know full composition and manufacturing method (inaudible) filing, they're letting product on the market with the manufacturer saying it's identical, but you have no proof of that.

And that's why the entire scheme -- and to say -- and I, I know we have a legal disagreement here, that a dietary supplement is food under 413's

exemption for commonly food that's used by humans and not chemically altered, but that writes 413 out of existence (inaudible).

So I just wanted to ask, Steve, if the FDA believes other than what the (inaudible) that calls itself GRAS that if there's any reason not to require everybody to file even if it's a one line NDI saying I'm filing pursuant to the master file (inaudible) the first company.

MR. TAVE: Well, that's a broad question. I don't know if I can give an authoritative answer to everything. I mean, I, I think -- you know, I said before it's not (inaudible) that everybody on the market needs to file a notification. Our view is that a notification should be filed for the products (inaudible) and that's a somewhat circular answer.

I want to ask something about your question. I want to open it up to the panelists, but it, it sounds like you're suggesting that a manufacturing process change requires a new notification requirement, and that was my understanding of stakeholder positions after we

released the draft guidance in 2016. So I'm curious --

MR. BASS: Depends on the change. It depends on the change. It's mostly a GMP issue. If you have filed a full NDI notification GMP is supposed to cover major changes especially (inaudible) controlled, controlled guidance which applies to drugs, devices, and food.

MR. TAVE: But is it mostly (inaudible) and can we use that (inaudible) cooperation charge for (inaudible)?

MR. BASS: Not if it's somebody who already filed a full NDI. But certainly for a subsequent company who didn't file, absolutely.

MR. TAVE: (Inaudible.)

MR. FABRICANT: I don't even think you need that. It's a subsequent, it's, it's not -- there's nothing in the statute that says if somebody files everyone just gets to ride on it. I mean I don't know where the heck that interpretation's coming from. It, it's specific to the ingredient.

You can talk about safety, that's fine,

but there's an identity to any ingredient. If one person makes an ingredient, Cara makes an ingredient, (inaudible) makes an -- she can say it's the same ingredient, but I guarantee you (inaudible) different. That's part of the 190.6. So that's the trigger. You don't need to know the trigger.

MR. BASS: That's a better answer than mine. Thank you.

MR. FABRICANT: I know. You're an attorney.

MR. SIROIS: So I, I don't, you know, one, another way to look at this is, okay, so you have the whole GRAS process. You know, obviously we're all concerned about L-tryptophan. Scott and I and a few others were involved in trying the parse out the, you know, the, the destruction of the, of everything after that and, and how to figure out how do we assure that things are safe, particularly when I don't think we ever really pinned down exactly what, what caused the L-tryptophan problem in, in the first place.

So there was a time where nobody wanted to market L-tryptophan because it, you know, we didn't

know for a long time, and eventually, you know, L-tryptophan came back on the market and it's, it's there (inaudible).

So we, we have, we have these issues, L-tryptophan may be a, an outlier, but that doesn't mean we don't worry about them and we worry about them in the context of GRAS self-affirmation also. But, you know, in -- we have ways, much better ways these days of determining which, what the ingredient is and how it's made. I, you know, I, I still think the law's pretty clear in terms of what, who, who's (inaudible). Maybe Justice Scalia would agree. (Inaudible.)

MR. SCHONEKER: Dave Schoneker from Colorcon. I'm also very involved with the International Pharmaceutical Excipients Council and I guess I, I'd like to sort of do an analogy here a little bit and get your thoughts. Let's not reinvent the wheel, okay? A lot of what we've heard here about the concepts of master file exclusivity, etc., I have to say (inaudible).

We've already got the same system on the drug side that we could just incorporate here. It's

all about ingredients, right? So if you look at excipients, we're very familiar, okay? We already have a typed (inaudible) excipient or master file that is used for exactly what we're talking about here. Anybody who develops a novel excipient, it's never been used in a drug before, it's going to have to be reviewed by the Agency as part of drug a application, or at some point you do massive amounts of safety studies, etc.

You have a lot of, you know, innovation and a lot, a lot of investment by a particular excipient company. They put all that safety data in (inaudible) drug master file it is, it doesn't give you any exclusivity, but your safety studies are protected in a drug master file. Your specifications are, are protected in a drug master file until such time that you want to get a monograph or make it public, which is at your bidding whenever you want that, okay?

And then if anybody else wants to make that material, they have to file (inaudible) drug master file, do their own safety data and their own

specifications, and, and get reviewed in, in, in, in a drug application later on.

So it seems to me that you've already got a system that does almost exactly what I heard Jay outline and I know Andrew is pretty much in line with that, which seems to give us everything we're looking for to help give innovation.

I could tell you from an excipient company's perspective if we didn't have that type 4 drug master file system, there would be no new excipients. Nobody is going to do millions of dollars (inaudible) studies and expose themselves to somebody just taking notes and using them. And, and, you know, the master file system we have works very well in terms of protection of the data and, and allowing a company (inaudible) that information.

And we have some other issues (inaudible) in terms of having the ability to have an independent qualification of that data like in the new, in the I (ph) system. We wish we had that there in the drug side. You got to put all of it in there. Then you have to wait for some drug company to

actually decide they want to put in a drug application, and at that point your file gets reviewed.

That part I don't like and isn't working, okay? But the concept of protecting the data and, and, and providing that protection and innovation incentive is already there.

So what would it take to put a system like that in place here? It seems like to me the (inaudible) there. It's a matter of is there some sort of legislation that's needed to do this? Is it just a matter of somebody coming up with a system to manage the DMF?

We could learn from the CDER guys. They already have it. It's all electronic (inaudible) master file system. You just copy and paste. So I'd be interested, especially, Steve, your thoughts about what would it take to institute a system basically copying a type 4 (inaudible) master process and put in place for this and why not. Let's learn from what we've already got (inaudible).

DR. TAVE: Thank you for your question.

(Inaudible) we'll make sure everybody has a chance. So I, I don't know (inaudible) to the extent that I've worked (inaudible), but I, I (inaudible) had a question earlier (inaudible). And that is a point that I didn't get a chance to linger over, but we were never a one size fits all (inaudible) explaining again the differences from a previous (inaudible).

Andrew had some points during his presentation especially on master files to where (inaudible). We probably couldn't have done a better job of (inaudible) some of these things are things that (inaudible) and so we encourage firms to submit (inaudible) and it doesn't have to be (inaudible) product (inaudible).

We have no problems at all with firms (inaudible) their notification letting other people use that so there are ways to use the (inaudible) that are already in practice and we certainly (inaudible) and other communication with our office if somebody is interested.

One challenge (inaudible) is confidentiality and I think, you know, where we accept

is the statutory system under 413 requires us to disclose an application (inaudible) or 90 days after we receive a completed application (inaudible).

And so when we want the master file to be reviewed that there is an obligation on our part to (inaudible) as possible and I understand that. I don't know (inaudible) the Agency necessarily because (inaudible) and we wouldn't be able (inaudible). So I think, you know, in terms of what's not in place right now, but that could be different (inaudible).

MR. SHAO: The, the only thing I would say -- this is Andrew with CRN, and I would say follow up comment is a big question is what does, what, what would the FDA do if an ingredient manufacturer went to market and failed to file a notification assuming it was identical to a previously notified (inaudible) ingredient that the confidential information which was maintained in the master file.

So in other words, would FDA go out and enforce to maintain the integrity and the utility master file in that situation, or would it say, well, you know, the ingredients appear to be the same, so

we'll just let it go? More of a question than a comment.

MR. TAVE: No, it's a fair question and I think, you know, it's impossible to answer (inaudible) with certainty that philosophically that's a case where we would want to take enforcing action. The (inaudible) between philosophy and reality is where it gets difficult and becomes less, you know, (inaudible), you know. And, and so we have the likelihood that we would be able to prevail the willingness of (inaudible). So there's a lot of (inaudible), but it certainly is a fair question.

MR. SIROIS: So I'll, I'll reiterate a couple of points (inaudible) and Andrew (inaudible) said this in his comments, the use of the E word. We're definitely not talking about that in this context. It's an, it's an incentive for a company to have to do this, to do these innovative (inaudible) studies and to be the first to submit a notification, but in no way would this be, you know, I want to use the word (inaudible) and I can't, can't say the study, study number or it's an innovation incentive for that

company that files the initial notification, but I'll leave this to the lawyers in the room to argue about how to, you know, go about the provisions in 413 and whether, you know, what needs to be disclosed or not, but there are many other master files.

You know, Dave, you alluded to the (inaudible) master file and I know there are several other examples of master file concepts that are, that are viewed as (inaudible). This requires a little more discussion, but we've heard from several folks here today (inaudible) mentioned it early in his, in his talk. Dan talked about it, Andrew, and myself so I think the discussion should be continued.

MR. MILLER: Mark Miller at INW Manufacturing and I've, I've enjoyed the discussion on, on primarily safety and, and the master file, but I'm drawn to the title of the event today which is innovation and who does innovation? Truly entrepreneurs. And they do it for a marketing advantage and I think that we haven't probably spent enough time thinking about either protecting or fostering some marketing advantage based on

innovation.

And so there's a sort of general question related to that and specifically just to sort of narrow it down, I think that we have a great need for clinical research to give us some comfort in both safety, but also efficacy and consumer responses and that should be encouraged.

Is there a way to sort of protect a company that devotes it's, it's efforts into really decent clinical research given the context that many consumers still want peer reviews so it's going to be in the public place? So there's no sort of hiding it in the file buried somewhere and, and allow you to have some degree of the E word.

So how do we, how do we engage with the consumers in an innovative way that, that, and encourage companies to do clinical research to, to show benefits as well as safety?

MR. TAVE: Nobody's jumping to answer that one. Is there a (inaudible) question.

MR. FABRICANT: I'm always happy to put my foot in my mouth. I think as far as FDA goes, that

the NDI process does -- and maybe not for, for, to some degree clinical research, but does -- I think the DNI process does have an, an avenue to, to reward people who are doing research and I think more and more you're seeing cases get turned over to FDC when folks are out there making claims and have no research.

So now that that's said, necessarily a way to incentivize, but I think you're dealing with a regulatory agency there. They're fresh out of carrots. They generally deal (inaudible). So I don't know that that would be something that (inaudible).

MR. TAVE: Please feel free to plant a garden for us (inaudible). I, I think it was an excellent question (inaudible), but your question is (inaudible) there are people out there who (inaudible) research and, and develop quality products and (inaudible) and that would make that worthwhile. So (inaudible). It was a good question. Let's -- I think take a few more questions and then (inaudible).

MR. GIANCASPARO: My name is Gabriel Giancasparo and I'm from US Pharmacopeia (inaudible)

here that product specifications are a way to compare different products in determining whether to stick with it or not.

So it is important then to have transparency about the (inaudible) specifications because otherwise what do people know about the same product or (inaudible) submit another NDI or who we intended (inaudible) NDI? So it's a possibility of considering also that within the (inaudible) information (inaudible) the specifications that make up (inaudible).

And therefore that way also the people (inaudible) can also get protection (inaudible) and somebody else comes in, it doesn't (inaudible) and it doesn't (inaudible) that product again (inaudible) our product specifications (inaudible) safety needs to be demonstrated (inaudible).

MR. SIEGNER: I think -- I'm not sure I completely understand that. I think -- so one of the things that when I was talking about the word he won't use, exclusivity, the -- or, or any kind of market, you know, advantage. I mean there are -- I think what

you've pointing at is that there are things that are important to ingredient safety such as an, and particularly in the herbal extract area that (inaudible) some of those (inaudible) where you can't make your ingredient unique.

It would also be important to the safety of the ingredient, but would also cause FDA to want to file your NDI notification. And, you know, so I'm not, I'm not trying to suggest that that's not important or that that could not lead to some kind of advantage for your ingredient under the way the law is written now. I'm not sure that that fits specifically what you're asking.

MR. GIANCASPARO: Yeah. (Inaudible) information, information goes into process, how and (inaudible) ingredient in the reviews and that doesn't need to be disclosed of course, but in terms of the determining the equivalency (inaudible) those things should not be (inaudible) in, in, in our reviews. It should be a (inaudible) specification so that, that the (inaudible) also the, the -- have the ability to know whether or not (inaudible) because the, the drug

ID (inaudible) specifications of an impurity requiring (inaudible) another safety (inaudible).

MR. SHAO: My name is Andrew Shao (inaudible). So today let's say companies that are paying attention see a notification is filed because it's public record, see that FDA hasn't objected, and then purport that their ingredient is the same and they go to market. So they are paying attention. They do know that a competitor has already filed a notice of successful notification.

So in a situation where specifications may make a difference between whether something is the same or different, they can go and contact that manufacturer and say, can we, you know, we're, we're trying to decide if we should file or not. You know, that's an approach that could be made. And if they had a master file system, they'd have to request permission. So they'd have to come to some sort of agreement.

So the, the process would require some amount of transparency for those companies that are paying attention already and deciding not to file

because the competitor already took care of it for them. So if we had the right system in place, they would have to go to that company and they'd have to exchange information before doing that.

MS. MACCLEERY: Laura MacCleery with Center for Science in the Public Interest. So I think we have a bit of a (inaudible) thing on GRAS. So I've heard several times that because there hasn't been any things that have been de-GRASed over time that there's no problem, and I would say, in fact, that is evidence of a problem.

You know, we all want to see absence of evidence of (inaudible), right. We filed a citizen petition which is what you have to do to De-GRAS a substance. (Inaudible) had 20 years before it actually was taken out of the GRAS-listed substances and FDA took interim steps of putting it on the label first. There's actually no systemic (inaudible) approach for reevaluating the safety of an approval of a GRAS substance or a food additive once it's put onto the listing or whether once, once there's been a notification filed on the GRAS case.

And so that lack of a systemic look back has been a problem that we are trying to address as a community, with (inaudible) organizations. We filed petitions to withdraw approvals on food additives in recent years on perchlorated compounds, which was successful on perchlorate and potassium bromate which has been caught up in Agency delay. There's some interest in (inaudible). We won one on carcinogenic flavors and we have a pending petition on sugar 'cause we think that condition of use for sugar-sweetened beverages, of excessive amounts of sugar, is actually already (inaudible).

But to get the Agency to do these things, at least the food additives side, you have a petition process and you're supposed to have a process by moving the decisions. On the GRAS side, you just set up the files (inaudible) petition and FDA can take as long as a week unless you sue them for delay.

So I, I think there's a whole host of things that could be de-GRASed if there was an adequate system of look back, but there just isn't. And I don't want there to be a misunderstanding that

that absence of action by FDA, which we view to be deeply problematic, is actually evidence that the system works fine.

MR. TAVE: Okay. I'm, I'm looking (inaudible) to see if we have any questions from our monitor. We want to try to keep us a little bit on schedule and I'm not seeing any, but if we have any we can get them and we review them over time.

So we're already at the time where we were going to begin session five. How about, how about if we take a break and come back at 3:10; is that (inaudible)?

(SESSION BREAK.)

MR. TAVE: If we could start moving to our seats so we can move to the open public comment, please? That way we can make sure we get everybody out of here on time and on schedule. The lights are flickering. Wonderful. If we could get our panelists to the table and our speakers lined up and we'll do a very short introduction. (Inaudible - background noise). We will enforce that judicially. So if you need to enforce that judiciously. So if you need

three minutes and three seconds, we're not going to stop you, but if you will (inaudible - background noise).

So with that, let me first introduce our panelists very quickly so you all know their faces that are up here. Everybody's tired of hearing from me all day. (Inaudible) Dr. Welch this morning. I don’t know a few people who have responsibility in (inaudible) Office of Dietary Supplements (inaudible). Dr. Sybil Stretch (ph) is the special assistant here at USD and (inaudible) policy adviser.

So we will (inaudible) your questions, taking comments, and I believe our first speaker is Frederick Blake. And again, just as (inaudible) if you could please identify your name and affiliations for those who are following along via webcast. Thank you. And for those who are next, feel free to come on down to the microphones just so we can (inaudible).

MR. BLAKE: Okay. The word innovation was used (inaudible - background noise and crosstalk). And I think the innovation is going to be enforced on. It's not, it's not something, -- it's something that

industry is responding to the government to be (inaudible). Patient groups and (inaudible - coughing), dietary supplements along (inaudible) drug (inaudible) and it's just, they're not (inaudible). So what do you do here is, okay. I think this is a great (inaudible - coughing).

Physicians' groups need to be here, Patient advocacy needs to be here. This needs to be way more open in terms of what, what's actually done here 'cause this is not a -- it was an in-house thing. It thought it was interesting and people were very friendly. (Inaudible.) I, I just think that (inaudible) a zillion patient advocacy groups and representing federally qualified health centers and, and (inaudible) hospitals, it's, you've got to open up the conversation to make this worthwhile for patients know where it's at.

Having said that, this is particularly important for those who are threatened with life-threatening diseases like HIV and AIDS and the gastrointestinal conditions that present themselves in these communities. And we are not going to have these

communities included in substantive dialogue with the FDA and the industry.

More than 30% of all HIV medications show gastrointestinal symptoms with a high prevalence. And in fact, those gastrointestinal symptoms greatly impacts the quality of life in the HIV patients in this era of highly active antiretroviral therapies. And, and we know very little about the interaction of, of, of dietary supplements in these kinds of (inaudible). People who are so, so diminished.

These and other patients communities must have guidance of physicians. It's, HIV physicians aren't here either for physicians and patients at the point of care because they need that guidance. There are a (inaudible) nutritional supplements and medical foods on the market that support the restoration of the intestinal barriers of people living with AIDS and HIV.

This can, this can help prevent nutritional absorption and (inaudible) Michael Biota (inaudible) symptomatology in the HIV community such as insulin tolerance, intestinal infections,

(inaudible) constipation and diarrhea. These are ongoing problems with long term AIDS survivors and you have no idea the suffering that goes on in this community. Maybe you do. I hope you do.

The majority of these conditions are experienced a higher prevalence in the HIV positive community. We would like to work with the FDA to ensure that people living with AIDS and HIV and other diseases are (inaudible) safe and effective nutritional (inaudible) food choices to better their condition, and that the FDA develop (inaudible) guidance and other means of communications to physicians, the HIV community, and the general public concerning nutritional supplements and medical foods that can be used in the HIV community to restore, help restore their health.

We view this as a, a priority for the president's efforts at (inaudible) HIV and AIDS as he stated in the Union Address. Thank you.

MR. TAVE: Thank you, Mr. Blake. Just a quick response. We really appreciate you being here. You made some good points. And (inaudible) it's not

the end (inaudible). So we would love to hear from patients (inaudible) message at our office is open and (inaudible).

MR. BLAKE: Well, if you know the HIV community, reaching out is not going to be an issue.

MR. TAVE: Our next speaker is Berit Dockter.

MS. DOCKTER: Hi, everybody. Ms. Berit Dockter. I represent the International Food Additives Council. IFAC is (inaudible) association representing manufacturers and users of food ingredients including life microbiotics ingredients, cultures, and probiotics, and dietary supplements. Thank you for the opportunity to provide comments today and recommendations to work with IPA to share (inaudible - coughing) on behalf of our organizations.

Today I want to highlight a few of our points from a letter I faxed, submitted to FDA last month regarding the dietary supplement work. I've had supports (inaudible) the FDA's involving new ways of altering, alerting consumers to concerns regarding dietary supplements that contain potentially unsafe

ingredients. IFAC suggests that FDA be the only, about these specific producers and/or exact ingredients involved when an issue arises unless they can prove the issue is more broadly applicable.

In regards to the new dietary ingredient notifications promotions statement, IFAC has concerns regarding the use of the term exclusivity for dietary supplements. We believe this (inaudible) applicable to drug manufacturers where (inaudible) is required for the introduction of new products into the marketplace which is not (inaudible) for dietary supplements.

Regarding the safety of ingredients on a permitted list, IFAC would like to restate our recommendation provided launch letter to FDA to use the existing FDA food master file system to develop a similar process for live microbial dietary ingredients and probiotics.

We strongly support FDA permission for dietary supplement manufacturers to label the quantity of probiotics in their products in calling for unit, CFUs, a more scientifically appropriate measurement of

viability regarding to our letter on CMU labeling submitted to the docket.

We would also like FDA to be aware of California Assembly Bill 1178 which was referred to by the Senate Health Committee this month and would require GMP labeling at the state level. IFAC encourages FDA to consider a national regulatory change on this topic since the issue is being raised by states.

In regards to the modification of DSHEA, IFAC is concerned that changing the law would require an act of congress, which may be difficult or unlikely. So we seek clarification from the FDA if there are non-legislative changes that could be made to DSHEA.

We also would like to remind FDA of our letter submitted to the docket on February 27th, this year, regarding annulment of a pre-DSHEA exact ingredient database.

In summary, IFAC strongly supports the work of a dietary supplement working group and we're glad that it will continue under Acting Commissioner

Sharpless. So I'm happy to answer any questions.

MR. TAVE: Thank you very much. And we'll have time for people to ask questions after we're done. We appreciate the offer. Harry Rice is next on the list.

MR. RICE: My name is Harry Rice. I'm from Global Organization for EPA and DHA (GOED), which represents the worldwide industry for the Omega 3 fatty acids, EPA and DHA. GOED is interested in ensuring that consumers continue to have access to safe, high quality EPA and DHA rich ingredients. That said, GOED thanks the Agency for the opportunity to provide public comments concerning responsible innovation in dietary supplements.

While the market for EPA and DHA rich dietary supplements does explode on the passage of DSHEA in 1994, the first fish oil, cod liver oil, in Wisconsin (inaudible) was launched in 1790 of the United States and continues to be marketed; thus representing what GOED believes to be the oldest continuously marketed dietary supplement in the US.

In addition to cod liver oil, prior to

October 15, 1994 multiple forms of fish oil was launched, including fish body oil concentrates, both ethyl esters and (inaudible) triglycerides in salmon oil. In common to all passage of the (inaudible) is it that the primary composition of EPA, DHA to make sure it monitor fatty acids.

GOED believes the major sources of EPA and DHA ingredients including concentrates are being lawfully sold since they were marketed as dietary ingredients prior to October 15, 1994. To support this position, GOED has a considerable amount of documentation including, but not limited to, patents, (inaudible) press articles, advertisements, labels, peer-reviewed scientific articles, and information from the NIH and biomedical fish oil test materials program from the '80s and '90s.

For years EPA and DHA rich ingredients have been sourced from multiple organisms and species. Since the FDA issued its final rule on June 5, 1997 affirming the hidden oil generally recognized the same with limitations on maximum use levels (inaudible - coughing) categories in order to ensure the daily

intakes of EPA and DHA did not exceed 3 gm per day. EPA and DHA are considered valuable components from which these oils are standardized.

The products are principally comprised of EPA, DHA in a mixture of fatty acids. Subsequent to the final rule, more than ten companies (inaudible) marketing fish oils for addition to food have received letters of no objection from the FDA despite minor differences among the oils of fatty acid composition, FDA (inaudible) no potential safety issues (inaudible) intake EPA and DHA would not exceed 3 gm per day. From a whole food perceptive, consider the single serving of salmon, today's (inaudible) EPA, DHA (inaudible) fatty acids, (inaudible) fish oil supplements on the market today.

Over the years innovation has resulted in manufacturing changes to make the same or similar products on the market, but such changes should not be altered in NDI. These manufacturing changes should be addressed on a final rule for current manufacturing practice, the manufacture packaging, labelling, or holding operations for dietary supplements.

GOED believes the focus should be on whether or not the change to the manufacturing process alters the safety profile or identity of the ingredient do not be specific to manufacturing changes (inaudible). After all, the principal ingredient (inaudible) omega 3 fish oil with prominent fatty acids being EPA and DHA, along with a mixture of minor fatty acids. That's all I have. Thank you.

MR. TAVE: Thank you. Our next speaker is Mark LeDoux.

MR. LEDOUX: You want me to go up there?

MR. TAVE: Yeah, if you wouldn't mind 'cause because (inaudible).

MR. LEDOUX: Good afternoon, everyone. My name is Mark LeDoux. I'm the chairman of the board of Natural Alternatives International, as well as the Natural Products Association.

First of all, I want to thank the Office of Dietary Supplements for hosting this meeting, including my old friends Cara and Steve, and Mr. Durkin, who is not here today. Nice to see you as well, Sybil and Laura, and it's great working with you

guys.

I'm, I'm standing here because I want to encourage companies to do the right thing. Our firm spent million of dollars and went through the front door of the FDA and we brought in our dossiers and we had our meetings, and we had our pre-meetings and we had our subsequent meetings. This is not a difficult process to do the right thing.

Filing an NDI notification should not be considered too difficult; however, spending those kinds of resources as either a private or public company begs the question we're a good citizen, now what.

So by helping the government do its job, which is to promote the safety of consumer products in our space, we're looking at ways to work together with the Agency to arrest those products that are in commerce that I believe are deficient in not only scope, content, but are, in fact, per se, adulterated because they have not gone through the font door of the FDA. They have not spent their money. They have not identified the toxicological implications or the

pharmacological significances of their particular products.

They are unwilling or unable to address issues such as diet problems such gave rise to altered DeFang in that fiasco in 1989. So what I'm suggesting is that there have been some great ideas shared here today. One is the master file concept. The other which needs to be addressed quite frankly is more alerts and (inaudible).

My company was started in 1980 by me. I am telling you right now there are many companies like mine that are willing to pay the FDA user fees to enforce the law, which means identifying products that are in the marketplace that are clearly adulterated per se under statute and either make it very difficult for them to enter the United States by eliciting the service of the customs officers and officials at the ports of entry, or by subsequent post-market surveillance when we provide to you lists of companies that are abusing the privilege of our efforts.

Recently your office has sent out, I believe, eight warning letters to different companies

involving DMHA, which I believe is appropriately identified by you as an illegal substance without adequate NDI work.

It's interesting to note that most, the majority of those products were also combined with beta-alanine not Pearson beta-alanine, which has NDI No. 1103, but just beta-alanine. So we've asked counsel to send them information to say, oh, by the way, not only is DMHA not appropriate, we feel that you're abusing the privilege even further by placing generic beta-alanine in inferior products under the guise that somehow the work that NAI has done with 55 clinical studies, not to mention appropriate pharmacologic data and toxicology profiles, you are free-riding on our efforts.

That's got to stop. So responsible industry is willing to work with you at the Agency level the fix this mess, but you have got to think about private industry getting a return on investment for doing the right thing. We're here partnering with you. We're here to support you.

One of the reasons you have an Office of

Dietary Supplements is because of the efforts of myself, Steve Mister, and many of the colleagues in this room, Dan Fabricant, and listed in the halls of congress to get you out of the watercooler and into a bona fide office.

So we believe in what you're doing. We are just encouraging you take some risks, go further. Start making it difficult for miscreants to prosper based upon work of solid citizens in our industry. And I thank you for this opportunity.

(APPLAUSE.)

MR. TAVE: Thank you, Mark. Next is George Paraskevakos.

MR. PARASKEVAKOS: Good afternoon, again. I'm George Paraskevakos, the director of the from International Probiotics Association. On behalf of our 110 member companies (inaudible - off mic) thank FDA for holding this important meeting and for allowing the IP the opportunity to present.

As discussed earlier today, probiotics have been part of people's diets around the world for centuries. Their common ingredients in dietary

supplements in the United States prior to the passage of DSHEA, they're one of the most (inaudible) categories of dietary ingredients from safety to health (inaudible - coughing) consumer's desires to supplement their diets with probiotics is undeniable.

As a general matter, IPA believes that while perhaps not perfect, DSHEA and FDA's regulations implement DSHEA have been and continue to be workable and effective, legal and regulatory framework to ensure that consumers have access to probiotics that are safe and effective dietary ingredients. But it's not perfect.

One probiotics (inaudible) regulatory requirement with the amount (inaudible) ingredients in a dietary supplement be declared (inaudible). As discussed (inaudible) petition (inaudible) vitamins, minerals and other categories of dietary ingredients, a way to provide a supplement and not provide consumers with useful information. In general (inaudible - coughing) a particular exceptions like cold culturing for probiotics.

Labeling the quantity of probiotics is

that there's something (inaudible) in terms of (inaudible) provides consumers with relevant information (inaudible). While we appreciate the FDA's willingness to allow (inaudible) in addition to milligrams, such dual labeling can be effectively challenging.

Of course the issue of what ingredients you require for the submission of (inaudible) notification is also very complicated and we appreciate the FDA's continued efforts to clarify that (inaudible). Along those lines, a qualitative list of the ingredients including probiotics would be extremely useful.

Similarly, as discussed earlier, the master file system is extremely useful as well to make, to make the process more efficient and effective. We appreciate the steps that FDA has taken (inaudible) exploring what a master file (inaudible) and we look forward to working with the FDA to make (inaudible).

In conclusion, IPA supports the work of the dietary supplement working group and hopefully

will continue (inaudible). We look forward to (inaudible) collaborating (inaudible). Thank you.

(APPLAUSE.)

MS. MacCLEERY: Laura MacCleery, Center of Science in the Public Interest. I think the really good news today is that I feel there's been a real shift since the last public meeting in terms of specific proposals to be put on the table to address some of the major issues facing the dietary supplement industry.

CSPI has a long concern about issues in this industry. We care most, first and foremost about safety and ensuring that consumers are not facing particularly acute or even chronic risks with regular consumption of dietary supplements (inaudible) the guidance again (inaudible) drugs out to consumers.

And we also care about efficacy. We haven't talked much about claims today, but we do see that there are (inaudible) disease and treatment claims being made in the dietary supplement marketplace. These tend to exploit vulnerabilities of consumers. So the additional ones like opioid

cessation addiction, or tobacco cessation addiction.

And the real tragedy there is that consumers come to these products with their best intentions and these are ineffective. And so they may blame themselves for the failure for them to, to get rid of their addiction even though it's the product that's actually failed them.

We see the same problems with weight loss supplements, for example, as a whole category and there are being additional problems, but these often contain drugs. And so we think in addition the proposals that have come to the table, FDA should have mandatory vehicles for the (inaudible) containing unapproved drugs. Right now those are classified as drugs and so therefore (inaudible) ironically.

So I, I also think that we've identified a number of really important low hanging fruit on the ground type proposals that we can all get behind, including product listing and registration with some teeth behind it. So failure to list a product, it actually renders the product illegal. And that will create obviously visibility for the Agency.

I think we would be in favor of closing the GRAS loophole not only because we are, you know, skeptical about the value of GRAS as a mechanism assuring consumers of safety and the (inaudible) for consumer trust. But also because that would assure that the mechanism that was designed in DSHEA to provide visibility on dietary supplements, which is the NDI mechanism, would actually do its job.

Then we would love to see specific oversight in a, in a more constituted way of high risk categories of supplements so we know that there are protein with drugs where they are targeting particularly vulnerable groups of consumers like infants or people with addictions where we know that there is a history of contamination or susceptibility to adulteration.

So those, those product classes (inaudible) high risk could be subjected to some third party system of audits and I think that would be preferable to trying to propose to roll back the clock in DSHEA and say everything needs pre-market testing. We know where the problems are and we could just

target with FDA's discretion our own high risk categories (inaudible) nation.

We also think there could be some improvements on product labeling including changes to the clarity and comments of disclaimers, warning labels pertaining to drug interactions, and then a 1-800 number for consumers to directly report adverse events to the FDA, which would be a lot more transparency than we currently have around adverse events and supplements.

And then mandatory reporting of all adverse events like we have on the medical device side so that FDA can really see what's going on in the marketplace and its not the manufacturers that are deciding what's serious or not serious in terms of reportable events.

Then we also agree with (inaudible) FDA needs more resources. We'd certainly be in favor of user fees or some other mechanism to naturally quadruple or quintuple the budget of ODSP regardless of what the budget was for Health Canada, and that's just a premarket side, but it's already three times

the ODSP's budget. We've been working with (inaudible) to double the budget to ten million for this year for ODSP (inaudible).

And then lastly I think we're not opposed to a master file particularly if it was part of the package that included all these additional (inaudible) preventions for consumers. I think that's an idea that incentivizes more research on safety is worth exploring. So that's what I have. Thank you.

(APPLAUSE.)

MR. TAVE: Thank you, Laura. There's no objection between that, but you went a little bit overtime, but I didn't want to interrupt you while you were talking about the (inaudible - laughter). Next we have Daniel Gastelu, but I think Mr. Gastelu may have left. If he's not here, then we'll move on to Bonnie Patten.

MS. PATTEN: Good afternoon. My name is Bonnie Patten and I'm with Truth in Advertising. Thank you for the opportunity to provide comment today on behalf of TINA.org. We are a nonprofit consumer advocacy group that works to out stuff and prevent

deceptive marketing. While we focus on advertising of all kinds and in all sectors of the economy, we pay particular attention to the marketing of supplements.

From autism to Alzheimer's, Ebola to epilepsy, there is a supplement that is being marketed to cure, treat, mitigate or prevent almost any disease we can think of. On our website, TINA.org, we currently have more than 3,000 examples of companies and marketers promoting supplements with inappropriate disease treatment claims. With the marketing hype surrounding CBD, a growing scepticism and distrust of the medical establishment and the rise of the wellness industry to (inaudible) right (inaudible), there can be no doubt that deceptive and misleading marketing of supplements is a problem that's only going to get worse.

Given this growing problem, TINA.org appreciates the FDA's focus on the issues before us today. The unfortunate reality, however, is that the FDA will never be able to eradicate all of the deceptive product including use of (inaudible) supplements. As such, we would urge the Agency to

take (inaudible) where consumer harm is greatest.

By way of example while (inaudible) the FDA's work with regard to brain health supplements, more needs to be done. One in three people over 70 suffer from some form of memory loss and a new poll indicates that nearly 75% of adults report engaging in some kind of activity to help with dementia, including taking supplements.

Of the countless memory supplements on the market, one stands alone on the industry's self-proclaimed leader, Prevagen. It first became available to consumers in 2007 and has since sold these pills to hundreds of thousands of aging Americans. This product is available in more than 40,000 stores across the nation with more than 2 millions bottles sold to date.

In TV commercials and on its label, Prevagen promises to improve memory despite the fact the experts in the field have concluded that it is biologically inconceivable that a protein taken by mouth would have any effect on memory. As I'm sure this panel knows, Prevagen is no stranger to the FDA.

In 2007 after an NDIN was submitted, the FDA said it had significant concerns regarding the safety of the ingredient and it reiterated those concerns in July of 2012.

In October 2012, this Agency sent a warning letter to the makers of Prevagen indicating that not only was the product marketed as an unapproved new drug, but the sole ingredient in the product, synthetically produced apoaequorin, did not meet the definition of a dietary ingredient such that Prevagen could not be marketed as a dietary supplement. And yet seven years later the company continues to market Prevagen as a supplement that improves memory.

It is critical that more be done to rein in supplement companies that use inappropriate disease treatment claims to take advantage of susceptible populations like the elderly. Tina.org thanks the FDA for its efforts to date and looks forward to working with the Agency to help ensure development can be done (inaudible). Thank you.

(APPLAUSE.)

MR. TAVE: Thank you very much, Bonnie. Our next speaker is Dan Fabricant.

MR. FABRICANT: Thank you for having me. National Products Association. Thank you for the time, time to make a few comments. We recognize (inaudible) important and it's a set for FDA box to check in getting out the final guidance or the draft guidance, whichever the Agency would have to pursue.

But with that said, I'm reminded of an important part of regulation 21 CFR 10.115, good guidance practices where it says that FDA will (inaudible) would have to follow up guidance standards and simply (inaudible). While guidance is incredibly important, the statutes makes it more important (inaudible) here today.

There is (inaudible) makes (inaudible) relatively simply, especially as resources or (inaudible) resource by itself. We look forward to having those discussions first and foremost (inaudible) discussions on guidance and things like that that are not (inaudible) where the statute is. Thank you.

(APPLAUSE.)

MR. TAVE: Charles Jolly is our next speaker.

MR. JOLLY: Thank you, Dan. Charles Jolly. Thank you. I want to thank you for the opportunity to participate in this important discussion. I'm going to try not to go over time, but I will talk about resources (inaudible) in developing countries. I'm Charles Jolly. I'm an attorney with the Baltimore office of Baker Donelson Bearman Caldwell & Berkowitz.

I spent my entire career of more than 50 years working in food and drug law matters. It has been my privilege over that period of time to advise and represent some of the most iconic and well known dietary supplements ever offered in this country. So I'm not sure whether I'm here as a public commentator or historian, but I do wish to warn you that I'm not speaking today on behalf of my clients or even for my firm. Rather I'm going to offer a personal perspective and offer some suggestions for making contributions to a business that makes an important

contribution to public health and wellbeing.

The, there's been a common theme today and I think the common theme is enforcement resources. And Mark LeDoux commented -- I don’t know Mark. I've just heard him for the first time, really struck a cord with me, but I, in thinking about this over the more than 50 years that I've been practicing, I have given some thought to why the FDA is so under resourced in the area of dietary supplements and what possibly could be done about it.

There is a policy which is part of the 1938 act, which is the core of, of, you know, the statute that we all follow that prohibits private rights of enforcement of the food and drug in (inaudible). And in 1938 when that statute was adopted, there were good and sufficient reasons for that. Remember in 1938 -- and no, I wasn't practicing in 1938 -- that came a little later -- the, there was concern that if there was a private right to enforce federal food and drug (inaudible), you would wind up with a hodgepodge of inconsistent decisions around the country. There would be burdens on discovery that

would prevent FDA from doing its job and, you know, and on balance, that policy has served the country well.

As you know, Peter Hutt and the commissioner put in the OTC review in 1971. Now almost 50 years later we're still not quite done with all that process, but a huge part of what, what is the administrative burden of the Agency in 1938 is now in a different posture. The no private right to enforce model works best if FDA has premarket approval. And in a context where we're talking about dietary supplements, and I was parenthetically the same concept applies to monograph drugs, the Agency is really dependent on the regulated industry self-execution against known and public standards.

This is not a serious process. Law firms like Baker Donelson are asked every day to assess a particular set of facts and circumstances regarding ingredients, claims, training, procedures, processors for products that are not subject to premarket approval. And we do, I think on balance, a pretty good job of advising our clients as to what the

factors are for compliance.

The fabric of self-regulation for these products which so much depend on the determination of the regulated industry depends on FDA's actually being predictable, consistent, and uniformly applied. In fact, we look at the Code of Federal Regulation, we look at administrative practices, look at the statute, and yet scarcely a month goes by when I have had a dietary supplement marketing manager come to me saying so and so is doing this and you told me I couldn't.

And the problem is there really isn't any recourse. Now, yes, I can send a letter to FDA or, yes, I can pick up the phone and call, but it is on balance a non-satisfactory system. And in many cases I have to say because dietary supplements are largely safe products, there's not a huge overhang of public health concern which mandates, you know, an immediate alarm.

And so the frustration of the regulated industry, and I would distinguish myself from Scott Bass a little bit, to there is no one profile for the regulated industry. There are careful, precise

factors, and there are wild, wild west (inaudible). And if the industry doesn’t have one profile; however, the responsible members of the dietary supplement industry really want double lines where it's no pasture. They want solid fences. They want solid rules and understandings.

So I come to the question of what could be done to look to, to find more compliance in the industry. And my, my answer is one that is somewhat familiar to HHS and that is the Qui Tam lawsuit. Under the Qui Tam theory, the complainants were able to put the HHS on notice that there is a violation and allow the Agency to taken over the case if it has the sort of merit that the Agency thinks deserves it, or they can leave it to private litigants to, to go ahead.

I am not suggesting an abandonment of the no private rights of enforcement by FDA either for NDIs or for new drugs or in general. Rather I am suggesting that there be an appropriately structured private enforcement permitted for qualified stakeholders in the dietary supplement community, and

I think it would do wonders to enhance good product law.

MR. TAVE: Mr. Jolly, I'm sorry to cut you off, but you're well over time. I do hope you'll submit written comments of your full thoughts.

MR. JOLLY: I shall.

MR. TAVE: Thank you very much. Mark Miller will be next.

MR. MILLER: On behalf of three minutes. I just want to follow up on a question I really posed earlier about stimulating research because for such data, it will give you information, it will give you familiarity, it'll give you context, and they're all good things. And what can we do to stimulate research in this industry that will help everybody share information and improve consumer responses? And I think we kind of struggled with that a little bit earlier when I kind of posed it, but I think there is an answer here today. But it may not be terribly helpful, but I'm going to pose it anyway.

I really was enthusiastic and, and, and tickled to see that you invited our colleagues from

the north, Canada, who reviewed what was happening with our industry for ten years and designed their own system, and included in that system is a reward for research that you can get albeit being somewhat tepid, but you can get some claims associated with a study or research effort that you've done.

So the question is even though it's very difficult under the current regulations, there is an attractiveness to encourage more research and collection of information by giving a reward at the end and that is about validated structure of function (inaudible).

MR. TAVE: Thank you very much. Mark Blumenthal, you're next.

MR. BLUMENTHAL: Howdy. Good afternoon, everybody. I'm Mark Blumenthal, founder and executive director of the American Botanical Council. I want to thank the Agency, my good friends here, of course, for putting on this event and for allowing me to take a few moments to offer comments.

The American Botanical Council is an independent, broad research organization 30 years old.

We're a science organization with members in 80 countries, which 3,000 or so members, Canada. So we have a global perspective on what's going on in research and education, quality control of dietary supplement industry, the herbal medicine industry, etc., and the communities that use these products.

About nine years ago we started a new project called the botanical adulteration prevention program out of our concern about what appears to be rising incidents of the attachment of adulteration of various botanical products, herbs, botanical materials, extracts, essential oils, etc. I'm not just talking about technical adulteration we referred to earlier back to items not having -- actual adulteration where the identity of these materials have been altered for fraudulent purposes by the seller or the reseller in a nondisclosed manner according to USP definition of adulteration.

Our program has over 200 supporters over the last nine years and support our work in this area, and we've published over 50 peer-reviewed publications identifying adulteration problems and dealing with

analytical methods to determine the fitness for purpose and the robustness of various analytical methods dealing with technical adulteration, and to help guide industry and regulatory, laboratory as to which analytical methods are appropriate.

We're finding out that more people seem to be concerned about this and we're grateful for that concern. We're grateful for all the partners and other stakeholders who help promote the information that we are putting out so that we can try to reduce or hopefully element, maybe idealistic, the idea of these type of adulterations going on in the world. We know that the, the GMPs prohibit the use of ingredients without specification, but for regulations they're silent on guidance for disposition of materials.

So consequently we come up with a best practice SOP for the disposal and destruction of what we call irreparably defective materials and my friends and colleagues in the room have already heard to discuss this (inaudible) as we put this out for public comment previously. We're concerned that when

companies reject irreparably defect materials, it goes back into supply and it gets rerouted somehow back into the supply chain. And that we believe is unacceptable.

And we believe we have a self-regulatory mechanism that can reduce any burdens that might be on the Agency and its resources that need to go into enforcement, but we believe that responsible, honest, ethical members of the herb and dietary supplement industries, of which there are many, many of whom have already come forward and endorsed and/or supported our draft proposal on this matter.

There are many companies that are willing to do what it takes, which includes if they, even if they qualify their supplier, they still receive what they consider to be irreparably defective material, as in our articles as we defined it under the SOP, which is something that is adulterated beyond mediation or reconditioning, contaminated beyond remediation, or contains illegal ingredients.

Those would be the factors that make for an irreparably defective article. Those should kept

under quarantine, they should be tested by an appropriate third party laboratory, by appropriate validated and with valid scientific methods, and then that material should be disposed of or destroyed by a qualified third party that is experienced in this matter.

We have also draft contract language for suppliers that industry members can require as a priority stipulation that in order to supply them with any kind of botanical or other kind of material, that the supplier must agree to this contract claims so you have an agreement between the two that if there's a problem like, and there's the detection of irreparably defective materials, that this material can be destroyed. The supplier doesn't get their money back. They don’t get their material back. They have to pay for the extra testing. They have to pay for the destruction or the disposal and doesn’t require anything (inaudible - sneezing). So it's really based on a contract agreement.

We put this information out in public comment. ABAC members, past members, that was the

acronym for our botanical adulteration prevention program. In the fall of this last year we received 106 what we consider substantial comments. By the end of this month we hope to have all the documents revised with those comments and responses to those comments including a new document of FAQs, which has all of the 106 comments listed and how we resolved them and/or revised the language of the contract language and of the SOP and response to the comments.

So we're doing this is an extremely transparent and open manner so that anybody can see this. After this review and revision of our legal community and voluntary attorneys from the industry who review it, and then at that point we'll determine whether we want to put it out as a proposal final or put it out for review again from stakeholders to see how they can review the revised version before I finally (inaudible).

Again, this is being driven by and supported by responsible elements in this community, responsible health industry, including suppliers and manufacturers. Ironically, it's those companies that

probably least have to ever resort to use of this SOB because responsible suppliers test their material before they ship it as they're supposed to do so they're not shipping bad material, irreparably defective material. And responsible manufacturers have robust quality control systems and also properly and adequately qualified as suppliers.

So these are the companies that are the least likely to have to use this SOB and they're the ones that are supporting us. We welcome the Agency's input in this matter. We welcome anybody else's input that's interested in this because we believe that we can help increase consumer confidence in this area, as well as industry and other component stakeholders including health professionals and researchers if the industry fully adopts this SOB and basically does it on a self-regulatory basis. Thank you for your time.

(APPLAUSE.)

MR. TAVE: Thank you, Mark. (Inaudible.) So Daniel Wang is our next speaker.

MR. WANG: Can you hear me? I'm Daniel Wang, CMU associate, and associates for science-based

consulting (inaudible) pharmaceutical and consumer health companies all the time (inaudible) development and (inaudible) assessments of (inaudible) drugs and other products. We also advise the dietary supplement industry on (inaudible) filings and the (inaudible) guidance association. (Inaudible) input into my comments today or (inaudible) meeting. And we'll be submitting more written comments later as well.

So as we've heard today, millions of people use dietary products every day in order to support their health and wellbeing. Globalization seems to be introducing us to more and more of these (inaudible). Many consumers find these products to be helpful (inaudible) and in some cases with few or less destructive side effects (inaudible). However, the products that affect how people feel and function, (inaudible) CNS effects, are a particular challenge to regulate.

With that (inaudible) understanding of mental health (inaudible) use of these products for health and wellbeing and attributing to disease (inaudible). FDA's evaluations of CNS drugs can

impact scheduling status, which in turn can drastically affect consumer and patient access.

FDA has suggested that drugs with consultation activity undergo abuse potential evaluations. How does this inform how FDA will evaluate CNS active dietary products like (inaudible)? While there are limited data on the health effects and risk of these products, surveys suggest that millions of Americans use them similarly to other dietary products to treat minor aches and pains, dealing with energy, (inaudible).

For some (inaudible) a (inaudible) opioids. They find it to be effective and substantially easier to access than FDA approved treatments for their pain and mental health (inaudible). When regulating these product we urge FDA to focus on, of course, the risks, but also to their potential public health benefits. We also encourage FDA to be more active and communicate the Agency's approach to assessing the CNS effects of dietary ingredients, including what evidence to include in any item to support a product's safe use

and acceptable claims for CNS active dietary ingredients. All at the same time while recognizing a few companies are able to amass hundreds of millions of dollars required to develop their products (inaudible).

We believe that a perspective approach to policy making around dietary supplements, additional active engagement by FDA and with consumers and industry, and additional guidance by FDA can help to avert problems before they happen, and to ensure consumers get the information they need to guide (inaudible) sponsors crossing the often (inaudible).

MS. PAVLICK: (Inaudible - off mic.) But in an effort to support modernization and innovation in our industry and to allow continued access to safe, quality, compliant, and affordable dietary supplement products, UNPA members, investigator training should be addressed. Investigators are our first line and the filter to which responsible innovation is monitored. They must have an in depth understanding of DSHEA. They need to understand dietary supplement GMPS, and most

importantly with need data to understand our industry.

This month the Food and Safety Modernization Act has identified preventative controls role, and it does mention for a qualified auditor, qualified auditors and individuals with the appropriate background, training, education, and experience. If you continue to look at the definition (inaudible) you'll find a qualified individual not only has the education and training, background, and experience, but they also have specific training related to knowledge, background, and risks of the product for which there are working with. And food safety risks including (inaudible).

They also have to have standardized training using the standardized curriculum that's been developed by (inaudible) compliance. (Inaudible) comment we do not have the time to share with you the differences between a four day dietary supplement training compared to an approximate ten weeks of training received by a drug investigation. But after that time they're being qualified for the investigations to which they conduct.

In the times of limited resources in the FDA, we suggest that the FDA and responsible industry are allowed to collaborate with the FDA by people in the drug industry to provide additional technical there for the investigators.

We've heard a lot of discussion today about the need to enforce and to separate the good actors from the bad actors. Another constant refrain has been that FDA simply doesn't have resources it needs to focus and market the, to police the marketplace adequately. UNPA's devoted considerable resources toward ensuring quality manufacturing and we believe that there's a role for industry (inaudible) bolster FDA's work in this regard.

Let's work together to provide solutions, to ensure qualified auditors are conducting the audits, to provide consist audits with the same mission between industry and the FDA, which is to protect public health while allowing safe access and consumer choice to safe, quality, compliant, and scientifically based supplements. Thank you.

MR. TAVE: Thank you, Larisa.

(APPLAUSE.)

MR. TAVE: We'll hear now from Frank Jaksch.

MR. JAKSCH: Good afternoon. I'm Frank Jaksch, the cofounder of ChromaDex and (inaudible) present at this meeting. I'm here today with our CEO, Rob Fried, because we have transformed the science and chemistry company most of you have known for many years to become a consumer product dietary supplement company that does develop responsibly with innovation, science, and safety at our core.

Enforcement of dietary supplement regulations and their modernization is critical. ChromaDex like other innovative science-based companies we consider as peers supports NDI or the NDI notification process, at least about our products, champions the integrity of our industry, and most importantly protects consumer safety.

However, without enforcement the door is open for bad actors to ignore NDIs, to steal intellectual property from responsible companies who have made their science public through the process,

and then bring a product to market with limited substantiation or consumer safety protections.

By enforcing our current regulations, incentivizing clients, and modernizing policies, we could recognize a number of important benefits, such as IP protection, more robust science, enhanced consumer safety protections, intentional expanded health claims. Companies who invest in research and resources to developing their IP should be able to protect it.

The second step is to introduce to new incentives for compliance and investment and good science. For example, the same approach to the FDA use of drug companies who afford exclusivity rights could be applied to the dietary supplement industry. While the exclusivity rights have definitely been a hot topic or a hot word to be using around here, but one thing I'll comment on to assure you is if you can't find a way to incentivize companies to make an investment in science, then the NDI process, the number of NDI applications isn't going to go up; it's going to go down. It's going to go down probably

lower than the rate that you're seeing today.

This approach would not only provide intellectual property protections, but it would also incentive investment in science which would in turn elevate the integrity of the entire industry and we'd have companies (inaudible) substantiation for their projects. Consumers are looking for products that promote health, support their health and wellness, should be able to trust the market and the companies providing them with those options and the safety of what they're consuming.

And we should explore providing consumers with deeper understanding about benefits that are supported by sound, well-documented science. This would allow consumers to be better educated about the steps they can take today to improve the quality of their life.

The landscape has changed dramatically since DSHEA was written. The size of the industry is expanding and the speed in which supplements are brought to the market has, has been accelerating greatly. The sales channels are dynamic. The science

and business information is now conveniently available on the internet. Through strike enforcement of current regulations and modernization of DSHEA, responsible companies would be the norm, not the exception.

Our industry, it's our industry, it's our science, it's our health, it's our responsibility to protect them and by working together we can grow a thriving marketplace in which good science is rewarded, compliance is attractive, and public safety is protected. Thank you.

(APPLAUSE.)

MR. TAVE: Thank you very much, Frank. Jack Mitchell is next.

MR. MITCHELL: Good, good afternoon. I'm Jack Mitchell from the National Center of Healths Research, a nonprofit think tank which analyzes and researches identifications for public health patients and consumer safety. We strongly support FDA's recent efforts to crack down on manufacturers who make false or misleading claims about dietary supplement products. We were given a good example this morning

with supplements masquerading as legitimate opioid treatments.

Last fall a team from the California Department of Public Health concluded that there were unproven and sometimes dangerous drugs in almost 750 dietary supplements, most them marketed for sexual enhancement, weight loss, or muscle growth. Numerous representatives would respond it's not fair to compare these so-called fringe products to legitimate vitamins and other more conventional dietary supplements. (Inaudible) the public mind, these products are all part of the same family.

For it's own protection, the dietary supplement industry has made substantial progress in weeding out the bad actors since the so-called wild, wild west days of the advent of DSHEA in the 1990s. At that time I worked in the commissioner's office and my office conducted an investigation of the industry, responded to reported harm to consumers, and the gross underreporting of adverse events.

The senior FDA pathologist told me at the time that this substantial number of adverse

events reports made FDA regarding dietary supplements probably represented only 5 to 10% of the true number.

Nonetheless, there is substantial progress being made and I thank you for holding this meeting today. As the recently departed FDA Commissioner, Scott Gottlieb, told the New York Times in February people have (inaudible) framework to address this case in really decades. I think it's time we do so, close quote. The promise online, online watching this specific dietary supplement ingredients that the Agency was concerned about has recently been published and that's a good step forward.

However, there's a long and not always encouraging history involving the ingredients in dietary supplements and I'm here talking about safety, not innovation. In 1997 with the instruction of the then commissioner, I helped organize the Scientific Advisory Committee on the safety of the supplement ephedra, which was widely use in supplements. The committee after reviewing the evidence overwhelmingly voted there was no safe level of ephedra in these

products. Nevertheless, it took FDA seven years to remove or ban ephedra for these dietary supplement products.

And something that dangerous is not required to report serious adverse events to the FDA until 2007. The regulatory environment did not change substantially a dozen years later. In 2010, 16 years after the passage of the DSHEA law, I helped convene the senate committee oversight hearing which the DA identified numerous examples of misleading or false advertising by dietary supplement vendors. FDA also discovered phonetically hazardous contaminants in no less than 37 of the 40 products they tested.

The chief executive (inaudible) consumer lab (inaudible) and a former FDA official also testified that fully one quarter of 2,000 supplement products tested had a quality problem. The hearing concluded that senior citizens be especially vigilant about the potentially hazard interaction of dietary supplement ingredients with drugs they may be taking.

Again, certainly with this history there's been substantial progress over the last decade

or more and there are a lot of legitimate players here today who want to give safe, well-approved products to their customers, but unfortunately questionable marketing, phony claims with some phony control problems, fairly or not, are associated with some elements of this industry even after 20 plus years.

After a quarter century with the industry, it's a dozen times bigger than it is in 1994, the FDA still has to prove harm before regulatory actions taken (inaudible) industry. especially with, in this online age with limited control over both internet marketing and advertising such that FDA needs to move more quickly to keep up with the explosion of products and ingredients and claims made by suppliers in this industry.

The DSHEA law is now 25 years old and the Agency will struggle to keep up with the explosion of new ingredients, question of ingredients in the global marketplace. We need to all work together to better protect consumers and tighten oversight of this industry. The consumers include 50% of American consumers. Thank you for the opportunity to talk to

you.

(APPLAUSE.)

MR. TAVE: Thank you. (Inaudible.)

MR. MISTER: Good afternoon. My name is Steve Mister. I'm the president of the Council for Responsible Nutrition. I want to express my thanks first of all to FDA for hosting this dialogue and for the opportunity be here hear and present earlier today. And so these comments will respond on what we heard today and I'll try not to repeat Andrew's remarks from earlier this afternoon.

The question of whether an article is a dietary supplement is not a safety question, nor is it a question of whether an article is a new dietary ingredient, a safety question. Now whether or not it gets objected to because it's not safe, that is a safety question. But I think we'll get to safety, but we don’t need to let it color these other decisions that are inherently not safety decisions.

And as I said on Tuesday in another context, safety is always job one, but it isn't always the first job. And here I do realize that I sound, my

remarks sound a little similar to something I made, some comments I made on Tuesday regarding a certain three letter ingredient in it that I promise not to mention today.

But, you know, as I'm listening today, perhaps the issues that Scott Bass raised this morning, maybe it makes us wonder if this additional condition about adding nutritional value to the criteria was originally injected by those of FDA because of a distrust of the ability to be NPI and GMP provisions to address safety questions on their own.

And so there was this effort to interject safety into an earlier stage in the global market flow chart. I suggest that we use this moment to restart and determine what is the role of each step in the regulatory path to the market for old ingredients, the market for new ingredients, the pathway to market for synthetic ingredients and, yes, even for (inaudible). There, I said it.

So my message to FDA not unlike the Philadelphia 76ers is trust the process. You will get to safety and when you do, that evaluation should

absolutely be a robust one, but for companies to invest in safety they have to know there is a pathway to market and that the ingredient is a viable one. They have to know that their investments will be protected. And these issues need to be resolved first in order to incentivize the kinds of investments in safety that FDA wants.

Even if the (inaudible) synthetics, we've heard some interesting questions today about whether it's going to (inaudible) whether it's bioequivalent, again, a synthetic ingredient fit within the six categories in the law. If it can, then a synthetic copy of a botanical constituent is definitely a dietary ingredient as much as a synthetic vitamin is a vitamin. And at that point the Agency can and should demand an NDI notification and a full demonstration that that particular ingredient is reasonably expected to be safe. And then we'll let the chips fall where they may. But you have get to that point first.

The second point I want to make is regarding the NDI guidance process. I think we can

also use this as a moment for clarity because it's taken far too long to resolve. And if FDA believes that there are deficiencies in the statutory provision for NDIs, then maybe this is the time to have that conversation with the industry and see if we can address it through legislation and clarifying the expectations. But we need, need to move to a period of certainty and predicability if we want to foster innovation and investment in the industry.

And then the last thing I will say, we'll underscore something that Andrew mentioned earlier, and that's enforcement. Whatever we do, there needs to be meaningful enforcement, enforcement, enforcement. We can't say that enough. I note that FDA is quick to lament that the NDI process is, quote, "the only method by which to evaluate the safety of new ingredient before they get to market" and often that's made to sound like it's a hindrance to the Agency that it's the only way they can monitor safety.

But at the same time I note that the FDA is typically unwilling or unable to use the robust tools that were given to it with the NDI provision to

go after companies that blatantly violate it.

Any successful effort in this area requires enforcement, enforcement, enforcement. Thank you.

(APPLAUSE.)

MR. TAVE: Thank you, Steve. Robin Marles.

MR. MARLES: Hi. I'm Robin Marles. I'm the volunteer chair of the USP Botanical Dietary Supplement (inaudible) medicine expert committee along with my colleague, Dennis (inaudible) chair of the (inaudible). We have a team of about 40 international experts working on all of the issues around dietary supplements and setting monographs that have legal standing in the USP. However, I also wear another hat. I am an employee of Health Canada where I'm a senior scientific advisor and a food director at advising on the addition of dietary supplement ingredients to foods, and prior to that I worked in the group that (inaudible) now chairs as the science on writing the NHG regulations. So I'm very familiar with how we worded the definition for a synthetic.

We also wrote in mandatory compliance with pharmacal standards for quality of which USP is one of our key sources. So the irony here is that in Canada USP quality standards are mandatory along with European (inaudible) choose, while being less, they're voluntary.

So in terms of innovation, what I'd like to suggest is a much greater focus on the quality of when you look at adverse reactions. Most adverse reactions to dietary supplements are due to issues of quality, whether it is identity, purity, strength, accidental contamination, or deliberate adulteration.

And in terms of rewarding industry for being complaint with a reliable source such as the monograph, which are harmonized to a very large extent of those of Europe and other countries as well, which facilitates international trade. But if you were then able to link that quality assurance to targeted FDA verification and link that to the number on the label, you would then greatly increase the consumer's comfort in using products if they were assured it had the quality and that creates fertile ground for innovation

when consumers really can have some confidence in the products there.

Now we've people express concerns about the challenges with implementing numbers on labels and as you heard from my colleague (inaudible) earlier, the Health Canada way to do that using a very simple electronic system for registering products. We've also looked at the Australian therapeutic foods administration's electric listing facility, the (inaudible) which is also very efficient.

So it's not actually a difficult thing to achieve. And then with the licensed natural health products database, there is a public listing of all those numbers so that consumers can actually check because, of course, when you have a mandatory number on the label, there are people who will fit those numbers. But by posting the list, this then makes it easy to verify.

And so you have the opportunities for increasing consumer confidence in high quality products which will resolve a lot of the adverse reaction issues and you also have a chance to become

more harmonized with other country's systems. And I'm sure my colleagues, (inaudible) and I will be happy to provide any advise or assistance in seeing how our system works, learning from our mistakes, and making your system better. Thank you.

MR. TAVE: Thank you, Robin.

(APPLAUSE.)

MR. TAVE: Karen Howard.

MS. HOWARD: Good afternoon. I'm Karen Howard, CEO of Organic and Natural Health Association. We're a unique trades association representing the interest of health-minded consumers and the best companies in the dietary supplement chain. Our tenets are really supper demand for access to the safest and highest quality products available, a demand our industry members subscribe (inaudible).

Even with an amazing safety record, I believe statistically it's more dangerous to eat foods or fill your prescriptions. Opportunity still exists for bad actors who sell inferior or dangerous products to unsuspecting buyers. Or in the lab (inaudible) resources to fund enforcement against most egregious

players that sell products online, in gas stations, in convenient stores, (inaudible) weight loss, energy or sexual performance. They cause the most harm. Let's fully fund the effort to clean our house with the laws we have.

Second, we see through innovation and modernization there is an intellectual flaw in the definition of health claims, vis-a-viv structure function claims, most also be addressed. Dietary supplements are, in fact, a category with no change in definition (inaudible) supplement and pharmaceuticals. However, it is far too easy to create a new disease. Osteoarthritis, the result of wear and tear on our joints, is a condition that will impact virtually everyone in this room as they naturally age, yet this categorizes disease in a supplement that may reduce their pain of this malady can only tend to support bone and joint health.

Circuitous label claims achieve technical compliance, but keep customers confused. With regard to health claims, existing regulation chokes often even science to document how

supplementation can reduce the incidents of disease. For instance, the FDA (inaudible) formal petition to allow health claims, saying that increased vitamin D serum levels reduces the risk of preterm birth by 60%. By the way, the Agency's response was that as an indicator of vitamin D status, serum levels do not meet the definition of substance. Serum levels are not found, are not food or components of food.

Given the strength of the research undertaken with the Medical University of South Carolina, it leaves one curious and then outraged to contemplate how existing regulations exclude health claims about the correlation of well-established nutrient levels with a well-defined health status.

Fundamentally it is not sufficient or accurate to define a supplement simply as a dietary substance produced by man or pregnant woman to supplement the diet by increasing the total dietary intake. This definition needs to be updated and modernized.

Lastly, dietary ingredients produce using genetic engineering and novel methods of

synthetic biology should be evaluated as new dietary ingredients even when similar natural ingredients exist. If in addition to designs of process of creating novel compounds and formulating products with them, then full disclosure through the entirety of the supply chain must be required as part of the regulatory process.

Anything less than 100% transparency completely fails consumer's desires and expectations. This misstep can potentially instill consumer distrust in a helpful category of dietary supplement ingredients, just as we have seen happen in food products. Lesson learned.

Any dietary supplement company that's confident in its products and respectful of its customers will not object to full, honest disclosure of how its products are made. Thank you for this opportunity.

(APPLAUSE.)

MR. TAVE: Thank you. Bernie Landes? Not here. And our next speaker and our final speaker for today is Kevin Bell.

MR. BELL: You know, (inaudible) I I think the guy between you guys in a bar would be a problem. So I'll try to keep this brief. I am (inaudible) my practice as primary (inaudible) litigation and regulatory enforcement. I'd like to thank the FDA (inaudible) fantastic. (Inaudible) equivalent of facing your accuser, your constitutional right, but I appreciate it, especially their existence in managing my procrastination (inaudible).

In February (inaudible) used the phrase idiotic within about ten words of IP. I got very interested because I do view NDI as the equivalent of some form of an IP right to proved the intellectual property protection (inaudible) exclusive protection (inaudible) use, but it really is almost the equivalent of what you would see when you file for a patent or for a trademark.

It gives you a period of exclusivity or a right to exclude others absent a license for a period of time and you dedicated that to the public. That's a patent issue. Trademarks can last longer. I do know this. Eighty percent of this discussion today

has been about enforcement and I think 100% of people agree that, maybe not 100, but pretty close, but if you do not have NDI for something, you run the risk of having a technical adulteration of the food, drug or cosmetic. Whether calling it a misdemeanor or a felony, it's a violation of the law.

And so when I hear about all of the things that need to be done to afford enforcement, I see a much more simple path on this that doesn't have to involve researches by the FDA. I think you should always have more money of researchers. But I don’t think it's something that we have to spend a lot of time on as far as what can be done to move forward with enforcement without the FDA having to do it themselves through the Department of Justice.

I think there are opportunities where if the AKL letter that you receive on NDIN from the FDA, which is a government document, is treated as equivalent as when someone gets a patent issued by the Commissioner of Patents or the patent office, that is a government document and has a presumption of validity to it.

The patent office doesn't go out through DOJ and enforce patents. People who own them do. Mr. LeDoux's remarks if you stifle that opportunity, you will see a decline in those filings because there is no market benefit even at this point. When you go to try to say, hey, I have an issue don't have a problem, the response is but the FDA's not going to come after me.

And so it should never be about whether someone only stole a VCR or also stole the jewelry, or killed someone in the process, to be a misdemeanor to a felony, the size of the crime or the adulteration should not be the decision. If it violates the Food and Drug Cosmetic Act, it violates the Food and Drug and Cosmetic Act. That's it. And we don't need the FDA, in my opinion, to have to go out and do that enforcement on behalf of the people that own NDIs.

That document should be enough. I have one; you don't. I'll go deal with it and the FDA doesn't have to wade in on it. I'm want to hear about what the attack would be on ingredients and whether an old dietary ingredient, that is the equivalent in

patent law of a prior (inaudible). We file patent cases all the time and end up in the world of somebody finding a doctoral thesis from a Russian institute from 1949 that says I did this before you. All right? I can tell everyone in this room if they saw one of their products, someone, someone using something that wasn't theirs, but had their trademark or their logo or their symbols on it, it would incense them beyond belief.

And so I believe NDIs need to be treated the same way. If they are not, they will be treated just like patent and trademarks are when they are not enforced. People will steal; people will knockoff. It that's, it is that simple. I believe the mechanisms then for how do you do it, certainly import alerts and import bans. If it's as simple as here's my NDI notification and that trips a standard import alert or import ban, I think that would show there's no more additional effort to meet everything else as to how safe something is.

It doesn't have to play into the decision making process at that point, but it does

give the stakeholder that has it the ability to move forward on their own because if they were all spending money on the NDI, trust me, I can tell you as usual, they're willing to spend the rest of the money to enforce it.

I, I believe that in the same way that we can register trademarks at customs through IP enforcement, and if someone brings something that violates your trademark and if you help monitor with customs your trademark, at customs, they'll pull those things over. I've watched it happen like lightning. When it comes to patents, import alerts or alert ban, patents, that's where you go to your district courts. You go to the International Trade Commission. And that's how you stop it; you get injunctive relief.

And I think here it's the same thing. I think, I think if anyone's going to start needing more assistance in enforcement, it might be the folks at the border. I don’t think that (inaudible), right? I think, I think your job should be making sure that the NDIs that are put in are the NDIs that should come out with the letters that you guys send. And I think that

letter should mean something.

You've really got to put a lot of effort into this. Those are (inaudible). I appreciate all the effort you put in and I think that's your job. On the enforcement side, I think it's time to let the dog off the leash and just -- that, that document gives you what you need to move forward upon enforcement. You're not, you don't need us. You don't need OCI and you don't need DOJ. All right? Go do it. This mean the same, the equivalent as if I got a patent. It's a government document.

So anyway, thank you for your time. I appreciate it.

(APPLAUSE.)

MR. TAVE: Am I on? Good. So we're actually reasonably close to schedule. At 4:30 I was supposed to come up here and give closing remarks. It's 4:35. I will be appropriately brief.

First I want to start with thank you to everybody who provided comment during the final session. Thank you to everybody who asked questions, offered thoughts during the panels. Thank you very

much to all of our panelists. Thank you to our audience who, who traveled from near and far to be here today.

I think we mentioned this earlier. The meeting has been transcribed. The slides that were presented, as well as the transcript will appear on the webpage, on FDA's webpage at some point. It won't be instantaneous, but it will be in the relatively near future. Keep an eye out. There is an open docket to which you can submit written comments. I think everything that we heard today was, was constructive and useful.

I would encourage everybody who has comments whether they shared them or not to think about submitting written comments to the docket. Everything that is submitted will be reviewed and will be considered. The docket is open until July 15th of this year.

I want to express some thanks to, to our team here who helped, Dr. Cara Welch who did a lot of work and even aside from figuring out the clicker issues, this meeting would not have happened with her.

Laura and Sybil who are on panel and were doing a lot of behind the scenes work today. Lori Papadakis, who is not in the room right now, and Juanita Yates who many of you encountered on your way in who, who did an enormous amount of work in helping this meeting happen so successfully. And our friends in, in the communications team, Julia Manges, (inaudible), Lindsey Hake. I'm sure there are names who I've forgotten to mention that is entirely my fault and not a reflection on their contribution.

I think that's it for the day. Thank you very much to all of you. We really appreciate everybody's partnership and participation and we look forward to continuing to work together. We are at ODSP@FDA.hhs.gov if you don’t know how to reach us. The address is on the website. Most of you know how to reach us, but we will always be responsive.

Thank you very much.

(APPLAUSE.)

(Whereupon, at 4:37 p.m., the meeting concluded.)

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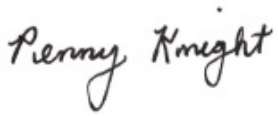

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