PUBLIC MEETING TO DISCUSS THE DEVELOPMENT OF A LIST OF PRE-DSHEA DIETARY INGREDIENTS

Conducted by Cara Welch, Senior Advisor

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Center for Food Safety and Applied Nutrition

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C O N T E N T S

P R O C E E D I N G S

DR. WELCH: Let's try that again. Better? All right.

So good morning, everyone. For those who missed the first part, my name is Cara Welch with the Office of Dietary Supplement Programs. This meeting is being webcast and transcribed and will be posted on FDA's website when completed. I'm not sure the timeline on the transcription of being posted. We try to get them done as soon as possible, but it could take a couple weeks.

If you're interested in the transcription, I would suggest you monitor the FDA meeting page that announced this meeting. And that -- it will be posted there.

To ensure our webcast participants can hear, please be sure to speak your questions and your answers and your presentations clearly into the microphone. If it's not spoken into the microphone, they have no

chance of hearing.

And then also for our webcast participants, if you have a question to ask during the Q&A session, you

are all muted. So you'll have to type your questions in, and we'll have staff monitoring the webcast to ask the questions on your behalf.

Restrooms. As you exit the auditorium at the top, both the men's and women's restrooms are located down the corridor on your right.

Wi-Fi. For those who have not yet asked, we do not have Wi-Fi connection available. My apologies.

Breaks and lunch. We have a couple short breaks and a lunch break scheduled throughout the day. Snacks and beverages are available in the Wiley building cafe, known as Ms. T's Cafe. It's located outside the front entrance of the building. You'll go to the left when you exit out the front doors.

And even though we didn't plan this in advance, we also have CFSAN's fall food court available today. That is some food vendors. Three or four food vendors will be available in the courtyard outside of the auditorium. That courtyard is actually just

outside the auditorium external wall; however, please only use the front entrance to exit and enter the doors. I'm not quite sure if you go out those back

doors what will happen, but let's not test that today.

Also, please be sure to wear your nametags because you will have to come in through that front exit and go through security each time.

Also, because of our fall food court, you may have noticed there are some cords extending from the auditorium out the back door. Please be careful. They have been taped down, but we don't want anyone to trip.

The folders. You were all provided a folder when you checked in at the registration desk. The webcast participants received it by email. That folder has some documents helpful for today. It has today's agenda, slightly updated from what was posted online earlier. It has the list of persons that are making public comment during the morning and the afternoon public comments session. It has the bios for our presenters, both the FDA and the panelists.

And it has the Federal Register Notice. And

on that I would just make note that we do have a comments session that is open. You can submit written comments to the docket. The deadline for that is December 4. So you have a couple months to submit

comments to the docket.

Another reminder -- there are no food or drinks allowed in this room.

For media and press questions, we have two communications staff available. I believe both of them are outside the room right now. But if you're not familiar, their names are Marianna Naum and Corinne Newhart.

On the public comments sessions, the sessions today, both this morning and this afternoon, we are having two comments sessions. As I mentioned before, the list of people who have requested an opportunity to make public comment is found in your meeting folders; however, we will have additional time for the public comment during the afternoon session. If you have not signed up but are interested in giving comments, please check in with Juanita Yates at the registration desk or in the back of the room.

Juanita, can you wave to the crowd? She's in the back of the room. If you have any questions throughout the day, Juanita is probably your best bet for a knowledgeable answer.

The public comments session is five minutes, so prepare to keep your remarks to five minutes or under.

And with that, I would like to turn it over to Dr. Ostroff, Deputy Commissioner of Foods & Vet Med Program.

Thank you.

DR. OSTROFF: Thanks very much.

I always think it's interesting when I speak in this room about how many more people are up at the top of the room than at the bottom. But it's really terrific to see all of you here. And let me welcome all of you -- not only those of you that are in the room, but those that are on via WebEx -- to FDA and to what should prove to be a very important and, I think, informative meeting.

But let me first thank Steve Tave, Cara, Bob,

and the others in the Office of Dietary Supplement Programs for organizing this meeting. And let me also in advance thank all of the panelists who have agreed to participate in the several panels that we have today.

The members of these panels, because I looked over the agenda for the day, certainly reflect the diversity of viewpoints regarding dietary supplements. And that is what we strive to achieve in public meetings of this nature. But hopefully, as we reflect over the course of the day and afterwards, as we reflect on these very diverse viewpoints, we're able to coalesce around a pathway to be able to address today's topic. All of your participation in this meeting and after this meeting is really valuable to us, and we look forward to being able to continue the work with each of you as we move forward.

It's worth noting that we're approaching the two-year anniversary of the creation of the Office of Dietary Supplement Programs. This is something that I very strongly championed when I was the acting commissioner at FDA back in 2015. That was the first

time I was the acting commissioner. And for me, elevating the status of this program within FDA was a very important step to be able to enhance our work and also sent a signal that we believe it's important to be doing more in the dietary supplement space, to be able

to oversee the industry, and to better protect consumers who are using these products.

Right now, we have an estimated -- an estimate that there are something like 75,000 to 80,000 dietary supplement products on the market. That's a huge market. When DSHEA became law in 1994, we were talking about maybe 4,000 products on the market. So if you do the math, that's about a 20-fold increase over a 23-year period.

The market for dietary supplements has grown from 4 billion in 1994 to around 40 billion today, and that's just in the United States. These are products that over half of the population and two-thirds of all adults in the United States take on a regular basis. Some see that rapid growth as a good thing; others see it as a problem and a public health concern. I see it

as a reality.

These products don't receive pre-market approval, although they can sometimes contain very powerful substances, whether they're supposed to be there or they're not supposed to be there. Some products make extreme health claims; some make drug

claims; some are potentially harmful.

And while we've elevated the dietary supplements group to an office and brought in extremely capable leadership, the group is still pretty small and under-resourced for the task that they have been given. This is an office that always has their hands full. I think that they're doing a great job using available resources to ensure that we are acting to be able to identify and remove dangerous products from the market and, in the work that they're doing, to establish and implement practices that ensure that these dietary supplements are kept free of adulterants as they make through -- their way through what we all agree is a very complex supply chain. And if anything, that supply chain gets more complicated every year.

Last year, ODSP issued the draft guidance on

new dietary ingredient notifications, and they are currently working to review the over 300 comments that we received. Today's meeting is an important adjunct to that effort. It focuses on the creation of a list of dietary ingredients marketed in the U.S. prior to the passage of DSHEA.

We understand that the law's requirement to submit a new dietary ingredient notification to us can be burdensome to industry, especially without an authoritative list of ingredients that were marketed prior to October 15th, 1994. I can assure you it can also be burdensome to us.

The program has limited resources, and so they need to be focusing on review notifications for ingredients that are truly new. Likewise, having such a list will allow us to improve our enforcement efforts by letting us focus more on our strategic priorities, which are consumer safety, product integrity, and accurate information.

We have heard from consumer groups about some of the concerns that they have about an ODI list, and

we have heard from industry about some of their concerns. These are the concerns that need to be properly balanced, and we hope to hear those concerns over the course of the day. We recognize that there's a lot we will hear and that we need to consider as we go forward. So today, we are here to listen and to learn from all of you and from each other.

In that spirit, I will once again welcome you and thank you for being here. I hope we all find this to be a productive and useful and engaging meeting. And let me just thank all of you for taking the time out of your busy schedules to participate today.

Thanks again.

(Applause.)

DR. OSTROFF: And I neglected to mention -- let me introduce Steve Tave.

MR. TAVE: Good morning. All right. People are engaged. That's good. It's not even 9:00 o'clock, and we've got dialogue. So that's a start.

I want to first take a moment to thank Dr. Ostroff for that kind introduction. He's been a very powerful force here at FDA both in his current role as

deputy commissioner and during his previous times as acting commissioner in support of enhancing the work that we're doing here in the dietary supplement space.

He's been an advocate for things, as he said, like increasing the program's profile by elevating us from division status to an office, as well as making sure that we have access to the resources that we need

to do our part. So if you've seen positive changes at FDA related to our dietary supplements work, then Dr. Ostroff deserves a share of the credit for that. You can feel free to hold me responsible for anything that you don't like.

Thank you all for being a part of this meeting. I'm thrilled to see so many people participating both here in person and virtually through the webcast. As you know, we're taking a collaborative approach to developing an authoritative list of pre-DSHEA ingredients, and it's absolutely essential that this process be participatory. We can't do this without active engagement from all of you, so we're already off to a good start, in my mind.

Let's begin with some background, what the law says and how that shapes today's topic of discussion. When DSHEA, the Dietary Supplement Health and Education Act of 1994, was enacted, it defined the term dietary supplement. As part of that definition, the dietary supplement has to contain one or more dietary ingredients. Dietary ingredients under the statute are defined to include vitamins, minerals, herbs or other

botanicals, amino acids, dietary substances for use by man to supplement the diet by increasing the total dietary intake and concentrates metabolites, constituents, extracts, or combinations of those or other ingredients.

As Dr. Ostroff said, under DSHEA, dietary supplements can be marketed without any approval from FDA. And most of the time, there is no requirement that a dietary supplement firm even tell FDA what products it's going to sell before it offers them to consumers. It's the one exception to that requirement that indirectly brings us here today.

DSHEA defined that the term "new dietary ingredient," or NDI, as we call it, to mean a dietary

ingredient that was not marketed in the United States before October 15th, 1994, which, incidentally, is a tricky date after Congress passed DSHEA but before the president signed it. So it's not exactly aligned with the date of enactment. But we call it pre-DSHEA, and that's close enough. In fact, the law actually repeats this twice in the statute, and it makes clear that the term "new dietary ingredient" does not include any

dietary ingredient which was marketed in the United States before October 15th, 1994.

Now, DSHEA included a requirement, with some exceptions, that firms notify FDA no later than 75 days before introducing a dietary supplement containing a new dietary ingredient into commerce and that that notification set forth their basis for concluding that the product is reasonably expected to be safe. This NDI notification process is an extremely important part of FDA's regulation of dietary supplements in the United States. It's our only opportunity to identify potentially dangerous products before they become available to consumers.

But there's also no question that not every dietary supplement is subject to this requirement. It only applies to a finite subset of dietary ingredients. Specifically, the requirement to notify only attaches to dietary ingredients that are considered new within the meaning of DSHEA. And even among the new ingredients, there might be an exception to the notification requirement.

So this leaves an entire category of

ingredients that are not new and, therefore, are not subject to the NDI notification requirement. Some people call these ingredients old. Some call them grandfathered. Some call them pre-DSHEA. But no matter what you call them, here is the $64,000 question: Which ingredients does this category include?

Over the years, a number of different organizations have attempted to compile their own lists, but we've never sanctioned or approved any of those lists, in large part, because we can't verify the data on which they relied. And in the nearly 23 years since DSHEA was enacted, FDA has never compiled our own

authoritative list of dietary ingredients that we consider to have been marketed in the United States before October 15th, 1994.

This brings uncertainty. Some firms might choose not to market products, continuing ingredients that most likely aren't new because they don't know for sure whether a notification is required. Some firms might already be marketing products containing ingredients that they believe aren't new, but they also

don't know for sure whether they might face potential liability for not complying with the notification requirement.

And some firms might invest the time, effort, and expense to prepare and submit a notification that wasn't actually required. We at FDA then have to use our own limited resources to review an unnecessarily submitted notification.

And everyone lacks clear guidelines about which ingredients are and are not new, preventing us from taking as focused an approach to regulation and public health protection as we'd like.

Last year in August 2016, we issued a revised draft guidance on new dietary ingredients and related issues, recognizing that the state of uncertainty is not optimal either for FDA or for industry. We stated in that revised draft guidance for the first time that we're prepared to develop an authoritative list of pre-DSHEA ingredients based on independent and verifiable data. We also stated that, because we generally do not have access to marketing records for dietary ingredients and dietary supplements, industry would

have to supply documentation to demonstrate that ingredients were marketed pre-DSHEA.

The revised draft guidance itself is a lengthy document, about 100 pages long, covering a multitude of issues. We have received about 300 comments on the revised draft guidance. And not all of those comments were enthusiastically in favor of all of the positions we articulated in the guidance, but there were a few areas where there was some consensus. And our willingness to develop an authoritative list of pre-DSHEA ingredients was one. We, therefore, believe that this is a worthwhile endeavor that will be beneficial

for industry and FDA alike.

That said, while there was a broad consensus that this is a useful task for us to undertake, a careful review of the comments that we received on the revised draft guidance reveals a wide variety of opinions on how it should be done. And in order to be successful, we need to be realistic, and we need to be honest about the challenges we'll face.

I'll be blunt. This would have been a completely different undertaking if today were October

16th, 1994. The exercise would have been objectively straightforward. We simply would have identified all of the dietary ingredients being marketed in the United States, figured out how specifically we wanted to identify them and describe them, and made a list. But as we all know, that didn't happen. And as a result, we now have a number of questions to answer and decisions to make.

There may be some sources of fairly conclusive evidence that should be pretty readily available. For example, there's an extensive legislative history from

the years leading up to passage of DSHEA. And if an ingredient was mentioned in that debate, that would seem to be pretty strong evidence that it was marketed at least in some form in the United States before October 15th, 1994. We'll hear about possible sources of evidence from our panel soon.

Unfortunately, that won't be the case for a large number of ingredients. But an absence of evidence isn't necessarily evidence of absence, which means we'll all need to play detective. It's possible that some clues reside here in FDA's files. But the

reality is, as we said in the revised draft guidance, that the bulk of the data is going to be in industry's possession.

Even today, there is no general requirement that firms tell us what dietary supplements they're marketing or what ingredients are in them. We certainly don't have that information from 1994 before "dietary supplement" was a term defined in law. We also can't assume that firms, some that were marketing in 1994 but no longer are in business today, and some that are active today but didn't exist in 1994 have

kept perfect records, especially when there was no requirement to maintain them over the years.

But there's a lot of middle ground between conclusive evidence and no evidence. And that is at the heart of what we want to explore during today's meeting.

To get a sense of some of the issues we'll need to navigate, here are some sample excerpts from the comments we received on the revised draft guidance. On the question of process, one commenter suggested that we should establish a joint panel consisting of

representatives from industry and FDA to meet regularly and to evaluate evidence submitted by stakeholders.

Another commenter also recommended an expert panel, but this commenter believed that the expert panel should also add questions such as how to develop the list, as well as whether developing an authoritative list is even viable.

Yet another commenter stated that a list should be developed subject to rulemaking so all interested stakeholders have an opportunity to

participate on the record.

And several commenters believe that FDA should just adopt some or all of the existing lists that industry has prepared in the past or may be preparing now.

There is also a threshold definitional question. Several commenters pointed out -- and we noted this in the revised draft guidance -- that until the passage of DSHEA, there was no definition in the law of either dietary ingredient or dietary supplement. As a result, they argue, it should be meaningless to attempt to superimpose those standards when evaluating

the pre-DSHEA status of an ingredient.

One commenter suggested that ingredients should qualify for the list if there is evidence that their intended use as a dietary ingredient or dietary supplement before October 15th, 1994, would be consistent with lawful dietary supplement marketing under current law. This seems like a reasonable interpretation. But as always, it's not difficult to imagine scenarios that may merit some additional discussions.

Suppose, for example, that the relevant date in the law were October 4th, 2017, instead of October 15th, 1994. I think all of us would acknowledge that there are ingredients now being marketed in dietary supplements that shouldn't be considered lawful. FDA had acted against some of these ingredients. In other cases, we may not have acted yet, whether because of resource or other constraints. And still, other ingredients may be subject to vigorous debate about what the rightful status actually is. But there is no denying that these ingredients exist.

How would we treat those ingredients? And how

should we treat those ingredients from 1994 that's traveled the same line?

The identity of ingredients raises a separate but equally important set of questions. If we assume that an ingredient was marketed in some form before October 15th, 1994, does that mean that all versions of that ingredient should be considered old? And is this appropriate even without any evidence to suggest that they were marketed that way in 1994? In some cases,

the evidence, such as a patent application, might establish that a certain form didn't become available until after 1994.

Intertwined with this issue are questions about how to treat variations in ingredients, stemming from things like alternate preparations or manufacturing changes.

The question ultimately boils down to how to define in the list, as one commenter put it, an ingredient's identifying characteristics -- things like concentration, formulation, and specifications, such as plant part. Or as another commenter wrote, we need to clarify which changes do and do not alter the identity

of a dietary ingredient.

This question seems inextricably tied to the issue of evidence. A number of commenters argued that a single document should suffice to establish that an ingredient was marketed before October 15th, 1994. And I don't know that anyone would disagree that there may be cases where a single document is both reliable and detailed enough to establish the pre-DSHEA marketing status of a specific ingredient, but that may not

always be the case.

And when the evidence gives us some information but not perfect information, is it possible to craft a flexible approach that recognizes, as commenter suggested, that some ingredients were very likely to have been marketed in the United States before October 15th, 1994? If so, how do we define the parameters of those listed ingredients in a way that preserves the balance intended by DSHEA without any sacrifices to our ability to protect the public?

We've also heard from some commenters who want to separately address specific categories of ingredients like probiotics and enzymes and fish oils

and omega-3-rich oils. We need to discuss whether there are any special considerations that we need to account for to appropriately recognize characteristics unique to these categories and possibly others, and we'll specifically invite discussion on this subject during the open public comment period later this morning.

Finally, a common refrain throughout the

comments was safety. For example, writing about manufacturing process changes, one commenter argued that these changes should only create a new dietary ingredient if the change affects the ingredient's safety profile. Several commenters who advocated reliance on existing lists of old ingredients, acknowledged that even some of the ingredients on these lists present significant safety concerns. And at least one commenter suggested that in adopting these existing lists, we should exclude ingredients for which of the -- for which there was a known safety concern.

We applaud the safety-oriented aim of these comments, but this suggestion may be either -- might be easier proposed than implemented. Although we know

that responsible industry members share a focus on consumer safety, in practice, our warnings about safety have not always been readily or uniformly accepted. Even ephedra, the only dietary ingredient which FDA has banned to date, which at least one commenter highlighted as an example of an ostensibly old ingredient that could be excluded for safety reasons, went through a contested years-long rulemaking process

before it was finally deemed unsafe.

This brings me to a very important point. An authoritative list of pre-October 15th, 1994, dietary ingredients will not be a list of safe ingredients. And again, the simplest example is ephedra. FDA had determined that ephedra and alkaloids present an unreasonable list of illness or injury, and a federal court has upheld that determination. Yet ephedra was unambiguously marketed in the United States before October 15th, 1994. So it would be on a pre-DSHEA list.

And there are surely other ingredients that are both old and whether in all of their forms or only some, whether in any population or only limited in sub-

populations, are unsafe. Future experience and studies might yield new information about the safety profiles of other ingredients. But the plain language of the definition of new dietary ingredient in DSHEA does not incorporate safety. And so in developing a list of pre-DSHEA dietary ingredients where the fundamental question is whether a certain ingredient was marketed

at a certain point in time, it would appear that questions of safety don't factor directly into the equation.

With that in mind, it's absolutely critical that we be precise in how we describe this effort. This is at its core a regulatory exercise, rooted in figuring out which ingredients were marketed on a date specified in the statute. We, therefore, need to be exceedingly careful to make sure that consumers and healthcare practitioners do not fall under the misimpression that the appearance of any ingredient on a pre-DSHEA list suggests that the ingredient is safe. And looking ahead, as the list becomes a reality, we may need to work together to ensure that we prevent consumers from being misled by representations about

ingredient status.

At the same time, even though it's not a direct factor in the chronological question of marketing status, there may still be room for safety to guide us. I want to qualify what I said a minute ago. The legal definition of new dietary ingredient does not entail a safety assessment. But the significance of

being a new dietary ingredient under the statute most certainly does have a nexus to safety. It's only if a dietary ingredient is new that it is potentially subject to the requirement of the a pre-market safety notification.

We said this repeatedly, but it rings true. The NDI notification process is critical because it's FDA's only opportunity to spot dangerous products before they become available to consumers.

So as we consider seemingly mundane questions today about things like expert panel composition and bills of lading and authorization, I would implore you to keep in mind that the way we answer all of these questions could mean the difference between whether we first identify a safety concern through a pre-market

notification review or through a serious adverse event report.

In a few moments, we'll hear from our panelists who have prepared thoughtful and thorough presentations touching on all of these subjects and more. Before we begin, it's important to be clear

about what we're working towards.

The list that we envision would be authoritative, but it won't be comprehensive. In other words, an ingredient's inclusion on our list would be conclusive evidence that FDA considers the dietary ingredient to have been marketed in the United States before October 15th, 1994. But an ingredient can still be pre-DSHEA and, therefore, exempt from the notification requirement, even if it isn't on our list or anyone's list.

As we stated in the revised draft guidance, the mere fact that an ingredient is not on the list would not establish that the ingredient is an NDI. Rather, the omission of an ingredient from the list would be regarded as neutral and would not affect the ingredient's regulatory status. The list would reflect

an ingredient's pre-DSHEA status. But being included on this list is not necessary to confer that status.

More immediately, we don't expect to emerge from today's meeting with a list of pre-DSHEA ingredients, even an incomplete one. But we do hope to begin to agree on the contours of how a list should be

developed and what it should look like. And we fundamentally believe that the best way to accomplish this is through an inclusive process that is transparent to all of our stakeholders. The same standards that are -- that inform our determination of whether one ingredient was marketed before October 15th, 1994, should apply to all ingredients.

So if a firm is deciding whether to sell an ingredient that we haven't yet had the opportunity to evaluate -- and to be sure, developing a list will require resources; and ours our limited, so this won't happen overnight -- then that firm will have access to our thought process, where if a firm has proprietary information that it doesn't want to risk sharing, then that firm will have access to our thought process. Knowing how we are approaching these questions, all

firms will be able to independently make their own informed determinations about whether we would likely consider their ingredients to be pre-DSHEA.

And just as everyone will have an opportunity to contribute their ingredients as we decide how to

approach these questions, we think it goes without saying that everyone should reap the benefits of this effort. The result will be that both industry and FDA will be able to better direct our respective resource use. And then because of our collaboration, the dietary supplement marketplace will be a little bit more effectively regulated. Everyone will be better off. That's the goal.

Now back to today. As Dr. Welch said, you should have a copy of the agenda in your folders. For those of you participating by webcast, it should be available electronically.

We structured the day in two parts, each with a panel discussion followed by an opportunity for questions and public comment. In the morning, we're going to discuss issues related to standards and evidence. In the afternoon, the focus will be on

process.

There will be moderators from FDA to facilitate the discussion throughout the day, but we don't plan to say too much. Our goal is to listen. We're approaching all of these questions with an open

mind, and the point of today's meeting is to begin a dialogue and to hear ideas.

We're fortunate to be joined by 10 panelists representing a diverse range of experiences and perspectives. And we very much appreciate the time and effort that they all went into in order to be here today to share their thoughts and help move this discussion forward.

We know that many of you also traveled to be here. And regardless of how far you came, we appreciate everyone's participation both in person and virtual.

We're looking for contributions from everyone in the form of both questions and comments. And as Dr. Welch noted earlier, there will be several opportunities today for public comment. We've also opened up a docket so that you can submit your views in

writing.

There are no special ground rules, just the baseline for normal civil discourse -- listen, be respectful, and please pay attention if we let you know

that you've reached the end of your allotted time.

But I would like to add one modest plea: Please stick to the topic of this meeting. We know that many of you have opinions on a range of matters related to dietary supplement regulation. But today we're focused on the development of a list of pre-DSHEA ingredients. We hope to cover an ambitious amount of ground in a limited amount of time, and we need to stay focused in order to be successful. There will be a time and place to talk about other issues.

And I'll note, for example, that FDA recently opened a docket and requested information on areas where stakeholders believe there may be an opportunity to modernize the Agency's regulations.

So with all of that out of the way, and following my own rule, it's time to start hearing from our stakeholders about today's topic. I'm now going to turn things over to Bob Durkin, Deputy Director of the

Office of Dietary Supplement Programs, who will introduce and moderate our first panel.

Thank you all again.

(Applause.)

MR. DURKIN: Thank you, Steve.

Good morning. My name is Bob Durkin, the deputy director of the Office of Dietary Supplement Programs. This morning we're going to be brief and try to turn the topic over to our stakeholders as soon as we can.

We're looking forward to starting our first panel this morning. As Steve just mentioned, this first panel will be discussing standards and types of evidence, specifically, what level of evidence is necessary to demonstrate an ingredient was marketed before October 15th, 1994.

The revised draft guidance from 2016 states this list of pre-DSHEA dietary ingredients should be based on independent and verifiable data. This data should include the date of marketing in the United States as well as a description of the ingredients being marketed. There are almost four pages of

comments in our revised text on -- in the draft guidance discussing aspects of these two questions, aspects such as what does marketing mean, what

documentation shows marketing, what level of description is needed, and what does it mean to be marketed as a dietary ingredient.

However, our goal today is not to read verbatim out of the revised draft guidance, as we imagine some folks in the room are aware of it and maybe even read portions of it. But our goal is to hear from stakeholders that we've invited here to be on our panel today -- panels today as to what is important and what is feasible in developing this list of pre-DSHEA dietary ingredients.

With that said, I'd like to bring up our first panel of five stakeholders -- Loren Israelsen, Joe Betz, Michael McGuffin, Duffy Mackay, and Peter Cohen.

I won't take the time to read the bios of these five individuals off to you, as they're in your packets. In order to save time, we're going to get going with our first presenter. They're going to have 15 minutes to discuss their topic. At the 15 minutes,

we'll bring up the next moderator. Please hold your questions until the end of the panel.

Thank you very much.

Can we please bring up Loren's slides?

MR. ISRAELSEN: Good morning, everyone. Pleased to be here and to start off today's discussion. And given our time limits, I will move quickly.

The topic, as you know, is to develop a -- I still call it an ODI list. I'm having trouble with pre-DSHEA list, so I will use ODI. Our assignment is to try and divide our time so that we cover a range of issues around this topic.

What I will do is to take you through a bit of a timeline. I'd like you to be able to see and understand the broad picture of how we got to where we are now in 2017 and also a specific look at one example of the type of evidence that might be interesting as we're trying to figure out where and how to find old dietary ingredients that are still on the market. And as Steve Tave noted, they come in many ways and forms and from many sources.

This is a very old issue. This long predates

DSHEA 1994. We're talking the -- into the 1950s and '60s. And much of the problem started because of a

binary system dividing foods and drugs. There was really no place for dietary supplements that had been a friction point for many decades.

So first, a little bit of history. This is a document that's from 1985. There was a very famous case called Fmali versus Heckler that was about the question of whether overseas use of food could establish common history of use -- and this case that the herb company won and FDA lost.

And so this document -- actually, Cara, this is my old deck, so we'll just go through this one. Right. So this is a couple generations back, so this will change things a little bit.

So this began to set a template of how do we think about common history of use in foods and when did that begin and where are these products. It was then followed by this really important document published in May of 1992, which was a dietary supplement task force report that was requested by then Commissioner David Kessler. And the question was to the FDA panelists and

experts invited is imagine a new template for dietary supplements. Tell me what you think we should do from

a clean slate.

The proposals boiled down to this: For vitamins and minerals, it was to cap the potencies of vitamins and minerals; for amino acids, single aminos should be treated as drugs; and for everything else -- vitamins -- sorry -- herbs, botanicals, fish oils, probiotics, et cetera -- should be regarded as food additives. This was really the final confirmation that FDA's intentions were not to treat dietary supplements as we know them today, but to look at them as drugs, food additives, or something else.

This is really what precipitated the passage of the Dietary Supplement Health and Education Act. And part of that act, as Steve Tave mentioned, was the creation of a new dietary ingredient provision. But what was the context in which this provision was created?

Having been involved in those negotiations, this happened late in the process of DSHEA, which began in the fall of '92 and ended in the fall of '94.

That's very fast by legislative terms. But this issue

was really one of the last. And the reason was, is after we had worked out many of the other problems and challenges, those that were concerned about this bill and public safety said that we've got to do something to really look at the future. What will happen as innovation brings new and different ingredients that we can't envision in 1994?

So the decision was made to create a grandfathering date, which as you know is October 15, 1994, and all prior ingredients on the market would be left on the market for two reasons -- one, an assumption that they had been there with some presumptive history of use and that they would be presumptively regarded as safe. And that's just the judgment that was a legislative decision. The other key reason was to assure continued consumer access to those products. That was the primary goal of DSHEA.

If it was decided to remove all products to do some kind of go-forward safety review, it would defeat the first and primary objective of the statute itself. Both sides agreed that that simply would not work, that

DSHEA generated such tremendous consumer interest to

Congress that it was decided that this approach of adopting old and then look at the new was the better way to go. So that's why this section is written the way it is.

So what has happened in the post-DSHEA world? And remember 1994. So these were the tools that we were working with at that time. Some of these look very familiar and with some fondness, no doubt. And I actually brought with me -- this is a floppy disk, which is one of our UNPA ODI files. We don't have a computer in our office that can play this, and many of you may not as well.

So that is one of our challenges, is that the passage of time has changed technology. And it has also changed our ability to access the literal information that was captured and held above and beyond what is found on the ODI list which have been published.

So the question is where are your records. And the current said deck, there is a file cabinet which shows the actual physical paper records that were

held. And just by good corporate practice, every company has a sweep-out and a cleanout provision that we get rid of old records, and someone is in charge of doing that and what happens. All of these old aging documents that someone looks at and can't find any relevance to, they get tossed. Those are the key records that we really needed.

Of particular importance are manufacturing records that would show how a product was made, what solvents and extractions, what processes. So that's where the most damage was done from DSHEA plus 1 going forward. So now we're DSHEA plus 23 years.

And as Steve said, is that if we had been able to do this on day plus 1, it would have been really easy. Everything would have been in ODI, and a snapshot in time would have solve this quickly. And then you can begin to look and see how things change over time. But that did not happen, and that leaves us in the situation that we're in now.

So shortly after DSHEA passed, a number of trade organizations -- the American Herbal Products Association; CRN; NNFA, now NPA; and UNPA --

individually created ODI lists where we gathered our members and asked them to provide lists which were developed and created a few years later that this list was a compilation of those existing lists. And this represents the style and type of listing of these ingredients. And there are several thousand listed. But this is not complete, and we know that. FDA has never regarded this or any of the other lists as authoritative, and that is what is a real clear problem.

So where we are now is that, over the past year, that the August 2016 date is a significant one -- when FDA published the revised draft NDI guidance. Within a month after that -- and this is dated September 2016 -- is we organized the (inaudible - technical difficulty) industry members to comment to really discuss what this NDI guidance said and look also at the question of GRAS, generally recognized as safe.

So with that little period of 30 days to try and really understand this large, complex document, we also do poling. And the idea there is just to get a

sense of the audience of what is their feeling. And so we asked this question. We have these little poling units, so everyone in the audience can just click and do it anonymously.

And so -- but what we really wanted to know was what do you think is the best pathway forward now, just based with this 30 days of understanding. Is it time to ramp up ODIs or ramp up GRAS affirmations, which is an option in many people's minds, to an NDI filing? Or do you just hold for now because we just really still don't understand this? Or are you mad enough you want to push back and just tell FDA you've got to try it again; this is not really what we wanted?

So then in February, six months later, in 2017, we felt -- we held a third conference, all in the effort to keep educating industry to try and understand what this guidance really says and to find a proper response so that comments could be filed. So we asked the same questions again and looked at the change in view and opinion.

This is what's quite shaking, is to see a zero response to file new NDIs. What that suggests is that

there was a fundamental sense of stop, we don't know how to do this. There were too many unanswereds (sic) and unknowns. I was very surprised to see that. Even a drop in to ramp up GRAS, you would think there would be a shift toward GRAS if there was a drop in NDIs.

But this is what's astonishing, is to see that it's simply we don't know what to do. We just flat out don't know what to do. There are too many things that we just can't reconcile. And even pushback dropped down. That left us in a state of help. You know, we need to go back and think about this again.

And we're appreciative for this day, which gives us a chance to really try and discuss what we think is the core issue, is laying out a framework for an ODI list, which allows us then to begin systematically working on these other issues.

And as was said -- and I fully agree -- without a robust ODI list, many companies are unable to make a proper business decision, whether we invest in an NDI but find out later we didn't have to -- it turns out to be an ODI. Do we go GRAS affirmation as opposed to NDI? And many legal advisors and consultants have

told companies that GRAS affirmation is a good option to NDI filing under certain conditions. There are probably six to seven times more GRAS affirmations than there are NDI notifications to date, post-DSHEA, which is an indication of the shift toward GRAS because there's more clarity about the overall process and a lack of an authoritative ODI list.

So where shall we look for ODIs? I decided just to take one example because our other panel members will present other ideas in other areas. But this comes from a Chinese herbal restaurant in San Francisco mid-1980s. This is the first, as they say, herbal food restaurant in America. And what is of note is that if you look -- and I apologize list; it blurs out a bit -- is that you will see dozens of Chinese herbs, botanicals listed here that are clearly used in a food context. These are food dishes.

And it raises the question of how products, dietary ingredients, botanicals, and other things have been used over a very long time in this country and elsewhere that go to the history of its safe history of use and of brought common use in food. And that is an

important consideration as we're trying to think through an ODI list.

So the key issues -- and again, this is a prior deck, but I'll try and blend what you see with what current thinking is. The standard that we're to apply for ODIs is reasonably expected to be safe, and safety is a primary issue. Whether you're an ODI, there is no free card, there is no safety obligation there is as there are for NDIs. They are a little bit different.

The appropriate level of regulatory oversight is a central issue in the industry's mind, is if we have an ODI list, what level of enforcement should be given to that list? Where we see a problem if it's not present on the list, should FDA actively go and do something about it? We think not. The issue should really be a focus on is there a safety issue worth addressing. Let's look at where it fits into the scheme, whether it's an ODI, GRAS-affirmed NDI, before deciding that we need to take action. The industry is not in favor of having unsafe markets available to consumers in the absence of a proper regulatory status

for those ingredients wherever they are.

But there is a broad mandate for consumer access, and that is fundamental to the principle of DSHEA. And we think the resolution of an ODI list contributes to an understanding of what really belongs on the market and those things that do not. But until we create the separation between old and new, it's very difficult for us to really decide this is the small group of ingredients that really don't belong on the market and then focus our efforts both Agency and industry toward the end of removing those products. And it's not in our interest to have unsafe products on the market. That's self-evident.

Time has passed. This is urgent. We need to get this done quickly. As we lose time, we're in the fall season. This is typically when people go through record cleaning out once again. And we'll lose yet another generation of ODI documents. We've asked people please save them, but very often they don't.

There's also been a concern that the NDI notification process is returning to a food additive-like process. This raises a concern in the mind of

many who have been in this industry a long time and recognize that food additive red flag, this is something that was addressed by DSHEA to be sure that we didn't wander back into that food additive world.

So essentially, the last and key point I would like to make is that we are here to discuss developing an ODI list. But there are other core issues that were presented in the draft guidance in 2016. Principally, a -- the question of chemical alteration and manufacturing changes are the two key ones. And the reason those are so relevant is that they will help determine what is and is not an ODI list.

If we go through the process of creating an ODI list and then we ask the question well, what chemical changes have happened and suddenly realize that what I thought was an ODI is, indeed, an NDI or it's not what we thought at all because of a manufacturing change or a change in chemistry, then it will bring ambiguity once again to the ODI list.

So we need these three issues discussed and resolved in tandem to allow industry to make a reasoned judgment about how best to contribute and work with FDA

toward the creation of authoritative list, which we fully support and would like to see proceed. But we're hopeful that this will not be done as separated or segregated issues so that we can understand what we're dealing with together and then proceed.

And so with that, the people did speak. The Congress did speak. If NDI notification is not seen as affordable or protectable -- and this whole issue of intellectual property rights is becoming a major issue, not for discussion today, but this really goes to the heart of how companies protect their assets.

And so with that, I will stop and say thank you for the opportunity to speak. I appreciate being here and look forward to hearing from my panel members this morning, afternoon. And thanks to all of you.

(Applause.)

AUTOMATED VOICE MESSAGE: At the tone, please speak your name. This will be used to introduce you to the meeting. When finished, press the pound key.

(Number hit.)

AUTOMATED VOICE MESSAGE: By request of the meeting organizer, this meeting is being recorded.

MR. DURKIN: Thank you, Loren.

Of course, Loren is present of UNPA.

Our next panelist to speak will be Dr. Joe Betz, Director, Analytical Methods and Reference Materials at ODS of NIH.

Dr. Betz.

DR. BETZ: Good morning, everybody.

(Side conversation.)

DR. BETZ: All righty. So since I still do work for the government, I start off with a disclaimer. The views expressed today by me are mine and don't reflect the views of ODS, NIH, or HHS.

We're talking about a controversial subject, a little bit controversial. And it's the classification and consideration of what constitutes a dietary supplement in terms of all dietary ingredients.

I am sticking strictly to the stuff in red here, which is evidence -- which primarily concerns evidence of what constitutes an old pre-DSHEA ingredient. One item is -- especially is something that has been in the food supply. I'll concentrate on that. I'll let other people who are smarter in the law

than I am figure out how to find evidence of whether something was marketed versus simply in the food supply.

Loren mentioned this. I know Michael McGuffin will almost certainly mention it. These are potential sources of documentary evidence of ODI status; shipping documents from importers from pre-October 16th, 1994; bills of lading, records from contract manufacturers; master manufacturing records, et cetera; catalogs. When I was in graduate school, we did a lot of work on ginseng in the 1970s, and we had boxes and boxes of catalogs. My mentor has retired, and I don't know what happened to those boxes. I'd love to get my hands on them.

FDA taught a microscopy course. I helped teach that, and we bought powdered materials from companies like Pan Herbo and Frontier Herb and others. My mentioning those names does not constitute an endorsement. It's just a couple of the companies that we bought stuff from when we were teaching the course.

What sorts of information are available? So this is the 1970s -- or 1990 edition of edible wild

plants. It's a Peterson Field Guide. The plants -- there are over 300 plants in this book, wonderful pictures, descriptions, geographic ranges. These are North American plants. These were certainly in the food supply. Good luck finding evidence that they were marketed, although I do remember going through farm markets at the time and finding dandelion leaves and such, fresh dandelions, being offered for sale at farm markets.

This seems a little bit facetious, but this is my Boy Scout handbook from 1965. And at the time in 1965, there was a requirement for the second-class rank to know edible wild plants. And there were probably about a dozen, maybe a little bit more than a dozen, edible wild plants that one had to know. These were not necessarily things that one would make a regular diet of. Some were last-resort foods, but they were things that were -- could keep you alive.

So this is evidence. This book was published in 1965. I have it on my shelf. It's a little bit more beaten up than this book is because I carry it around everywhere. But you know, this is evidence of

things that were eaten by humans in the United States in 1965. Interesting that poke -- fresh poke shoots, young poke shoots, was one of the edible plants mentioned, not that I would want an 11-year-old making the judgment as to whether something was a young shoot versus an old shoot. But it was there.

This is something that I happened to stumble across. This is a resource I stumbled across when I was at FDA. There was a question about whether or not ginseng was suitable for use in foods prior to -- this was before 1994. This was well before pre-DSHEA.

That dark, hard-to-read copy of the United States dispensatory is the 20th edition published in 1918. The second edition there that I have is the 21st -- 25th edition published sometime in the '50s. It does not have an entry for ginseng, which is why I didn't bother to find out exactly what the date was. The 26th edition I think had no botanicals at all, so the book was about a third the size of these two books.

But it's interesting. That 1918 edition, yellowed with time -- I have two of them because I went

to the oldest College of Pharmacy in the country, and

they were throwing them out at one point. And they just had them out on a cart saying take one if you want it. But there is an entry for ginseng.

Now, I -- you probably can't read this because I can barely read it on this screen up here, but it says Panax quinquefolius. So it's American ginseng, not Asian ginseng. But clearly, there's an entry for ginseng in this 1918 edition of the United States dispensatory.

This is an excerpt from that, which I knew you couldn't read, so I reproduced it here so you could read it. "The extraordinary medicinal virtues formally ascribed to ginseng had no other existence in the imagination of the Chinese" -- not judgmental at all. It's a little more than a demulcent, and in this country is rarely" implied as -- "employed as a medicine. Some persons, however, are in the habit of chewing it, having acquired a relish for its taste, and it is sold chiefly to supply the wants of these," so evidence that it was used as a food and that it was sold -- 1918 for Panax quinquefolius root. These were

22 -- the people who were consuming it were the

1 collectors, the sang hunters in the Appalachians.
2 The scientific literature can be a source of
3 information about pre-1994 ingredients. So I
4 originally had several of these publications, mainly
5 for convenience because I was the author or coauthor on
6 several of them. I eventually took it down to just two
7 mentions.
8 This particular article was published in 1993,
9 clearly before 1994. It talks about the analysis of
10 commercial comfrey products. So there were commercial
11 comfrey products available on the market prior to 1994.
12 This one is about yohimbe. This one -- I
13 circled this because it's another source of
14 information. So the publication appeared in 19- -- if
15 I can read that correctly, I think 1995. But it was
16 submitted for publication prior to October 15th, 1994,
17 and you can see that in the little disclaimer box down
18 at the bottom.
19 Somebody's messing with my slides. It's not
20 me. My hands are here.

So that's evidence that the work on this -- these products was actually done prior to 1994.

We -- when we published these at FDA, we carefully transcribed the ingredients list. And so we analyzed a number of yohimbe products. And so there you can see that there was yohimbe extract in the marketplace prior to 1994. Let's see. There was yohimbe bark extract in that prior to 1994, just ordinary yohimbe bark as an ingredient prior to 1994.

And then -- oops. Sorry. There's supposed to be another animation.

That long footnote down at the bottom had one product that had a whole kitchen sink's worth of ingredients listed, including things like sarsaparilla, testicle gland, branched-chain amino acids, beta-sitosterol, all sorts of interesting things. Those were ingredients read directly off the label of the yohimbe product prior -- that we collected prior to 1994.

Another source of information -- and this is something that's probably a little bit controversial, and I warned Dr. Welch that I was going to bring this

up. So these are where ephedra-containing materials that we collected. The first ephedra cases that we

worked on at the Agency were in 1993.

And I bring these up mainly because some of these samples were official samples. They had been collected in conjunction with, you know, some kind of a case that the FDA was investigating at the time. Some we just purchased for the purpose of developing analytical methods, so these were not official samples.

We -- we're required to deposit all of these in a sample room at FDA. Now, these samples are now well over 25 years old. And whether or not the FDA sample room still has these materials I have no idea. And that's the question that Dr. Welch would have to answer.

But all of these products had the date that they were collected, a sample number, and the date that the analyst opened them. So in some of these pictures here -- let's see. Here we go.

So some of these pictures have the date when they were collected and also initialed my initials and

the date that I opened the materials for the -- to perform the analysis. So this particular one, I think, is in June of 1994. So we were collecting materials

prior to October of 1994. So those materials were on the marketplace.

Now, alas, these were photographs that I took of these products -- actual photographs, not digital photographs. There's no metadata on them as you would in a digital photo now, so I can't tell you when these photos were taken. These were simple -- simply photos that we took because we made up old Polaroid slides for a presentation, something that doesn't exist anymore either. We're talking about old technology.

So we don't have the back of these labels with the ingredients list in these photographs. However -- thanks. However, in creating -- in populating our notebooks and create -- and populating our analyst worksheets at the time, we were taught how to Xerox entire labels by rolling the bottle as the light bar moves across the Xerox machine. And so that material is available if those analyst worksheets and if those laboratory notebooks, which I had to leave behind,

still exist at FDA.

And again, this is over 25 years ago. I believe that the mandatory recordkeeping for things

like notebooks is, like, seven years, or something like that. So yeah, good luck tracking any of this stuff down. But you know, it may or may not exist if somebody was a packrat somewhere.

Again, this is an example of a sheet from an analyst worksheet. This is some old-fashioned pharmacognosy where I -- before we had widely available microscope cameras where I use the old technique of looking through a microscope with my left eye and drawing using my right eye materials that I had gotten from the yohimbe capsule.

But again, here's dates; sample numbers up here. This is from an analyst worksheet that I had filled out for a yohimbe-based products. So these materials were current at the time. We did collect this information, and we had to save it for at least seven years either as an analyst worksheet or in a laboratory book. So FDA may or may not still have some

of this documentary evidence in existence.

As I said, I presented those scientific papers mainly for convenience because I was the author. I know where to -- knew where to find them, and I know

what the contents are. That doesn't mean you have to go for -- look for FDA analysts as authors of those papers. You can go to the scientific literature.

I cannot stress the value of going pre-PubMed. It -- you -- PubMed allows you to go farther and farther back in time now, but there will be a point at which you cannot go back in time any further. So anything published in the 1800s, the early 1900s might not be easy to find in PubMed. But you can go back in the literature as far as you can on PubMed, pull up an actual publication about a plant, and then hand-search the reference section of those articles. And that's how I came across those United States dispensatory entries, is the old-fashioned technique of hand-searching reference sections and old publications.

So that's all I have for today, just kind of some food for thought. There are some things that I punted on like marketing -- whether or not something

was in the marketplace. But I just wanted to kind of broaden people's mind in what they consider to be documentary evidence.

The nature of the extracts that are listed on

those ingredient labels, good luck with that. I know that they were yohimbe bark extracts or aqueous extracts that were permissible for food -- for the flavoring of alcoholic beverages. Those were devoice of yohimbe alkaloids because they were aqueous extracts.

I know that people were making tinctures for some of those products. So, you know, the nature of the extracts is a little bit fuzzy, simply saying that the extract existed may not be enough for the purposes of determining whether or not a particular extract is a new ingredient. But for point material, some of this stuff is pretty straightforward.

And that's it. Thank you very much for your time.

(Applause.)

DR. WELCH: Thank you, Joe.

Our next speaker is Michael McGuffin, President, American Herbal Products Association.

MR. MCGUFFIN: Good morning and thank you to the Office of Dietary Supplement Programs for inviting me to participate in this panel.

AHPA has previously communicated that it views the efforts by FDA to create an authoritative list of ODIs, or pre-DSHEA, ingredients as the Agency has previously described it in the revised NDI draft guidance is unlikely to be successful in actually compiling a list of these ingredients. AHPA repeats that concern here today, and AHPA and its members would need to see a significant shift in the Agency's thinking if we are to embrace the current effort.

My comments today address several points made by FDA on the issue of identifying ODIs in that draft NDI guidance, as this is the most recent Agency communication on the matter. My comments largely disagree with FDA on several details, but also provide suggestions for improvements and revisions.

Where is the -- how do I do this?

You can see here that FDA is consistent in

discussing documentation of the ODI status of dietary ingredients as necessary, recommended to show, or needed to determine that an ingredient was marketed before October 15th, 1994. The companies that sell only ODIs are not required to obtain or provide any

such documentation. They must register their facilities, comply with CGMP rules, label their products in accordance with all relevant regulations, and make sure to meet their requirements under the law if any adverse events are reported to be associated with those products. But they do not need to obtain old records to show that. For example, valerian root or saw palmetto fruit was marketed as a dietary ingredient before 1994.

This does not mean that supplement companies that market only ODIs are off the hook with regard to safety. As Steve and Loren both said, the NDI provision of the law only establishes that old dietary ingredients are old. It does not establish that every old dietary ingredient is safe in any quantity for any person.

Whether a supplement is made with pre-DSHEA ingredients or new dietary ingredients, it's held to the adulteration clause of the Food, Drug, and Cosmetic Act and so is adulterated if it presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling

or general conditions of use. Marketers of both ODI-based and NDI-based supplements thus have an affirmative responsibility to meet this unreasonable risk threshold.

I don't know what I did right to -- oh, there we go.

Let's move then to identifying the sorts of records that can be used to show a dietary ingredient is a pre-DSHEA ingredient. And here in introducing the idea of an authoritative list of these, FDA stated in the 2016 revised NDI guidance that since the Agency does not generally have access to marketing records, it would rely on records supplied by the industry. And the Agency identified these numerous kinds of records, most of which do not exist anymore.

We don't have sales records, bills of ladings,

sales contracts, manufacturing records, commercial invoices. These are all internal documents. They're just not there, as Loren mentioned. Maybe somewhere they haven't cleared them out yet with their SOPs that require them to destroy records after 7 to 10 years. They're just not there.

Even these more broadly available records that were broadly available in '94 -- commercial -- or rather, magazine ads, mail order catalogs, sales brochures, lists of ingredients for sale. Some packrats might still have a box or two of their own. I would be one of those, but they're still not readily accessible. They're not things that we can readily find. So identifying these documents as the type of documents that FDA recommends to show that an ingredient was marketed prior to the date, the Agency has identified records that are unlikely to still be available. So of course, we can glean some information from those, but they're unlikely on their own to provide a robust record of the 1994 supplement marketplace.

On the other hand -- I'm just not technically advanced here. Here we go.

Some records that have not been lost over time are the various lists submitted by the trade associations to FDA in 1996 and 1998 to identify ingredients believed to have been in the U.S. market when DSHEA was passed. But FDA has stated that it does

not accept these records as authoritative and has cited as rationale for dismissing them out of hand specific problems with each, some of which are articulated here. These problems, by the way, were first brought to the attention of the submitting organizations many years after they were presented to FDA. And so we didn't really have an opportunity to go back and try to repair these things.

AHPA completely disagrees that these records should be rejected out of hand and opposes the wholesale dismissal of these lists as relevant records for ODIs. Rather, FDA should accept these as documentation of pre-DSHEA marketing of the many ingredients for which there are no questions on these lists, which at least established that the listed

ingredients were very likely marketed in the United States on the date.

In discussing these industry-supplied lists, FDA has also stated its unwillingness to consider these as valid records because it's unable to verify the accuracy of the lists. Again, AHPA thinks that FDA should accept the good represented by these lists

rather than rejecting them for the absence of the perfect and so, therefore, strongly recommends that FDA state its intention to consider exercising enforcement discretion by recognizing each of the ingredients of these as -- in these lists as very likely to have been marketed pre-DSHEA.

There are some ingredients on this list, as others have mentioned, that are no longer allowed to be sold. I'll get back on that after my next discussion, which is on these two documents issued by AHPA in the first edition 1992 and the second edition in 2000. The first, of course, was published pre-DSHEA; the second one stated clearly, "We only included ingredients that we believe to be in the marketplace prior to October

15th, 1994."

Again, FDA stated that these are -- these can't be accepted as authoritative. And it gave as reasons that books do not identify the plant part or other extract part. But rather than simply rejecting these references as having no relevance, FDA should consider any listing in the text to represent the commonly used plant part -- so chamomile flower, but

not chamomile root; gingko leaf, but not gingko bark. We know what the parts are used. That information is readily accessible.

And as previously communicated to FDA, it's AHPA's view that traditionally processed extracts derived from any pre-DSHEA botanical ingredient should also be acknowledged as a pre-DSHEA ingredient. And we've articulated in detail in our written comments what we mean by traditionally processed extracts.

As noted with the lists submitted by industry, there are some plant species included in herbs of commerce that were lawful at the time of the publication, these -- this -- lists that -- and references that have since been removed under FDA's

extensive authority to regulate supplements. Examples include, of course, various species of ephedra. It would be a simple matter, though, for FDA to simply exclude these from any eventual authoritative pre-DSHEA list or to identify these with some kind of footnote or marker as unallowed through other provisions in the law. Either such approach would be far superior to completely rejecting the usefulness and validity of

these documents as accurate records of pre-DSHEA dietary ingredients.

Another perfectly legitimate record to establish that a dietary ingredient was marketed in the U.S. prior to the date would be a sworn affidavit attesting to this status. FDA has stated that it would not accept such affidavits. AHPA finds this position to be remarkable and to be completely contrary to the manner by which proofs are made in the courts of the United States.

FDA also considers marketing a dietary ingredient to mean selling or offering the dietary ingredient in this very narrow scope of as a dietary

ingredient for a dietary supplement or in a dietary supplement.

I know I'm running out of time now. Suffice it to say that AHPA believes this limited view of what constitutes marketing in the U.S. is unnecessarily narrow. It's inconsistent with the actual language of DSHEA and the intent of Congress when this good law was passed. AHPA believes that marketed in the United States simply means sold or offered for sale by or to

any U.S. company, largely irrespective of the end use in an oral dose product. And we will discuss this in greater detail in written comments to the docket.

When -- Joe mentioned that 1980 United States dispensatory. Every one of those was marketed in the United States prior to 1994. You can tell because the copyright date is 1918. The 1950 one Farmer's Almanac that I have, that was before 1994. Those -- that almanac listed dozens and dozens and dozens of herbal products for home use, and those were all marketed in the United States prior to 1994. And the idea that we would reject them because maybe they made a drug claim simply throws out the historical records.

With all of my comments to this point -- where am I on time here -- AHPA believes that there are other documents than those few types the Agency has previously identified and that I've described today as records that are likely no longer exist or only marginally exist. AHPA believes, for example, that any pre-DSHEA-dated letter addressed to a U.S. firm, whether from a U.S. or foreign supplier, to solicit purchase of a dietary ingredient is a valid record of

pre-DSHEA marketing, though these, too, may be difficult to locate at this late date. I have a few of them.

More readily available references that at least implied pre-DSHEA marketing include herb books, Jeanne Rose's Herbal, Jethro Klos's herb book. All of those herb books that we were all reading when we were kids identified ingredients that were in the marketplace. Even though there wasn't a dollar sign, there wasn't a bottle offered, those should be recognized as references that clearly at least strongly suggest that these products were marketed prior to the

date.

And pharmacopeia listings to dispensatories, the USPs -- the 1820 USP that included hundreds of botanicals that were marketed in 1820, which was prior to 1994 -- each of these must be considered as implicit evidence of pre-DSHEA marketing, in which AHPA believes a court of law would consider as such evidence should a court's opinion be requested.

To summarize, AHPA believes that for FDA to be successful in creating an authoritative list of ODIs in

a manner that balances this task with the Agency's highest priorities, FDA must make some significant changes to its previous positions. These include that FDA must accept records that are currently widely available, modified as needed to make corrections or to remove a few specific listed ingredient.

FDA should move away from any quests for absolute proof of pre-DSHEA marketing and move toward exercising enforcement discretion for dietary ingredients that are acknowledged as very likely to have been marketed in the U.S. as of the passage of DSHEA. This suggestion, by the way, is consistent with

FDA's statement in its September 6th Federal Register Notice that announced this meeting and, as Dr. Ostroff said this morning, that the Agency should "better focus our enforcement efforts in alignment with our strategic priorities of consumer safety, product integrity, and accurate information."

Next, any eventual authoritative list should identify as a pre-DSHEA ingredient any traditionally processed ingredient derived from a pre-DSHEA botanical ingredient.

And also, FDA should move away from its prior stated position that only pre-DSHEA use of an ingredient in a product that would today be identified as a dietary supplement actually demonstrates an ingredient to be a pre-DSHEA ingredient.

In closing, AHPA recommends that FDA seriously consider whether the significant Agency and industry resources that would be required to create the envisioned authoritative list of pre-DSHEA dietary ingredients is the best use of those resources. In the narrow context of DSHEA's NDI provisions, it's AHPA's

view that these resources might be better directed to providing guidance on how to clearly describe an ingredient that is the subject of an NDI notification, as this is the single issue that is most commonly identified by FDA as a serious concern in responding to submitted NDI notifications.

More broadly, though, if FDA, and especially the Office of Dietary Supplement Programs, has resources to spare, AHPA believes these resources might be better addressed to improving a mutual Agency-industry understanding of FDA's current good

manufacturing practice regulation for supplements and to assisting manufacturers, especially small entities, to comply with this complex rule. The GMP rule affects 100 percent of dietary supplement products, whereas the NDI provisions and rules apply only to that proportion of supplement products that actually contain an NDI.

Thank you very much.

(Applause.)

MR. DURKIN: Thank you, Michael.

Our next speaker is Duffy Mackay, Senior Vice President, Scientific & Regulatory Affairs at CRN.

Duffy?

DR. MACKAY: Thank you, Bob.

Good morning, everyone. It's great to here -- be here. I'm with the Council for Responsible Nutrition, one of the trade associations here in D.C.

It's great to see such a sincere interest in today's topic, and I want to host (ph) the Agency for this discussion. And I want to thank everyone that's -- - for adding their viewpoints to this. We clearly have a topic with a broad spectrum of interests. And I'm hoping that what we hear today gives you enough

information to find a path forward because I think the task at hand is very difficult.

MR. DURKIN: What you want? You need this?

DR. MACKAY: All right. So October 15th, 1994, a date we're going to hear a lot today, that's when the law was passed. And here we are today, October 3rd, 2017, 20-plus years later, and I would argue we are starting from scratch. We are starting from point 0 in time today, 20 years later. And therefore, we took the liberty to sort of start our

thinking from scratch -- big problems, new ideas.

Industry's had a position for a long time. Some of the consumer groups have had a position for a long time. We continue to play this tug-a-war. And it's time to really start mapping out a path forward that makes sense and allows both groups to feel confident we're in a good place.

So our task right now, the one we're discussing, is identifying independent and verifiable evidence ingredients were sold 20-plus years ago. We've heard a lot of rationale, very reasonable rationale why this is going to be a very difficult

task.

And I've got a spoiler alert that no longer is a spoiler. This exercise alone, especially if we continue to see the interpretation of the evidence constrained and limited and specificity required, this exercise alone is not likely to result in the desired certainty around a significant number of common dietary ingredients that common sense would dictate have been used either in food for a long time or actually in dietary supplement-like products.

So we really need to think about this in a way that allows the consumer groups to feel comfortable that is appropriate regulatory paradigm for these ingredients as well as for consumers and the people who consume these products as well as the industry is not strapped with unreasonable resources or unreasonable regulatory requirements. So we're back to this point of balancing consumer accessibility with appropriate regulation.

So what are our goals? I think it's fair -- and when I say stakeholders, I'm talking about industry. I'm sort of trying to think on behalf of the

Agency, and I'm also thinking about consumers. And I think it's fair that we all desire transparency and regulatory certainty regarding a very long list of common dietary supplement ingredients.

There are too many questions. Even industry has questions. Is this form of zinc old? I don't know. It's a hard question to answer when you're faced with a board of directors and business decisions and lots of different things that you're faced with and

people want certainty, transparency. Investors want it. Consumers want it. So let's move forward.

Stakeholders also want consumers to have access to safe dietary supplement. The industry I work with really values safety as a high priority. I think it's fair to say that industry embraces its obligation to file a 75-day pre-market notification for new ingredients when, in fact, there is no evidence to support a history of use in the food supply or as a dietary supplement. So on the flip side, the industry does not support unnecessary regulatory submissions for ingredients where we do have the common knowledge that these ingredients have been consumed for a long time.

So we'll go to the safety standard. Whoops. And I know I'm oversimplifying some of this, but for the sake of discussion, we have these three buckets that we have been given.

Old ingredients -- the infinite wisdom was their presence in the marketplace provides an adequate history of use to establish -- and I kind of overstepped here -- reasonable expectation of safety. We all know that's not true. If you have an ingredient

that was on the market, that's all it tells you. It was on the market. But as was mentioned, Section 342 of the Food, Drug, and Cosmetic Act would also, as an umbrella clause, say that you as a marketer have to understand that your finished product with that ingredient as formulated and as instructed is still safe for the intended use.

We'll take caffeine for an example, a great ingredient to talk about -- old ingredient, been around forever. No one would expect an NDI to be filed on it. However, when firms try to sell pure powdered caffeine, the form changed everything. It became unsafe, it became dangerous, and FDA said this is no longer a

dietary ingredient.

So again, Section 342 kicks in even if no notification is required, and we need to have that guide this whole entire discussion because just because no notification is required does not mean your obligation to establish safety is skipped. So we have to remember that as we move forward.

So then we have new dietary ingredients. And

all's that happens here is that the history of use or other evidence of safety that establishes the ingredient as reasonable accepted to -- for safety is given to the Agency so they can acknowledge it. That's -- you know, still, we're just looking that it's been consumed and there's evidence that it meets the standard.

One thing we're not talking about so much -- and clearly from the discussions, a lot of evidence is going to be out there that says this ingredient has been used hundreds of years, 50 years, 60 years. But getting into where it was marketed and whether it was marketed in a tablet or capsule, that's going to be a layer that's very tricky. So we have to remember that

ingredients that are already in the food supply, that in itself provides evidence that the -- there is a history of use which can link to a reasonable expectation of safety. And the guidance would say no notification is required. So these are new dietary ingredients, but no notification is required for ingredients which have been present in the food supply as an article used for food in a form which is not

chemically altered.

I would argue we are going to find way more evidence related into ingredients in the food supply than we are when we narrowly look for ingredients that were sold as dietary ingredients, which has been pointed out, did not even exist before 1994. So we're saying the law is telling us you've got to show us it was sold as a dietary ingredient -- whoops -- that didn't exist.

So we have this challenge. And I'm going to suggest that limiting our current efforts, the Agency and the industry, on only developing a list of ingredients for which there is pre-1994 evidence they were marketed as dietary ingredients is not an

efficient use of anyone's resources. And we will suggest a better path forward is expanding the scope of this effort to establish clarity with regard to all dietary ingredients that can be used in dietary supplements without notifying FDA 75 days before market. This is all based on what's in the current draft guidance. This is all based on legislation.

But why waste our time on a short list of ones we can find hard evidence? Why not make a nice, long list of ingredients that you don't notify where industry can formulate and use without concern -- certainty, transparency.

So where -- what will we do here? We would create a comprehensive list of all these dietary ingredients. It would include the pre-1994 ingredients. So we would do whatever we come up with regard (ph) what evidence, what process. We would all work together to get those things nailed down on the list.

But we would add to that all the NDIs that have been filed without objection. There are a handful of ingredients that have been filed, and believe it or

not, it's actually not that easy to find information on. So how we have our pre-DSHEA ingredients, we have our NDIs with no objection, but we could also create a much longer list that includes ingredients already in our food supply. This is going to be a much longer list, a much better resource for both FDA and industry. And it allow -- which I was really -- great to hear

this idea that if we get this all done and we do it right, the Agency and industry can focus our resources on the more important stuff -- GMPs, real safety reviews, getting those NDIs filed. We can create certainty around the low-hanging fruit; we can move on.

So where do we look? We have databases out there both for the global food supply and the domestic food supply. And you pull those databases out, and lo and behold, you find all sorts of ingredients that are used in dietary supplements. So instead of running around chasing receipts for chondroitin sodium sulfate, which is already a GRAS ingredient, why don't we just pop it on the list as an ingredient in the food supply, as an article used for food? If no one chemically alter it, done, no need to look for that receipt. Move

on to the next ingredient.

Bacillus coagulants, another common dietary ingredient, firms won't know. They -- I'm selling bacillus coagulants. How do I find the evidence? Where do I go? And instead, the Agency and the panel and whatever we come up with can vet these things, get

them on the list, and we can move on.

Here's another database the FDA has -- everything added to food. I sort of cherry-picked through this database to let -- you know, acai berry extract. I don't remember that before 1993. I really wasn't using a lot of supplements back then. But you know, again, no one has to find that receipt. Whey protein concentrate -- all of these different forms of zinc are in the food supply as articles used for food. Take them off the lists, no reason to talk about it.

So a reasonable path forward is developing a comprehensive list that includes all three of these buckets. Now, we had a pre-conference call. A couple things came up, and I think it's very fair to say there are two important considerations to make any of this work. One of them is that an ingredient in the food

supply is distinctly different and separate than any isolated bioactive ingredient or a constituent found within the same food. We'll talk a little bit more about that.

A second -- and I've already said it, and I'm going to say it again because it's so important --

manufacturers always have an obligation to evaluate the safety of all finished dietary supplements to ensure they meet the dietary supplement safety standard, even when the manufacturer is not required to file notification with the Agency.

So what do we mean by ingredients not equal in constituents? So important. Why so important? Because I think it's fair to say this is the issue that has dragged this thing out of the closet and caused so much tension. We have ingredients out there that are isolated constituents a botanical, and people are trying to say they don't have to file an NDI. It's just not true. It doesn't make any public health sense. We know that's the -- basically how drugs are made. You find cool compounds in plants, and you isolate them and you make drugs.

The dietary supplement regulatory paradigm would say that is new. Please submit to us that you need evidence that establishes safety. A great example is pineapple. Pineapple is an ingredient in the food supply. Long history of safe use -- we've probably all

eaten pineapple. So therefore, common sense would dictate any dried, ground -- and also the draft guidance would dictate a water or alcohol extract of that pineapple would not chemically alter it. And therefore, no notification is required. That's what we get for pineapple.

However, bromelain is a chemical constituent found within that pineapple, also has health benefits that might be worth supplementing with. But it has to be looked at as a completely separate ingredient that requires its own regulatory path to market, whether it's GRAS, NDI notification, whatever it is. It cannot piggyback just because it exists in pineapple.

Now, exposure date related to people eating pineapples can be used as part of its history of safe use to develop this argument; however, you need its own independent pathway. And in fact, in this example, I

looked up bromelain, and someone did a GRAS affirmation back in the day. So bromelain itself went to market independently as its own ingredient. It's now in the food supply as an article used for food. And if you choose to use bromelain in your supplement, no

notification required. Let's move on.

Safety. We've talked about this -- Section 342, an umbrella safety clause. Every time someone today tries to say no notification is required, this is FDA's only opportunity to evaluate safety, this is how DSHEA was enacted. These are food ingredients balancing consumer access. It was chosen at the time that people would be able to evaluate their formula and determine if it met the standard. That's what we have.

So in conclusion, a reasonable path forward -- I said it three times. That means everyone is going to remember this. Put a list together that has the old ingredients, the NDIs that have not been objected to, as well as a long list of ingredients found in the food supply.

With that, thank you, audience. Thank you guys.

(Applause.)

MR. DURKIN: Our final panelist to speak today for this first session is Pieter Cohen, Associate Professor of Medicine, Harvard Medical School.

DR. COHEN: Thanks for having me.

A few quick introductory notes how I got interested in this. My -- I'm a general internist at -- right outside of Boston, Somerville. And when my patients started becoming ill -- this was about 15 years ago -- the investigation eventually led me into this research that I now do into the safety of dietary supplements.

So prior to that, I had no specific knowledge or interest about supplements, per se. I assumed that they were all safe, and I hadn't thought this was an issue. But the last 15 years and the research we've done over the last decade has really changed my mind about that.

But at the same time, supplements are something that's -- that are absolutely essential and that I recommend every single day in clinic to my patients. So there's not a day that goes by where I'm

not talking to multiple patients about making sure they're taking their supplements on a regular basis or starting a new supplement.

So with that said, I also just want to mention

that I -- the only -- I don't have any conflicts of interest. But Consumers Union has read research of mine in the past.

I'm going to focus today on three issues that I think are germane to today's conversation -- the context under which we're making this important decision -- the FDA is making this important decision; then talk specifically about what an ingredient means to us from the research perspective; and then very briefly mention a comment or two on marketing.

So in terms of the context, this decision, this discussion, is so important, as we know, because the only opportunity for the FDA to be involved with ingredients prior to them reaching consumers is through these hard decisions. Is it a pre-DSHEA ingredient? Is it something that requires an NDI or GRAS?

So this is of the utmost importance, and we need to take this decision very seriously in the

current context. So we don't have time to go into detail about all these different aspects of the current context, but I'll just mention the things that aren't -

- that seem to be relevant to help us decide how lenient or not to be in terms of this decision.

Number one, there is no product list available. So the FDA has no idea what products are out there, and there's no -- therefore no way to track anything about the products out there. And of course, firms can change products at any time without informing the FDA as long as they're not involving an NDI. There's no requirement -- and this is from my patients' perspective -- there's no requirement that the label lists known adverse effects of the ingredients, nor is there any requirement that the label requires information regarding drug supplement interactions.

Secondly, since the FDA doesn't know what products are out there, it's not too surprising that there's not an effective way to detect dangerous supplements. We know that there are hazardous supplements out there. But the different -- they're detected in different -- by different people, and those

groups do not talk to one another.

So we know from investigations that the CDC has done -- epidemiologists at CDC that doctors report

over 20,000 people seeking emergency care due to harm from supplements. We also know from other research from the poison control centers that, additionally and separately, maybe people who don't seek care are calling the emergency poison control centers to seek help with harm from supplements. And then separately, we have the FDA's MedWatch system. None of these systems talk to each other or are accurately categorized and collected. Therefore, we don't have an effective system to detect the occasional harmful products that are out on the market.

With that said, I appreciate that the great majority of markets are entirely safe. But it's of our utmost importance to be able to in a timely fashion identify those few products that might be causing the most harm.

And then the third part of the context is that we don't have ability. The FDA has been unable to officially remove the products that are found to be

harmful when they do become harmful. So there's a long delay in terms of identifying those products, and then

the FDA has been unable in a timely fashion to remove the harmful products from store shelves. Ephedra's a great example because of course, as Steve Tave has already mentioned, it took a long -- prolonged 10-year process that went all the way up to the Supreme Court before ephedra alkaloids could be removed from the market.

In terms of -- and that's, of course, through the legislative process. But the more common process is either warning letters or recalls. And our research has found that neither of those are effective either. In the case of recall of individual supplement ingredients, we have found that the identical product has been sold years later with the same hazardous adulterants in it after FDA recalls.

And in terms of letters, the classic example currently would be DMAA. The FDA has, under Dan's -- Fabricant's excellent work, has been adamant and aggressive in trying to remove DMAA from the marketplace. But unfortunately, there are still dozens

of supplements opening selling DMAA today. And again, it's involved in a long of legislative process. So the

FDA has no way to remove in an efficient manner how -- these infrequent, rare, but ones that can cause serious consequences, such as dozens of cases of hepatitis from an individual product over just a few-month period.

So now turning to my thoughts in terms of the ingredient -- what ingredient means, I just want to second what Duffy has said. I completely agree with him, that we just -- one major step forward from a safety perspective would be to recognize that just because something has been found in trace amounts, meaning parts per million, in a food or a botanical somewhere in the scientific literature, that that doesn't mean that it should -- would be permitted to be introduced into dietary supplements as if it were a pre-DSHEA ingredient. So that's something that I'm delighted to see that we're completely on the same page about, as we are on so many things. In addition, I -- such as access, which I think we should have transparency and safety.

Now, there's another part of the ingredient

that I think we need to think about for a few minutes.

And that gets to a very challenging problem here, which is the -- how the ingredient's prepared. So what we've heard is that there are lots of lists, and some might be more definitive than others. But my concern is not -- is more in the details because what we have found -- and this is with colleagues of mine at University of Mississippi Ikhlas Khan's Lab. I'm going to talk to you about two of our recent studies. And what we have found is that how the supplement is prepared is the bottom line in terms of safety and that the consumers would have no way of telling the difference based on the -- because of the framework and the requirements for the labels at present.

So in the case of yohimbe, which Joe Betz has already mentioned, it's an African tree, and the bark is used -- the extract from the bark is used as traditional aphrodisiac. There would be no question that was traditionally used prior to 1994. The problem comes with when we take a closer look at the products.

Inside that bark is a very -- and the traditional bark would include less than 1 percent --

bark extract, less than 1 percent of a potent -- the

most potent chemical of yohimbine -- it's confusing because it's just I-N-E at the end, but it's the name of the chemical -- that's most potent in yohimbe bark extract. And that's so potent that it's been marketed as a pharmaceutical drug -- prescription drug at dosages of 5 to 10 milligrams per pill when prescribed by doctors. But that's much greater than the small amount that would be found in the bark extract.

When we analyzed supplements that were sold in the mainstream stores -- brick and mortar stores, not -- this is not fly by night or marginal firms -- what we found was that the amount of the active compound, the pharmaceutical ranged from none to greater than prescription dosages. So if we don't know how the yohimbe bark extract is being processed to get into the supplement, we would have absolutely no idea of how it's being -- what its pharmacological effects are and its safety effects. Therefore, what we need to know is both when yohimbe bark extract was sold prior to 1994, what was the manufacturing specifications in which it was used and then replicate those. I also appreciate,

as has been said, that's going to -- a lot of that data has probably been lost.

So a potential compromise here would be to use USP monographs to help us with combining what's on traditional lists using USP monograph manufacturing standards to then ensure that we're dealing with a product that's pre-DSHEA and not a new drug.

Another example of the same process is red yeast rice. It's different because here we have rice fermented with a yeast. And when red yeast rice is fermented in a traditional manner, there contains a small amount of drug in red yeast rice is -- that identical to a prescription statin that lower cholesterol. And this is, of course, one of the most current reasons why red yeast rice is used -- to lower cholesterol and for heart health, which makes a lot of sense.

But the problem is that, depending on the fermentation specifications -- whether or not what yeast is used, how much is fermented -- the amount of the statin, the drug, can vary greatly. In another study with Ikhlas Khan's Lab, my analytical chemistry

colleagues found that there was a 60-fold difference in the dose of the statin in red yeast rice products that we bought from mainstream retailers. The equivalent in medicine would be saying well, I might when I buy -- use Lipitor, I might be taking 20 milligrams, or I might be taking 1,200 milligrams of Lipitor.

I just want to briefly mention marketing. To me, a non-lawyer, it seems to me that it would be important to demonstrate that it had actually been bought and sold and consumed because often -- obviously the presumption of safety comes from consumption of the product. So a simple advertisement in a magazine doesn't seem to me sufficient information that it was actually bought or sold or marketed, but I'll leave that to the pros to sort out.

So I just want to conclude in saying that, while I am completely sympathetic and agree with Duffy's point about safety and that this -- the safety overrides everything, in an ideal world, that would make perfect sense. The problem is that, today, we have no way of detecting the unsafe products and then removing them from store shelves. Until those issues

can be sorted out, we can't move to this other place, which I think would be much better for all of us to be in.

So I think we should focus on how -- on distinguishing a constituent of an ingredient from something that's been found. We should focus on having solid manufacturing specifications, and we need to make sure that it was consumed prior to 1994.

Thank you very much.

(Applause.)

MR. DURKIN: Thank you to all of our panelists for your excellent presentations.

This is the time now where the other stakeholders in the room and joining us online have the opportunity to ask some questions of the panelists.

Folks in the room, if you notice, there are microphones on either side. Please feel free to avail yourselves to those for questions.

And folks online, you can submit your questions, and they'll be relayed to us up here at the panel.

MS. MACCLEERY: Hi, there. Laura MacCleery

with Center for Science in the Public Interest.

I really appreciated the panel overall. I wanted to follow up with Duffy on your idea about two things. First, are you suggesting that there would be a process that would sit atop of the current proposal to look particularly at safety? Because it -- on several points in your remarks, you focus on the fact that the obligation to safety attaches to any product sold as a dietary supplement.

And I wondered. What would -- what, in your mind, is the mechanism by which FDA and the industry and consumer organizations might sit together and look at this question of safety with regard to the development of a list?

DR. MACKAY: Appreciate that comment. Hard to answer because -- is the other microphone -- the mechanism -- the discussion today is not about establishing a pre-market review for all dietary ingredients, especially for the ones already in the food supply.

My recommendation was, the way it sits today, there's three buckets of ingredients that if you as a

manufacturer choose to use, you do not have to submit a notification. Notifications are expensive and time-intensive.

So if chondroitin sodium sulfate has already got a GRAS affirmation, it's in an FDA database, it's already being consumed by humans every day, a firm should not have the question do I have to file notification for this ingredient. They can put it in a formula.

Then what I was referring to in the umbrella of safety is, once they've formulated that product and once they have determined the intended user -- kids, adults, pregnancy, whatever it is -- they do a safety evaluation as per Section 342 of the Food, Drug, and Cosmetic Act that all food companies should be paying attention to and all dietary supplements should be paying attention to and is the law of the land with regard to adulteration currently.

So all's I'm suggesting is that an efficient process be put in place so that we don't waste time and energy and resources on ingredients that are readily available in the food supply already today. And then

FDA can peel back its energy and say which ingredients are we worried about and let's get busy on those.

MS. MACCLEERY: Okay. Thank you.

Two follow-ups, if you will. How would you think about the safety of novel combinations of ingredients that haven't been used in that form in combination before?

DR. MACKAY: Well, we are talking about food, so we are not talking about drugs. And so therefore, the current regulatory paradigm is based on these being articles of food. We are regulated as food. These guys sit in the jurisdiction of food.

And so we do not -- just like a GRAS ingredient, once you've established a GRAS ingredient is GRAS, if I put together a protein bar, I do not have to do a safety toxicological submission to FDA to say my protein bar where I've added a probiotic and some vitamin C to needs to be submitted to FDA. I know these are two safe ingredients already in the food supply consumed by thousands and millions of consumers.

But I do have Section 342. So I will go to my chief science officer and say please look at this.

Now, if that chief science officer says I used caffeine and some herb that contains a stimulant, then he's going to say I need to assess the additive effects of these stimulants to make sure that it's safe for the intended user.

These are all rules that are in place today that keep our category of ingredients incredibly and why our numbers of adverse events are so low and why millions of consumers enjoy our products daily.

MS. MACCLEERY: And so that example is really interesting because I think that's at the heart of some of what we've seen with the energy drinks where you do have multiple stimulants stacked in the same ingredient. And it's not really clear that the combination has been evaluated for safety at the end product because companies are using GRAS self-affirmations.

And so the -- my third question would be, you know, your examples all had to do with public notifications and use of the FDA GRAS affirmation process. What about GRAS self-affirmations by companies that are really made in a back room and held

private and where the public and FDA has no visibility?

DR. MACKAY: Well, the whole GRAS process is laid out very explicitly, including how you put the panels together and how you do the toxicology. And the wisdom of the people who put these policies together, we know that FDA does not have the resources to look at every single GRAS affirmation for dehydrated bananas or powdered chlorophyll. These are food ingredients, and so these decisions were made a long time ago. And at one point, they did require notification to FDA. FDA could not keep up. And therefore, the self-GRAS affirmation was put in place.

And we're not here today to argue the merits of the self-GRAS affirmation. I'm here today to say these ingredients are in the food supply as articles used for food and, if they are not chemically altered, can be used in a dietary supplement with no notification.

And we should help the industry and the Agency to decide which those ingredients are. Let's be transparent about it. We're not here to discuss changing the GRAS process. We're not here to discuss

introducing safety panels into this process. Those would require changing the law.

MR. DURKIN: I'll invite anyone else on the panel to opine on the questions if they'd like. No pressure.

MR. MCGUFFIN: Just a comment that I think reiterates the point that Duffy made is the general premise in making a food is that if I combine safe food ingredients, I have a safe food. I tried to give Cara, but I ran out. I made some fig jam, but I did this crazy thing. I put fennel seeds in it. It had never been done before as far as I know. And as any of you know that study botany, the APACA, those seeds, they're filled with all kinds of chemicals. I had no idea. But it was really delicious. I used safe fennel seeds with safe figs and safe vinegar. I'm not going to tell you the whole recipe, but it was amazing and no one was harmed.

And so we have the same theory here. And I think that the example that Duffy used that was really good. We also had this obligation to ensure that we comply with 342, that we're only selling safe foods.

And so if you do take two ingredients that you know might work together, two stimulants being the most common issue that we address, then you are going to have to, as a company, take responsibility for ensuring that the product that you put in the marketplace is reasonably expected to be safe.

And then to something that Dr. Cohen said, we do have an obligation to provide material information on that label. So if it's supposed to say not for use by children under the age of 18, then it should say that. And we read the law as requiring that. In fact, one of the advances of DSHEA is that, prior to its passage, we were all afraid to put any warning on a product. We were all afraid to completely inform the consumers of what we know about safety because only drugs do that. And DSHEA specifically allows cautionary statements on product labels.

And you know, we owe it to the consumers to make sure that we are adhering to that provision of material information that's relevant to any combined food.

MR. DURKIN: Okay. Thank you.

As you ask your question, could you please state your name and your affiliation?

MR. FRANKOS: Yeah, I'm Bill Frankos with Herbalife.

Duffy, I would like to also add to the list of ingredients any direct food additives that's proved in 21 CFR. There's also an extensive list of flavoring ingredients, spices, herbs, and they are listed. And they don't specifically say for the herbs, for some of them, what part is extracted. It's just listed as an herb.

And I would also suggest that FDA be clear that if an herb is listed either as a GRAS ingredient or as a direct food additive that FDA would specifically indicate that that can be used and process in a way that doesn't alter the identity. And that would include, based on Congressional history, water and alcohol extracts.

So I think -- globally, I think this list should be very clear about that ingredient on this list can be extracted with water or alcohol and not have to submit an NDI notification.

So that -- I would add that to this list.

MR. DURKIN: Duffy, that was in response to something you said. Do you have any --

DR. MACKAY: The answer is yes.

MR. FRANKOS: Yes.

(Laughter.)

DR. MACKAY: And Bill, that's exactly -- when I talk about traditional extracts of old botanical ingredients, we certainly mean water extracts, ethanolic extracts, probably also vinegars, oils, but fairly simple almost processes that you could do in your kitchen, but certainly traditional food processes that were established by 1994.

MR. FRANKOS: Thank you.

MR. DURKIN: Doctor?

DR. COHEN: That also allows me an opportunity to explain the distinction I have because what we also know is that you can take an extract -- an aqueous extract, for example -- and through chemical processing, greatly increase one component.

So when we're talking about these active compounds, it's the nature of the extract that I'm

concerned about, although I certainly appreciate the point about the general acquiesce in other, you know, general methodologies.

MR. FRANKOS: I agree. But the way you extract, whether it's water, alcohol, or tincture (ph) -- and it's the processing as you're doing the extraction that you have to look at -- that evaluation is done in the safety review of that specific product that's extracted. So putting it on the list is the first step. But then you have to do the safety review, as many of you suggested.

DR. COHEN: Just from my perspective as a physician consumer, it's -- if you're looking at what was marketed, you're looking at what active ingredients are being consumed into the human body so that those details are absolute essence, you know, and not have to do with a separate safety eval. I'm not asking for a safety evaluation of all those products, and I completely agree.

UNIDENTIFIED MALE SPEAKER: Compositional.

DR. COHEN: Exactly. It's composition.

So it -- on the other hand, if you had very

specific details about what was in the final product and you could, you know, retrograde, figure out how to manufacture that, I would also be completely comfortable with that. The question is, what was being consumed by humans prior to 1994 as a supplement or food, is that what's in the supplement?

MR. FRANKOS: Thank you.

MR. HENNINGFIELD: Good morning. I'm Jack Henningfield.

Outstanding panel session this morning. Every one of you touched on issues that our company and clients are working with.

I'm a pharmacologist, professor of behavioral biology at Johns Hopkins, and I'm a consultant at PinneyAssociates. And we work mainly in drugs and tobacco and dietary.

And two issues came up, and one is the substances that are basically under the conventional radar screen -- you know, before internet, before other things -- and that came in with immigrants. And one that I'm working on is kratom, a leaf from a tree in

Southeast Asia.

Now, documenting, marketing, and sales and use through conventional means, just I don't think it's going to happen. I'm from Minnesota where a long of Hmong immigrated to, and I very quickly found through my Hmong friends and colleagues that kratom has been used and brought over and was used pretty commonly. I thought, well, maybe you -- we can get affidavits. I found out that might not be acceptable.

There is also a history of foreign use and actually a lot of science in Southeast Asia. And what I'm wondering is what might be the standards that might be in a guidance document for the use of affidavits. So it seems to me it shouldn't be a black-and-white issue -- you can or you can't use affidavits. But what are the conditions? What would satisfy? What would be reasonable evidence?

As a scientist, I always look for convergence. So me running to Minnesota and getting affidavit from a friend probably isn't enough. But there's got to be some way you can use that information.

The same applies for ex-U.S. data. Some ex-U.S. data is garbage; some U.S. data is garbage -- are

garbage. But some ex-U.S. data are great.

What do you think about coming up with standards that would allow us -- somebody like me working with clients to say okay, here's what we've got to do to get affidavits that would satisfy FDA and be reasonable evidence, and here's what kind of convergence we need from ex-U.S. information that would be reasonable, instead of bringing it in and then, well, that's not good enough?

I'd love your comments on that.

MR. MCGUFFIN: Let me start with I'm not going to be able to answer the question about what information in an affidavit would satisfy the Food and Drug Administration. But I do think, Jack, you're pointing out these ethnic botanicals that have come in. We know that has happened for a long time. The first death notes were British, and they certainly brought their -- or Dutch, probably -- and they brought their herbal medicines with them. Absolutely. And those were marketed in the United States before there was a

United States in herb shops in Manhattan.

Certainly in -- the Chinese immigrants that

came in in the 19th century, there are at least two Chinese herb shops that I know that are maintained -- one of them is on the National Registry of Historic Places -- that was an herb shop. Every single herb that was sold in that herb shop was marketed in the United States prior to the date.

Now, some might argue yes, but those were marketed as drugs. My view, AHPA's view, is that any oral use establishes use in the United States prior to the date. We know that immigrants from Vietnam in the mid-'70s, they brought their botanicals with them. The immigrants from South America and Central America brought all of those botanicals into their botanicas (ph). Those were all in the United States prior to 1994.

And I do think we need to figure out a way to recognize that and add to Duffy's lists pretty much all of these ethnic -- they were medicines, but they were also being consumed in a manner that was a home

medicine, a traditional therapeutic agent. We think all of those are old dietary ingredients.

I can't really help you with your specific

question about an affidavit, though. Maybe Steve can. I don't know. No, not today.

MR. DURKIN: Does anyone else on the panel have anything to offer on the topic?

DR. MACKAY: You know, I would. We have a few botanicals out there currently that raise a lot of questions from a lot of sides of the aisle. And I just don't think we should let today's conversation be guided by those extreme points of view.

You know, we have cannabis coming back. We have kratom (ph), and we have all this stuff happening. But what we're talking about today is not that. What we're talking about is the common ingredients that people consume as dietary supplements and getting clarity and certainty around those.

Your kratom story is going to go on for a very, very long time, and this is not the time to solve that. This is the time to get the current dietary supplement industry that has been around since '94 the

clarity and transparency it needs to market health-promoting products. There are botanicals out there that clearly fall in the category of medicine, drugs,

and there's a route-to-market currently for that.

Or you need to get together with your friends and create a new market for these products and a new regulatory category. But you know, right now, we're talking about dietary ingredients that were used in dietary supplements.

MR. DURKIN: Question from this side of the room maybe? Your name and affiliation for the question.

(Laughter.)

MR. TAVE: I'm happy to wait my turn if there are others, but since there was a lull, I thought I'd take a chance.

Let me make a quick point on affidavits since there -- it was brought up. I mean, if you look in the revised draft guidance, we did not rule out the absolute use of affidavits. What we said was an affidavit unsupported by contemporaneous documentation

is not likely to be persuasive.

So affidavits, I think, can be a part of the puzzle. But at the same time, I think an affidavit saying I swear I consumed this 30 years ago is maybe

not as likely to sway us.

MR. DURKIN: Let's throw that to the panel for any comments.

MR. TAVE: Only since I was put on the spot.

MR. DURKIN: Yeah.

MR. TAVE: That wasn't --

MR. DURKIN: Yeah.

MR. TAVE: I'm happy to take responses if you …

MR. ISRAELSEN: Yes, the question which -- that's good news to hear. The challenge will be that the important date is 23 years old. And if no affidavits were taken contemporaneously at that time, how do you fill the gap to have someone who says yes, this happened pre-DSHEA; I'm prepared to state that? How do we get around this problem?

MR. TAVE: Yeah. And maybe I misspoke, and I don't want to go too far down the rabbit hold. I

didn't mean to suggest we're looking for an affidavit from October 14th, 1994. It could be an affidavit from 2017 that points to different pieces of supporting evidence that tend to lend reliability to the

affidavit. But you know, my point in bringing that up was just to say it's not a black-and-white issue.

MR. ISRAELSEN: Okay.

MR. TAVE: But the reason I stood up -- and number one, I want to thank all of you for your presentations. I think, you know, as panelists, collectively, you give us a really good overview of the spectrum of issues we're facing.

And one of the things that I mentioned -- and Loren I think reiterated it a bit -- was we have to address these questions about chemical alteration and identity. And Duffy and Dr. Cohen mentioned it. It's an issue that's there, and it's very easy, I think, as we start to look at sort of the absolute perspectives of here's something that, you know, from an industry perspective we think should be sufficient to establish pre-DSHEA status. From the other side, we could say,

you know, on its own, a certain document might not be adequate to establish pre-DSHEA status.

But as we are here together trying to forge a common path forward to create a list that will, you know, have utility for industry, for other

stakeholders, how -- and this question is not necessarily for Loren. But you know, feel free to start it off if you want.

Does anyone have suggestions or thoughts about how we can define identity? And maybe the other way to look at it would be how can we talk about processes that might actually change the identity or the pertinent characteristics of an ingredient? Because I think in the comments I saw an acknowledgement that there are often changes, or there can be changes, that do change these relevant characteristics. And when that's the case, an NDI might be required.

So I'm looking for some suggestions or some examples or some ways to think about how we can define those so that, you know, if we have a list of ingredients that were clearly marketed pre-'94 and a list of ingredients that clearly weren't, we, you know,

potentially adopt Duffy's suggestion of looking at other sources. There's still a very big middle ground. And how do we help stakeholders navigate that middle ground or looking to the right sources to figure out what they want to do?

DR. BETZ: Yeah. Joe Betz, NIH Office of Dietary Supplements.

Documenting the existence of certain plants and even sometimes plant parts in a marketplace prior to 1994 is relatively easy. I mean, there's a sliding scale of easiness, you know. So I know St. John's Wort, for instance, was -- nobody will dispute that St. John's Wort was in the marketplace before 1994. Some of the more exotic herbs that we've only started to hear about more recently, kratom, you know, maybe not so much.

One of the first things you need to lay out are some definitions, perhaps a lexicon. The United States Pharmacopoeia has started wrestling with this issue about the definition of raw material versus an ingredient. A lexicon of those terms would be useful.

So for instance, a raw material might be the aboveground parts of St. John's Wort, Hypericum perforatum. The ingredient that ends up as the named ingredient in your master manufacturing file might be something other than leaf material. It may be a hexane extract spray-dried onto maltodextrin. That would be

the dietary ingredient that goes into your master manufacturing record, and that is very different than what we have documented as being in the marketplace that -- prior to 1994.

And so I think it would be useful to use -- not reinvent a lexicon or a dictionary, but to use some of the authoritative sources who are creating these lexicons. That would help you with the nomenclature of the ingredients and the names so that you can make some easy decisions and kind of defer on the hard stuff. And I think that would be a good first start -- a good place to start before trying to move forward into any kind of discussion of what's not -- what is and what is not pre-DSHEA.

DR. MACKAY: I'll offer up that up that Dr. Cohen had a decent idea with regard to the assumption

if the plant -- we have proof, we would know that a water or alcohol extract is available. Whether it's USP or other, we do a compositional analysis what chemicals are in our water or alcohol extract.

And in our comments, we sort of introduced the idea of an abbreviated notification. So if we know

something is old and you're looking for an NDI from me because I've changed manufacturing, I'm starting from scratch with Phase I, Phase II toxicology trying to figure all of that out. Or I could just give you a compositional analysis of my product made by supercritical CO2 extraction and demonstrate that it has the exact same chemicals available at or below the same levels. And therefore, I'm consuming the same thing people were exposed to pre-'94 -- so some sort of an abbreviated way a manufacturer could just demonstrate through composition that you're selling the same ingredient without going through the whole NDI process of being reasonable expectation, safety. The reasonable expectation is just I look a lot like that or exactly like that.

DR. COHEN: I just want to say that I would completely agree with Duffy. If we could solve the issue of your being able to track an ingredient, detect quickly if there's a manufacturing problem or other problem, and then withdraw it promptly. So in -- on the -- this start, I would -- then I would be in 100 percent agreement with Duffy's position.

MR. ISRAELSEN: Stephen, while you're up and while the mic is here, just to comment on a number of points that had been raised this morning is that the synonyms for what was a -- what we call a dietary supplement pre-DSHEA really seems a significant issue. We're not sure what the scope of that intended use includes.

But we do know is that there was a tremendous amount of usage that is -- that was both common and in the United States and overseas. It's relevant to the question of safety. And all of that we think is relevant to the question of whether it should enjoy ODI status. But in what way?

There was a great deal of hesitation, I think, trying to think through would it include something that

would be a traditional medicine by that working definition culturally or as a food and a food preparation and so on. That will help us a great deal to be as specific as possible going forward. So that helps us know where to go look for the evidence itself. So we would hope that that could be an early next step.

MS. MULDOON JACOBS: Hi. Good afternoon. My

name is Kristi Jacobs at USP. And I'm a toxicologist, and I've been doing risk and safety assessment of food additives and food ingredients for nearly a decade.

And I noted this morning in Steve's opening comments he said this ODI list would not represent a list of safe ingredients. But as we've listened this morning, we see that it's really difficult to keep the issue of safety separate from the issue of any ingredient that would ultimately belong in ODI list, whether it's an FDA or it's an industry list or it's, you know, my neighbor's list.

The -- keeping safety out of it is very difficult and especially as this morning has evolved into this consideration of GRAS substances. GRAS

substances are -- generally, GRAS substance is for use in food. And how we would consider or we would recommend that we would consider, that information could be incorporated into a list of things that don't require an NDI notification.

I can't help but wonder how you would take that process forward, especially when we know, if you look under the hood for a lot of these GRAS notices

that have been submitted to FDA and for which all the information is available, we know that those ingredients are GRAS for a very specific use. And part of that risk assessment involves a consideration of the dose and the expected exposure based on that use. And a margin of exposure is calculated. And they say as long as the use in food doesn't exceed this and the margin of exposure is still 100, then that ingredient is safe for that specific use. And we know in dietary supplements the -- that dose calculation might not be relevant and -- for the use of that same ingredient as a dietary ingredient in a dietary supplement.

And so I wonder, since it's impossible not to think about this, that you guys have considered how

would you do that portion when we know that the ingredients that we've seen on these lists don't have any information on dosing concentration. The method of manufacture really influences not just the amount of the ingredients itself, but especially a lot of these constituents which we know maybe toxicologically different and distinct from the final ingredient itself. Would we want -- would we go all the way to

say, if the margin of exposure isn't 100, therefore it is not safe? I would imagine that I would hear resounding no's from this room, and I don't think we should be saying that.

But I'm curious on your thoughts, how you would consider using this safety information and this approach to risk assessment as it applies to GRAS ingredients in the paradigm for dietary supplements.

DR. MACKAY: Well, that's how it is today. If you have an ingredient in the food supply and you don't chemically alter it, no notification is required. So what happens is you look -- you take your obligation at Section 342, and you look at that GRAS notification.

You evaluate target population intended use. And if you're within that, you do nothing. If not, if you want to double the dose, you have an obligation to determine that doubling the dose is still going to be safe for the intended use. That's how it happens right now.

So there's no discussion of process, change, anything. GRAS ingredients are in the food supply as articles used for food. They can be used in a dietary

supplement, but you have to pay attention to the evidence in that GRAS notice to determine how you plan to use it.

The same thing applies to the food additive idea. If a food additive is used in micro-dose amounts, you still have an obligation if you want to put milligram amounts to determine that it's going to be safe for the population you put on the label that it's for.

That's it.

MR. DURKIN: Any other questions from the room? We have none online.

We'll adjourn now. We'll reconvene back at

10:15. 11:15. 11:15. Sorry.

(Break.)

DR. WELCH: All right, everyone. We're going to get started here with the public comments session in one minute.

(Pause.)

DR. WELCH: All right. Good morning. Now is the time in our day where we're going to have our public comments session following Panel 1.

As a reminder for our audience, they -- the people are registered to give oral comments. They are listed in -- on a sheet in the folder that you were given this morning at registration. I will go through the morning session in order, just to note that Michael Tims will not be giving public comment today.

And then a reminder that this afternoon we will have extra time. So if you are interested in giving public comments this afternoon, please see Juanita Yates at the registration desk, and you can sign up for that.

With that, I will start the public comments.

We have five minutes per commenter. I will try to give a warning at about a minute left, and then I will interrupt at five minutes, so heads up on that.

With that, let's get started. Harry Rice from GOED.

And the commenters, again, please, when you start, start with your name and affiliation. And that really goes for anyone who's speaking into the mic -- name and affiliation so that our transcription and our webcast attendees have an idea of who's speaking.

Thank you.

Harry. Yeah, make sure it's on if you can.

MR. RICE: Is it on?

DR. WELCH: I think so.

MR. RICE: Yep.

UNIDENTIFIED MALE SPEAKER: No.

UNIDENTIFIED FEMALE SPEAKER: No.

MR. RICE: No.

DR. WELCH: No.

(Side conversation.)

MR. RICE: Okay.

DR. WELCH: Thank you.

MR. RICE: Okay. Thank you, Cara.

My name is Harry Rice, and I'm with the Global Organization for EPA and DHA Omega-3s, an association of processors, refiners, manufacturers, distributors, marketers, retailers, and supporters of products containing the omega-3 fatty acids, eicosapentaenoic acid, EPA, docosahexaenoic acid, DHA.

GOED is extremely interested in assuring that consumers continue to have safe access to high quality EPA- and DHA-rich ingredients.

Thus said, GOED thanks the Agency for the opportunity to provide public comments concerning considerations specific to certain classes or types of ingredients that should be taken into account as the Agency develops a list of pre-DSHEA dietary ingredients.

Though it is very much in favor of the creation of a list of pre-DSHEA dietary ingredients, which would provide a safe harbor from the NDI notification requirements, with a long history of safe use since long before October 15th, 1994, EPA- and DHA-

rich ingredients for fish oil fit well -- I should have had these hard-copied. Before October 15th, 1994, EPA- and DHA-rich ingredients for fish oil fit well within such a category.

While the market for EPA- and DHA-rich dietary supplements has exploded since the passage of DSHEA of 1994, the first fish oil was launched back in 1760 in the United Kingdom. In 1790, the cod liver oil known as Scott's Emulsion was launched in the United States. Over 200 years later, Scott's Emulsion continues to be marketed, thus representing what GOED believes to be

the oldest continuously marketed dietary supplement in the U.S.

In addition to cod liver oil, prior to October 15th, 1994, multiple forms of fish oil were launched, including fish body oil, concentrates, both ethyl esters, and re-esterified triglycerides, and salmon oil. In common to all past and present EPA- and DHA-rich omega-3 ingredients is that their primary composition is EPA, DHA, and a mixture of minor fatty acid.

GOED believes the major sources of EPA- and

DHA-rich ingredients, including concentrates, are being lawfully sold since they were marketed as dietary ingredients prior to October 15th, 1994. To support this position, GOED has considerable amounts of documentation, including but not limited to patents, popular press articles, advertisements, labels, peer-reviewed scientific articles, and information from the NIH's biomedical test materials program from the '80s and early '90s.

Despite a wealth of information, such documentation does not necessarily exist for each

unique ingredient currently being sold. However, given the widespread demonstrated safe use of EPA- and DHA-rich ingredients, the absence of documentation for each unique product from fish oil currently on the market should not yield an NDI, requiring an NDI notification.

For years, EPA- and DHA-rich ingredients have been sourced for multiple organisms and species. Since the FDA issued its final rule on June 5th, 1997, affirming menhaden oil is generally recognized as safe with limitations on the maximum use levels in specific

food categories in order to ensure that daily intake of EPA plus EHA did not exceed three grams per day, EPA and DHA have been considered the valuable components to which these oils are standardized. And the products are principally comprised of EPA, DHA, and a mixture of minor fatty acids.

Subsequent to the final rule, more than 10 companies wishing to market their fish oils for addition to food have received letters of no objection from the FDA. Despite minor differences among the oils and fatty acid composition, FDA has raised no potential safety issues, given that all companies indicated that

intake of EPA plus DHA would not exceed three grams per day. From a whole food perspective, consider that a single serving of salmon contains more EPA, DHA, and a range of other minor fatty acids than the majority of fish oil supplements on the market.

Manufacturing changes used to make the same product in the market -- that is, no change to the identity of the dietary ingredient either before 1994 or even after submission of an initial NDI notification -- should not yield an NDI. These manufacturing

changes should be addressed by the final rule for current good manufacturing practice in manufacturing, packaging, labeling, or holding operations for dietary supplements.

GOED believes the focus should be on whether or not a change to the manufacturing process alters the safety profile or identity of the ingredient and not be specific to the manufacturing change itself. After all, the principle ingredients produced is always an omega-3-rich oil with the predominant fatty acids being EPA, DHA, along with a mixture of minor fatty acids.

To conclude, thank you for considering GOED's

comments as you work on a strategy to create a list of pre-DSHEA dietary ingredients. GOED is ready to assist in any capacity with the creation of such a list.

Thank you.

DR. WELCH: Thank you, Harry.

We just found out that we have some audio problems. So I'm going to wait just a minute or two until we get those fixed so not everyone has to repeat.

(Pause.)

DR. WELCH: Though I would mention -- and we'll mention it again when the webcast participants are back on -- the oral comments are entered into the transcription. So we will make sure that they can get those handed to them in written form.

We have a number of people up in the booth figuring it out. So we'll give them just a -- all right. There we go.

All right. I think we have our webcast participants back on. And just a note for those who are listening online, the oral comments, you've only missed one set from Harry Rice at GOED. He -- they will be transcribed and included in the transcription.

So you will have access to them when that gets posted online.

Next we're going to hear from George Paraskevakos from IPA.

George, start with your name and affiliation, please. Thank you.

MR. PARASKEVAKOS: Here you go. Sorry about that.

So good morning, everyone. My name is George

Paraskevakos. I am the executive director of the International Probiotics Association.

We want to thank the FDA for holding this meeting, for going -- for giving us the opportunity to present, and its willingness to meet with the IPA, participate in different IPA workshops, and consider our comments and citizen petitions over the years.

The International Probiotics Association, for those of you who don't know us, is an international nonprofit organization with a mission to promote the safe and efficacious use of probiotics globally. IPA holds an NGO status at the CODEX, and it's -- and is the global voice of probiotics with 100 members coming

from 26 countries, including the majority of the world's probiotic producers.

The WHO defines probiotics as live microorganisms, which when administered in adequate amount confer a health benefit on the host. Probiotics have been safely consumed by people for thousands of years in different forms such as yogurt, sour milks, fermented foods, food supplementations not only in my

forefathers' country in Greece, but across the globe internationally.

The health benefits of probiotics are well recognized. Indeed, as I speak, we know that probiotics in our bodies are helping us digest our food and support our immune system. And it seems that our researchers are discovering other roles that they play in supporting our health every day. The combination of well-established safety and health benefits has led probiotics to be one of the largest categories of the dietary supplement ingredients.

In many respects, probiotics are like any other category of dietary ingredients and should be treated the same way. They are subject to the same

manufacturing requirements, safety standards, and are included in dietary supplements to increase total dietary intake. Like other categories, probiotic manufacturers often have trouble identifying pre-1994 sales information that meet the criteria FDA has set out in the draft NDI guidance document. On the other hand, as living organisms, probiotics are a very unique category of dietary ingredients, and FDA has recognized

that in several section of the draft guidance.

We hope that FDA will extend its willingness to recognize the unique nature of probiotics when creating a list of dietary ingredients that do not need to be the subject of a notification to FDA. For one, the law has not kept up with the scientific advances. And we heard this a few times this morning about technology being where it was. Modern science and technology not allow probiotics to be readily identified by genus species and strains. However, science was not as advanced before '94, and, therefore, probiotics were generally only identified by their genus and species.

Importantly, FDA's labeling regulations then

and now do not require that product labels declare the strain of the probiotics in the product. Those two realities make identifying exactly what specific strain of probiotics were sold in the United States prior to '94 uniquely challenging.

Now that we can readily identify probiotics to the strain level, we agree with FDA that each strain

should generally be treated as a unique dietary ingredient and, in fact, recommend to our members declare probiotics to the strain level on the supplement labels. However, we also believe that when developing a list of dietary ingredients that do not need to be the subject of an NDI notification, probiotic ingredients should not be penalized by advances in science and ambiguities in some of the FDA labeling regulations.

Therefore, such lengths -- such lists should include all probiotic species that were marketed prior to 1994, and all strains of such species should be considered to be covered by the inclusion of the species on the list. Of course, if it is -- it is also incumbent on each manufacturer to ensure that the

inclusion of any probiotics in a dietary supplement meets established standards of identity and safety. In the event that the FDA determines that it must review information on a strain in order for it to be included on such a list, then such lists shall include all strains of any species marketed pre-1994 that meet specified identity and safety parameters.

In our comments to the draft guidance in 2016, IPA provided a complete list of species as well as the parameters for which every strain must be screened, whether the information is to be submitted or not to the FDA.

On behalf of the IPA, we'd like to thank you for your consideration and look forward to continuing collaboration with the FDA on these lists of probiotics.

DR. WELCH: Thank you, George.

McClain Haddow, Upstream Consulting.

MR. HADDOW: My name is Charles McClain Haddow, and I'm speaking here today on behalf of the largest kratom consumer advocacy organization in the United States, the American Kratom Association, often

referred to as the AKA.

You will be hearing probably my remarks from Dr. Henningfield, who will document -- or give you some of his research that documents the long history and safe use of kratom in the United States today by millions of Americans.

I thoroughly enjoyed the panel discussion this morning and found it illuminating for the FDA about some of the alternatives that exist to address the issue how you document the substances and dietary supplements that were in use prior to the magic date of DSHEA.

I did disagree, however, with Mr. Duffy -- or Duffy's remarks when he said that kratom probably isn't going to resolved here today because it's too controversial. In fact, prior to the passage of DSHEA, every dietary supplement in food was controversial in the United States, and that's why we had to have DSHEA. It was the purpose for which the act was established. And in fact, I would argue that it's the purpose for which the FDA now has to find an appropriate standard by which the drugs -- to judge substances like kratom.

When President Clinton signed into law the DSHEA Act on October 25th of '94, he stated, "It is appropriate that we have finally reformed the way the government treats consumers and these supplements in a way that encourages good health." And here we are today still arguing about the standards by which we

allow DSHEA actually to protect those consumers.

It was well developed this morning that, in fact, 413A-1 provides a standard that if a food was in the global food supply that it should be covered as a pre-DSHEA-protected substance. Now, I know that in 413C we get into a conflict because a separate pathway was established by the Congress in order to allow for those substances that are chemically altered in terms of their extraction methods that they change the actual way in which it interacts with a consumer. They should not be conflated together. In fact, they should be separate. And if there is a substance that uses an inappropriate extraction method that's not covered by the current methodology that's approved by the FDA, then certainly it should be covered under 413C.

But we have the protection of safety that

overlays all of this that's found in the statute that Congress wisely enacted. According to the FDA requirements, this documentation of the actual sale or marketing is an interesting one.

I grew up in Pittsburg, Pennsylvania. One of

my best friends was an Italian who frequently invited me to dinner at his home. Ms. Biachi (ph) prepared authentic Italian dishes. She brought over all of the ingredients from her home country of Italy. And it wasn't until later when they developed these small grocery stores that imported these ingredients was she more comfortable with being able to serve it. She never would have allowed us to go for an authentic Italian meal to the Olive Garden. She wanted it to be authentic ingredients that were used at the time.

That's the case with kratom. We saw a dramatic increase in the utilization of kratom as we -- after the Vietnam War as we saw our soldiers returned and as the Southeast Asian immigrants came to the United States and that same kind of culturally ethnic food practice was followed. They had their relatives ship-crate them to them. Then as demand grew, you saw

small mom-and-pop convenience stores start to sell it.

Can anyone document that? Not today because, as we know, there was no documentation that was widely done or records retentions protocols in place that follows that. So to use the strict standard of saying

you have to be able to produce a piece of paper to document what Congress said just had to be documented in the food supply seems to be contradictory to and out of compliance with what the Congress intended for that to be done. The clear intent was for -- that Congress had was to allow kratom products and similar products present in the food supply prior to the enactment of DSHEA to be classified as old ingredients.

The more restrictive evidentiary documentation for the marketing of kratom products should apply only to those products that have been chemically altered to determine if they were in commerce in the United States prior to the cutoff date. The separation of these classes of products is essential to maintaining the consumer access to products to fulfill the mission of DSHEA as President Clinton articulated, and that is that we reform the way the government treats consumers

and these supplements in a way that encourages good health.

The American Kratom Association favors appropriate regulatory schemes to govern that class of

products that have been chemically altered. But it is unfair to take the broad stroke and brush and say all kratom products are therefore classified that way when you have this body of evidence that is clearly available that demonstrates its safe use by millions of Americans today. We recommend the FDA do that -- apply that standard in going forward.

Thank you very much for this opportunity.

DR. WELCH: Thank you.

Jack Henningfield.

MR. HENNINGFIELD: Thank you. Is this one working? I'm Jack Henningfield, Vice President of Research and Health Policy at PinneyAssociates and Professor of Behavioral Biology at Johns Hopkins Medical School. PinneyAssociates provides guidance in prescription drugs, over-the-counter, and dietary.

As you've heard, kratom illustrates a promise in the peril of regulation. And how the regulation is

developed, written, and then interpreted can well help products realize their promise or remove them -- inappropriately in some cases. And your approach will also determine the range of the diversity in the

marketplace. And like a lot of marketplaces, this marketplace is not satisfied by any one product or one type of product. It's millions of people using lots of different types of products. Perhaps some of them should not be out there, but you need reasonable standards that help sort them out and not eliminate the small players that are often the innovators providing a product that small markets like.

PinneyAssociates has been working with the American Kratom Association for more than a year on these issues. These opinions are my own and my colleagues at PinneyAssociates.

You probably already heard kratom is a tree in the coffee family that produces some effects like caffeine. But it also produces some effects that substitute for opioids. And so in Southeast Asia, it's been used for decades for a century or more to threat minor aches, pains, and so forth, help people get

through the workday. And that's what we're seeing in the United States in, at this point, at least 3 or 4 million people, probably more.

And the three major surveys -- one by colleagues at Johns Hopkins, two other that are published -- show that this includes some people that have gotten off of prescription drugs and are now satisfied with what they're getting from kratom products. I work on prescription drugs. They're really important and necessary for some people -- and over-the-counter. But it's clear that there are a lot of people that are perfectly happy with alternatives that are natural and have strong safety records.

As you've heard, it's been used in Southeast Asia for decades and was probably introduced to the U.S. probably in the '70s and '80s with waves of Asian immigrants. How do we document this?

I mentioned earlier I could go to Minnesota where I grew up, don't you know, and get affidavits. But what would -- can constitute acceptable and reasonable evidence? I don't think that should be excluded, but there has to be rules. Guidances can

help there. Same thing with foreign data. There's a wealth of Southeast Asian data that are useful. What constitutes acceptable foreign safety data? We in

PinneyAssociates have helped document that kratom is used by millions of people to health benefit with a very good safety profile.

The other thing that came up earlier today is what's the level of the ingredients. Now, most commonly, kratom is used as a tea made into tea-like products. So that's an extract. Making tea or coffee is an extract. It doesn't take everything out of it. Most of the products we're aware of provide amounts of the desirable ingredients in amounts that are comparable to what have been used in Southeast Asia and what are used if you chop up tealeaves and put them in water. Some products use extracts that are probably higher. We need a way of sorting them out that is reasonable and doesn't kill the small innovators.

Finally, let me go back to opioid issue. We are facing an opioid crisis. And what has been documented now is that there are a lot of people that have gone from conventional opioid pain medicines and

said, you know, I couldn't tolerate ibuprofen. It upsets my stomach. I can tolerate kratom tea even

though it tastes terrible. It does the job.

As a professional in this area, I don't want to see those people going back to opioids. So we need to provide the diversity of products that meets their needs with reasonable standards. And we need guidance as to what constitutes reasonable evidence.

We need balanced regulations, and that includes packaging, labeling, and claims. You know, coffee -- you don't know if Starbucks if you're getting 300 milligrams of caffeine or maybe 100 milligrams of caffeine from your cup at Dunkin' Donuts. But if you get Coca Cola or Pepsi, you now know how many milligrams of caffeine are in it.

So we've faced these issues in other product categories, and I think we need to face them here in a way that helps this area innovate and thrive and serve the millions of consumers that have come to rely on these products.

Thank you.

DR. WELCH: Thank you.

Scott Polisky.

MR. POLISKY: Thank you. Good morning.

I'm Scott Polisky, an attorney in the FDA law field for over three decades. I'm speaking on behalf of Jarrow Formulas, Inc., a 40-year-old and well-known dietary supplement company, and Jarrow Industries as well. Along with other counsel, I've represented Jarrow on regulatory, legislative, and intellectual property matters since 1991. Jarrow Rogovin and everyone at the firm is most appreciative of the continuing dialogue with FDA.

I'll be brief with a few points. Number one, although it's our position that Section 8 of DSHEA does not specify whose burden of proof it is to demonstrate that an ingredient is grandfathered in, we realize that compilation of this list is a fait accompli, and we hope to cooperate and provide helpful input.

Number two, many of our points are contained in our December comment on the NDI revised guidance and the 2nd May comments specifically devoted to issues concerning probiotics. Jarrow is one of the founding members of IPA and agrees with their positions.

Number three, we're pleased that FDA agrees

that the pre-DSHEA ODI grandfathered, grandmothered list should not be considered exhaustive and exclusive, where to be exclusive such a list could become similar to the EU's commission on -- with a list of 121 ingredients for nutritional supplements are reminiscent of the 1958 GRAS list that of course did not contain all substances generally recognized as safe and, thus, was a source of confusion.

Number four, we agree with IPA that new strains belonging to well-established species should not be considered new dietary ingredients.

Number five, Jarrow concurs with the list of over 40 well-established species that IPA provided to FDA and is common, a list of grandfathered species known to have a long, safe history of use in foods. After being screened for toxins and antibiotic resistance, a strain belonging to such species would be considered, or should be considered, safe. Again, contrary to FDA's position, any strain of a grandfathered species should be considered safe, as well with no need for an NDIN. Thus, Jarrow is of the

opinion that only 2 simple tests rather than the 10

outlined in the guidance are necessary. Those two would be antibiotic plasmids test, ABP, to test for antibiotic resistance; and number two, a test for any contamination.

Thank you.

DR. WELCH: Thank you.

Susan Brienza.

MS. BRIENZA: And here, a little height challenged.

So good morning, everyone. Susan Brienza of the law firm Riley Carlock and also representing Jarrow Formulas and Jarrow Industries.

Jarrow Rogovin, the founder of both of those companies, would be here himself, except that he's in London the past couple of days at a probiotics conference, probiotics for babies and children.

There is a third person here today also representing these companies, and I'd like to introduce John O'Connor.

John, if you could stand.

John has been with Jarrow Formulas for 19 --

over 19 years in R&D and regulatory.

So with that, I would like to make three points today. If I don't get to the third one, I would like to reserve the right to have a little time at the end of the day. I think that's what they say in Congress, right -- reserve part of my time.

Is this not coming through? Oh, okay. Well, I can -- you know what? Okay.

So first, following up on some of the points of George of IPA and my colleague, Scott Polisky, with whom I've worked for about 17 years, in addition to working on a pre-DSHEA ingredients list, we believe that FDA and industry should also agree that neither a new fermentation medium for a probiotic nor a new solvent for an extract will transform an ODI into an NDI.

So for example, for a pre-DSHEA strain of a probiotic or a new strain belonging to a well-established species, changing the medium does not change the ingredient, we believe. As stated in the Jarrow Formulas comment, we filed a follow-up comment in May of this year on specifically probiotics,

"Changing the fermentation medium does not change the genetics of the microorganism and, thus, does not change its safety profile." So on this point, we agree with both IPA and with DuPont Nutrition, made a similar point in its comment in December.

In addition, Hank Schultz, a very good science writer, science and regulatory writer in NutraIngredients-USA, quoted in a December 2016 article on this very point quoted an expert who had a very good downhome example. And to use myself for that example, if I as an Italian woman, eat, consume, feed on Japanese food, that doesn't suddenly transform me into a Japanese woman. So I very much like that analogy.

Continuing with a food metaphor, for my second point, I'll also start with a personal example. And this second point is about thinking outside of the box and thinking about a possible third category beyond just old ingredients and new ingredients.

Last night, I had a terrific white wine called Complicated Chardonnay. I've never had that before, and I recommend that to you all for your supper tonight.

So I want to complicate the picture a little bit and talk about a -- something in the middle. In Philosophy 101 in college, if you ever took that course, we talk about the excluded middle. So instead of just old ingredients and new ingredients, perhaps we should also think about a category of what we'll call middle-aged ingredients.

So Jarrow Rogovin personally has a proposal, a modest proposal, for a fast-track system or an abbreviated notice only for middle-aged ingredients, those on the market in the U.S. or internationally for five, seven, eight years and no serious adverse events.

To get more precise -- and this proposal is in our December 2016 comment on the revised guidance -- for post-DSHEA dietary ingredients with a history of safe use in any country, we propose that the full procedure of the notification 7 to 10 safety and toxicology tests recommended in the guidance should not be required. Instead, a much more streamlined procedure, but one still providing the Section 8 statutory standard -- safety standard of "a reasonable expectation of safety" for the new supplement should be

permitted by the FDA.

I want to just pause at this point and mention that we agree with Duffy and CRN. I personally do. And I want to note that the GRAS standard is a higher standard of safety. General recognition of safety is higher than the NDI Section 8 standard of reasonable expectation --

DR. WELCH: Thank you, Susan.

MS. BRIENZA: -- of safety. So I'll have to end there.

DR. WELCH: We will take your request.

MS. BRIENZA: We -- and we will file written comments by December 4th as well.

DR. WELCH: Thank you for that.

MS. BRIENZA: Sure.

DR. WELCH: And finally, we end with Gabriel Giancaspro.

MR. GIANCASPRO: Hello. My name is Gabriel Giancaspro. I am the vice president of Dietary Supplements and Herbal Medicines in the Science Division at USP.

On behalf of USP, I would like to thank the

Agency for allocated time to offer -- for us to offer out thoughts and the development of a pre-DSHEA list of dietary ingredients.

USP's mission aligns closely with that of the FDA Office of Dietary Supplements Programs, ensuring the safe quality dietary ingredients that are available, along with adequate information for informed decision-making by manufacturers, suppliers, and the general public.

We are an independent scientific nonprofit public health organization devoted to improving health through the development of public standards for medicines, foods, and dietary supplements. We are governed by the USP convention, comprising over 450 academic institutions, healthcare practitioner organizations, industry groups, and government representatives.

For nearly 200 years, USP has been building foundations essential for assistant aimed at providing quality products to consumers by ensuring that manufacturers have access to the reliable standards of quality that regulators and industry need to satisfy

consumer expectations. Our work includes the development of the standards for identity, purity, and strengths, limits of contaminants, and labeling of individual components, unfinished products, as well as the development of reference standards for analytical testing.

USP develops public quality standards through an open, transparent process with public participation and input of the stakeholders, including representatives from academia, industry, and government.

Particularly relevant to the topic today, USP has some longstanding program of developing identity specifications for dietary ingredients used in dietary supplements. Creating an authoritative list of pre-DSHEA ingredients, as proposed by FDA, could provide the positive contribution to industry and the advancement of public health. Such a list, if sourced appropriately, could serve the community by providing information under regulatory status of many dietary ingredients used in dietary supplements. The list could increase transparency in the dietary supplement

marketplace, thus reducing the burden on FDA and the regulated industry alike.

We acknowledge that development of such a list may prove challenging. Ideally, the list should contain the ingredient name along with the specifications sufficient to define identity. For example, many botanical ingredients from the same source are available in several forms, such as powders, dry extracts, tinctures, and aqueous extracts. These ingredients vary in composition and quality.

It will prove helpful for an FDA list to include clear parameters related to the form and identity specifications that will enable industry to be sure whether a specific ingredient is included on the list.

Regarding the types of information that may provide evidence of pre-DSHEA status, publically available information, such as pharmacopoeia monographs, public health (ph) in records, or scientific literature may provide additional identity information to help support the construction of a pre-DSHEA list.

Along with materials clearly establishing marketing, these sources can be valuable to FDA to consider. A clear understanding of identity specifications is fundamentally important for manufacturers to ensure compliance with regulatory requirements. Without adequate identity specifications, such as those provided in the official compendia, transparency will be impaired and compliance would be more difficult.

USP has demonstrated expertise in developing old (ph) quality specifications for dietary ingredients and is willing to work with FDA and industry to develop identity specifications for those pre-DSHEA ingredients that are not currently in the compendia.

DR. WELCH: Hey, Gabe. Time's up.

MR. GIANCASPRO: Consistent with our share of public health mission, USP stands ready to engage with FDA and industry and seeks to do this in a way that would have the greatest impact.

Thank you for the opportunity to comment. And we look forward to exploring ways to expand our partnership with ODSP and the industry and to serve as

a resource to FDA and the regulated community.

DR. WELCH: Thank you, Gabe.

MR. GIANCASPRO: Thank you.

DR. WELCH: With that, that closes our morning public comments session. Again, if you want to give comments in the afternoon, there are -- there will be time available. Check in with the registration desk so we can make sure to get your name and organization.

You now have a break for lunch. A reminder, Ms. T's Cafe is out the front door. In the courtyard, which you also need to go out the front door, is the CFSAN fall food court. And we will welcome you back at 1:15 to begin again.

So thank you. Make sure you keep your badges.

(Lunch.)

DR. WELCH: All right, everyone. I think we're about ready to get started for the afternoon session.

Adrian, are we going on the WebEx? All right. I think we're ready to go.

So thank you all. It's time to get started with our afternoon session. I very much appreciate

this morning's discussion. I know the conversation could continue on this topic, but it's important to give time to the second topic as well where we're talking about process.

Specifically, once we have the standard of evidence questions all answered, which I'm sure will be very easy, what process should we use to develop this list of pre-DSHEA dietary ingredients? There are probably any number of paths that FDA can go down in developing an authoritative list. Hopefully, you'll hear a number of these from our panelists.

For our situation, of course, the law isn't requiring us to develop this list. And, as is quite obvious, by the 23 years that have passed DSHEA, we aren't exactly staring at a ticking clock. However, as Steve was discussing, I think we're hoping that the transparency will be valuable for both our industry stakeholders, our consumer stakeholders, and FDA.

So Steve gave some insight into the comments that were submitted last year in response to the draft guidance specifically regarding how FDA should go about developing this list. For example, we heard we should

form a joint industry consumer FDA panel to review. We heard an advisory panel should be formed. We heard we should develop a list by rulemaking and keeping it easy for us. We heard that we should adopt the industry lists that were provided upwards of 20 years ago.

However, now is the opportunity to hear from our five panelists. Hopefully, what we'll hear are some of the pros and cons of the different processes, maybe what worked well for other commodities or what has not worked well, important things to consider as we develop this list, and what the end product should be looking like.

Similarly to the first panel, I'm not going to read the bios of our five presenters to you. You have those in your folder. I encourage you to check them out, though maybe not during the actual presentation.

And then we're going to let our presenters give their remarks in succession without Q&A between each panel, much like the first time. We will have a dedicated question-and-answer time with all five presenters following.

The order that we're going to go in will be --

we're going to start with Dr. Fabricant, move on to Dr. Scarmo, Laura MacCleery, Dr. Sirois, and Chuck Bell. I'm not going to be popping up to the podium each time, so I'm going to welcome Dan Fabricant to the podium. And then he will then present the next presenter and so on.

So without further ado, let's get started.

Can we bring up Dr. Fabricant's slides?

DR. FABRICANT: Thank you, Dr. Welch.

My name is Dr. Emmett Brown, and I made a time machine out of DeLorean. You know, I -- a lot of talk about timing and things like that and process, too, which I think is interesting here because I think we've heard a lot of discussion about people's thoughts on the matter, but we haven't seen a lot of evidence. We haven't seen a lot of facts. We just heard a lot of talk. And that's fine, but I think there's a few binding things here that actually do have effect of law and can be implemented rather quickly.

So let's dive right in. And Daniel Fabricant, Natural Products Association, CEO and President. We have 11,000 members from retailers and suppliers all

the way through the supply chain, and that becomes important as we go on because I heard some comments about access. So as the oldest and largest trade association, I think that this is something that is unique to our membership in terms of getting access out there.

So in terms of "NDI issues" that came up after the guidance -- and you know, it's Washington, D.C., or the greater D.C. area, so a day without issues is like, you know, a meal without wine, I guess, or a day without bread, so to speak. But specifically, one of the things that came out of this last draft was that the Agency is very interested in developing an authoritative list. As you've heard prior, authoritative lists -- or the trade associations' lists are not deemed authoritative, and that's been -- and in fact, I see Bill, so it pre-dated my time at the Agency. I'm going to blame it all on Bill just because he's got big shoulders. He's that kind of guy. But we'll leave that there.

So what does the law say? And the law says,

because we don't have a statute here and -- with

Congress. And I think what we've seen in Congress not just this cycle -- people want to talk about this cycle because it's very interesting because you have a reality TV host as president -- you know, people are going well, the government's inefficient.

FDA really didn't get a whole lot of new statutory authority. You know, if you look at the food side, while there are a lot of new issues that keep coming up, not a lot are done through statute. And even the ones that are done through statute have kind have been slow to implement, and there are some that have been ripped entirely. So the concept of that and working together and getting something that was appealing on that I don't think is likely.

Furthermore, as no statute exists for FDA to do this by regulation, there's nothing in the statute that says FDA shall promulgate an authoritative list within X number of days. Probably not -- that dog may not hunt either. So how does it get done?

And I think that this is really where you look towards the other centers and not just the other

22 centers. How many of you have businesses you have to

1 be Part 11 compliant? If you have to be Part 11
2 compliant, you probably rely on a third party. And
3 that third party -- there's no clear process for those
4 third parties. There's verification -- electronic
5 verification, things like that, but they're constantly
6 presenting that data to the Agency and folks at the
7 Agency and making sure that they have access to things.
8 There's obviously computer IQ/PQ/OQ checks and things
9 like that that are relatively standard.
10 But in effect, it's somewhat on the fly, and
11 it goes through a Regulatory Flexibility Act, which,
12 really, given that this is still a small business
13 industry, flexibility is the law of the land here. And
14 it's really about the data. It's not about the
15 process, or it's less about the process. If people
16 bring things to the Agency showing that things were in
17 commerce pre-'94, the Agency really doesn't have the
18 grounds to stand on and say no because it doesn't meet
19 the process because there is no process.
20 So starting from there, I think we start with

what can be a dietary ingredient, and this is germane to this discussion. And one of the big issues is still

on 201(ff)(1)(e). We know the Agency's opinion is that that -- and you've heard it today -- largely just relates to GRAS and food additive petition compounds, which we think that's a good place to start. However, there is case law in this that's a bit more expansive. If you go to Ted Cartons (ph), that limits the route of administration, which I think is clear here, too.

So when we're looking at what would substantiate -- and Steve made a very good point. There was no dietary supplement in the marketplace pre-'94, obviously. But -- and I hate to use this example. But in some ways, it's like corn (ph). You know it when you see it. If it's in a tablet, capsule, et cetera -- it's a multivitamin -- you understand that. If it's something you rub on your skin, that's not a dietary supplement. If it's in an herbal catalog for ornamentals, that, too -- and someone may have gotten really drunk and started chewing on your tree outside your house, that doesn't make it a dietary supplement either.

So it's important to understand that intent is still really where a lot of this is driven and the

types of evidence will be driven -- so consumed through ingestion, something that's clear there. But also, you know, the case law is clear that the botanical that's ingested in traditional Chinese medicine as a drug, a synthetic copy of that botanical could qualify as a dietary ingredient. That's not to say it's grandfathered, but that is saying that it could qualify as an ingredient, which is important as people, I think, go back into their records and see what actually was on the market as a supplement in the U.S. pre-'94, so something to be looked at there.

And again, the Circuit Court ruling on substance upheld FDA's view to mean food or drug. So it's not a limited definition or as limited as some of the Agency might think.

And so again, the 2016 guidance reiterated further points by FDA. And this goes back a ways in terms of independent verifiable. And you'll see similar language in Part 11 compliance. You'll see

some similar language in medical device compliance. But independent is important, and verifiable is important. Affidavits are nice, but at the end of the

day, things get measured.

The Agency works on data. It's a data-driven agency, and so they have to have access to that data. And they were clear about by affidavit alone, any sort of objectives verifiable with documentation, time, and marketing. That could work. But really, it's been more towards catalogs, bills of lading, magazine ads.

And so -- oh, this is fast.

And I -- this is the other point I think that's key here and to reiterate in terms of the process. And I know some folks go we can't have this process at all because FDA's effectively weighing in on the safety of these things pre-market. And it's like, well, FDA didn't do that. Congress had a technical adulteration standard here. And by showing you were in the market pre-1994, that's one way of alleviating that standard, the other being you filed the NDI.

And so this is important to consider, that FDA has -- and I've heard some people talk about safety

signals. MedWatch is law. What the CDC does with mathematics, that's great. My kids like math, too. But FDA has law from MedWatch. And if there's a

problem with a product, FDA is compelled to act.

And so I think the authority is there that if there aren't problems with old or new dietary ingredients, FDA has ample authority to take action -- it -- should it be rendered adulterated by the scientists at FDA. So with that -- and just because something isn't on a list doesn't mean someone else doesn't have independent verifiable evidence to conclude it's an old dietary ingredient. And that, too, has to be reiterated.

So for our purposes -- and this is one of the benefits of having the retail component -- is we do have old magazine ads that encompass about 2,100 ingredients. And our members have access to it. So everyone going this data can't be found, it's impossible, we found it.

So it's not that huge a deal. And again, I think we'll cover some of the finer points here. But

there are already -- there is data out there. And we got lucky somewhat because it is 23 years after the fact. But you can certainly verify that an ingredient was marketed pre-'94. And I hear a lot of talk about,

well, is your zinc the same zinc that was in the market. Well, if it's a salt, it's the active moiety. And so there's case law that upholds that as well, too. And so we'll drive that point further.

There's the standard of -- a state of agreement from the legislative history. And so as someone pointed out earlier, it would cover solutions -- - and aqueous ethanol tincture would mean that -- as well as things that were filtered, solutions in water, dehydration, these sorts of things, would be covered if you saw a name of a product you can anticipate that any of these processes would still probably be included in a grandfathered list even if it was just the general common name. But we also have in a lot of our botanicals that we found from the old magazine ads they do have plant part, which I do think is significant and is tied directly to the labeling.

So here is the beta of our label database, and

we look forward to sharing this with the Agency relatively soon. And we'll bring the ads in for good measure, but this is -- our members will have access. And we're actually planning probably once we get a

board vote to publish a book that has this in there. So that information is out there both for members and nonmembers alike. But for nonmembers, there will certainly be a reasonable upcharge -- or an unreasonable upcharge, depending on who you ask.

So with all that said, it's important to note this, too, that the active moiety is the dietary supplement. And again, you do have case law that substantiates what the active moiety is. So if you have an ester group, a salt group, what actually people consume from a public health perspective is the same compound. So that's important, too.

If it's something that is -- isn't behaving as a salt, a clathrate or something that has a time release, that may be some -- an entirely different situation. But if it's salt, if it's something that associates to the active moiety, realistically, you can

expect that it is going to be the same as the article of the diet.

We've heard a lot about probiotics from a lot of different folks. And I think their comments are very good. Of course, start looking at the list from

the food side, the GRAS side.

But again, I think that there is more to it than that. There is a lot of new strain names that, in essence, have homology with some of the previous strains that were on the market. And so I think there's got to be some understanding and investigation into that. If you have homology that's 99.9 percent the same for different strains of probiotic and one was a grandfathered strain, what are the possibilities of using that as your substantiation it could be used safe?

I'm not talking about adding a new promoter region or anything like that. But again, looking at a sequenced -- not of the mRNA either, but of the DNA -- and it's 99.9 percent the same, really, where is the public health situation where you wouldn't have that product? You know, and again, it could be an

abbreviated NDI filing, but I do think it's significant and the sort of data that the Agency is looking for to make their job easier.

So -- and here is some of the decision matrix on this -- you know, did you sequence it? Was it free

of genetic elements and covariance (ph) factors, transfer (ph) antibiotic resistance, antimicrobial substance? You heard some of that prior. And there's the strain-induced undesirable physiological effects. This is critical, too.

If, again, there are no new promoter regions added or there isn't claims or there aren't claims that are advertising hey, this has a new promoter region, it's going to do something to, for example, bone strength that wasn't previously tied to that strain, well, that may be something that someone may need additional data on an NDI. However, we think that if they're the same -- you know, effectively the same by homology, there should be consideration by the Agency.

So in closing, we got lucky on this one. But NNFA, then NPA, was the first one to have a list back

in 1994. I think we're the only ones to have a list within the -- in what we think is independent and verifiable data. And I'd love to get the Agency to weigh in, though I don't expect an official endorsement or anything like that. But I think this is the sort of data that people have spoken about -- magazine ads,

catalogs, things that show the intended use.

I think if we go back to the one with the ad, you know, that was a mistake. That wasn't a conventional food. That was clearly a supplement diet -- same for that. So I think we're -- there is evidence there that suggest these things have been in the diet a long time. And per Congress's intent, there should be some sort of stability to the market to where people know that this was clearly in the marketplace and they can use that ingredient without having to fear of getting a letter saying hey, you should have submitted an NDI.

But I think this is the start of discussion on time of use. We've seen from other product centers time and extent application, and I think that this ties in nicely with that decision -- those decisions where

AERs as well as the time in the marketplace, number of units sold, distribution over time, correlated with AR certainly makes a difference in establishing safety of a product. So this is something we look for to further discussions with the Agency on. And again, I think that with regulatory flex here by not having a statute,

by not having a reg underneath this, that's really the only way we can move ahead. So we look forward to sharing data, and I think that's where the discussion starts.

We want to meet with the Agency. We want to share data with them and show them what's out there on the market so that we can go back to our membership and make it clear that where the box exists and where it doesn't exist, not that it's, as someone said, fiat or a closed discussion, I think we'll keep finding things as we go down this process. But we've got to start somewhere, and it starts with the data, not the process.

So with that, I will gladly shut the hell up and turn it over to Stephanie. So thank you.

(Applause.)

DR. SCARMO: All right. Thank you.

Hi, everyone. I want to thank the members of the Office of Dietary Supplement Programs for holding this meeting and for the opportunity to present remarks today. My name is Stephanie Scarmo, and I'm a research officer at the Pew Charitable Trust. Pew is a

nonprofit, nonpartisan research and advocacy organization with a longstanding focus on the quality and safety of drugs, medical devices, and foods. We've recently launched an initiative to improve the quality of dietary supplements.

So creating a list of pre-DSHEA ingredients can be a worthwhile process as long as FDA has the resources needed to accomplish this task. It can reduce the risk that industry spends resources on unnecessary NDI notifications, and it can prioritize FDA's limited resources to review submissions of those ingredients that are truly new and may pose safety concerns.

So today, I'll present the approaches that FDA can consider and also present five principles that Pew

16 believes are necessary in the process.

17 So as we heard earlier today, DSHEA amended

18 the Food, Drug, and Cosmetic Act by adding, among other

19 provisions, the requirements for new dietary

20 ingredients. Based on the findings in the bill, we can

21 imply that Congress's intent for this exemption was not

22 to impose barriers in products currently on the market.

1 And thereby, Congress legislated a presumption of

2 safety. It's important to recognize that these

3 ingredients have never been proven for safety.

4 And the marketplace has exploded since DSHEA

5 was passed. At that time, there were about 4,000

6 products on the market, and today there are about

7 80,000 products on the market. More than half of U.S.

8 adults take at least one dietary supplement each day.

9 So the implications of using pre-DSHEA ingredients in

10 products are quite significant.

11 Therefore, we think that the approach FDA

12 should take in building this list should be a

13 conservative one, meaning if the ingredient isn't the

14 same in all relevant ways as its pre-DSHEA status, then

industry should have to establish a reasonable expectation of safety through the NDI process.

And so there are different approaches that FDA could consider in building the list. I'll present the advantages and disadvantages of different models now. But ultimately, the right framework will depend on the evidence that FDA sets to prove that an ingredient is pre-DSHEA.

So first, FDA could act alone by issuing guidance or through a formal rulemaking process. Obviously, the advantages of the regulatory process are that there's a notice and comment period for the public and (inaudible). But we do know that that process can be lengthy.

FDA could also act with or without an advisory committee. The advantages of the advisory committee is that stakeholders with a broad range of viewpoints would have the ability to weigh in. But finding the right non-conflicted experts to serve on the advisory committee may be a challenge.

But regardless of which approach FDA chooses, we do believe that the public should be able to weigh

in at several stages in the process and that FDA should have the authority to be the final decision-maker for what goes on the list of pre-DSHEA ingredients.

That said, there are certain principles that Pew would like to see guide FDA's decision in building the list. The first is transparency. The public should know what's being considered and the timeline for consideration and should have ample opportunities

to weigh in. This could be, as I said, through a public and notice comment period and/or through public meetings. Consumers also need to know that the ingredients on this list have not been proven for safety. Just because they're on the list, they are not safe. It just means that they're pre-DSHEA.

The right expertise will also be required so that the manufacturing processes can be evaluated to determine if an ingredient meets the identity standard for being pre-DSHEA. As I mentioned, if FDA does not have this expertise in-house, they could consider using an advisory committee, or they would have to hire special government employees to complete the task. And

both industry and FDA will need clear certainty on what can and cannot be marketed without an NDI notification.

An importantly, this process should be accomplished in a reasonable and fixed time frame and on FDA's budget. We do not want another situation like the over-the-counter drug monograph process, which was established by FDA in the 1970s to review the ingredients on the market at that time. In order to create or to update an existing OTC monograph, it

involves a lengthy multi-step rulemaking process that often involves review by outside agencies. And some of those monographs have been under review for decades. There's no timeline by which they need to be finalized, and we do not want another situation like that here.

A separate point about feasibility is that we would hope that FDA would prioritize nominations based on potential for public health risks. That means that any ingredients with a questionable background of safety would be reviewed first.

And industry must be able to prove that an ingredient meets the criteria for marketing and identity to be a pre-DSHEA ingredient. This would help

prioritize FDA's limited resources to review ingredients that are truly new and may pose safety concerns.

And so a final list could have not only ingredient names, but also conditions for use -- so details on sourcing and how it could be manufactured to give industry clear parameters for the ingredients that are considered pre-DSHEA. One way that FDA could consider doing this process is that they could open a

public document, and stakeholders could submit ingredient nominations along with supporting documentation to prove not only that it's pre-DSHEA, been marketed pre-DSHEA, but that its manufacturing process has not changed its identity.

FDA could compile the list of nominations, and they would have the discretion to remove ingredients from the nomination list based on whether there is adequate supporting documentation. We have seen this in other processes, including the drugs base.

And a final really important point is that industry -- Pew believes that industry should ensure

that all the ingredients in their supplements are high quality whether or not they are on the list of pre-DSHEA ingredients. If they are on the list and FDA finds a safety concern later, industry should not be protected from enforcement action.

So in summary, creating this list of pre-DSHEA ingredients maybe a worthwhile exercise for FDA and industry, but it will take compromise on the part of all stakeholders. If this can't be achieved and the process diverts resources away from other important

public health activity, such as FDA's ability to go after tainted supplements, then FDA should revisit whether this exercise is worthwhile.

Thanks.

(Applause.)

DR. FABRICANT: Now we'll call up Laura.

MS. MACCLEERY: While they're getting up my slides, I'll -- here we are.

So I'm Laura MacCleery from Center for Science in the Public Interest. I want to thank Stephen Tave and Cara and the whole staff at FDA for holding this event. I think it's a really worthwhile conversation.

I'll speak a little personally. I got into consumer advocacy through auto safety. And for me, the idea of a grandfather clause is quite strange. It's as though in 1968 we said oh, gee, we can't do any better than the cars that are on the road today; we might as well just live with the steering wheels that impale people.

So, you know, my -- I also backed into the dietary supplement work. In 2014, I was reading the news, and I saw that there was a report that someone --

in this case, Logan Steiner (ph) -- had died from ingesting powdered caffeine. He was valedictorian. He was a week away from graduation of high school. And I reached out to his parents and met with them and the parents of another young man, Wade Swatt (ph), who was 24 and an engineer and who died only a month later from ingesting the same substance.

And I worked with those families to bring them to D.C. and to talk to members of Congress and eventually a citizen petition to try to FDA to get highly concentrated forms of caffeine -- not just

powdered caffeine, but also liquid form that looks like water and is deadly at a cup of ingestion off the market. We filed that petition, and we haven't heard a response.

And the reason why this is relevant today is I think what you heard in the conversation this morning from Pieter and others is that even though the notion of safety is not specifically part of a grandfather clause. It is the elephant in the room. It is always the consideration from the consumer advocacy perspective. And if the system wasn't broken, if we

had a system in which rapid response to dangerous substances either under DSHEA's provision for removal of imminent hazards to public health or under the reasonable safety standard in the form sold, then we wouldn't be as worried about a system that provides a so-called safe harbor or a grandfather list of pre-DSHEA ingredients. So there's definitely a relationship from a consumer and public health perspective between what you're doing with -- what you might do with this list and what the risk to the public is of supplements in general.

In addition, the case study of caffeine points to an interesting problem with a pre-'94 grandfather clause. Certainly, caffeine was consumed, has been consumed from time in memorial (ph). Who knows? And yet potency and dose and concentration and the disparate nature of the industry all create novel risks.

So what we see in the case of powdered caffeine or highly concentrated liquid caffeine is that when we ordered it online six months after FDA sent its five warning letters to the particular producers that

identified a powder caffeine was that we were still able to obtain highly concentrated caffeine in both powder form and liquid form.

And so the warning letters operate as a sort of sporadic incentive for the major players in the industry but certainly do not stop the public from being able to access this dangerous substance. In this case, we got powdered caffeine with little serving spoons, even though it was still in bulk powder. And what you're seeing is that bulk ingredients are being

sold directly to the public. That really bypasses a safety standard that we've heard a lot about today because you don't have the ability to pursue liability if somebody's putting this together in their garage or they're making a DIY smoothie from a bulk supplier overseas.

So the question for us is really fundamental. Is this a so-called safe harbor, which I would dispute, or is it a rabbit hole? There would be a huge benefit to the industry as a whole, no doubt, from making the list because not every company would have to maintain their own proof of safety. But how does this fix

things from a public-facing perspective?

If FDA's resources are limited -- and already we see that there are substances that are left on the shelves into -- until consumers are hurt or killed, and we have another death from a dietary supplement two days ago that was just making the news -- perhaps all of FDA's resources should instead be directed toward examining the data and getting the most dangerous or adulterated substances off the market. That's -- I just think that's a proposition that we should consider

as an alternative.

The risk here that -- is that FDA would spend time and energy on a list that used mainly for marketing purposes by the industry and incorrectly labeled a safe harbor, which we've already seen on the slides. Yet the Agency will not have made, in fact, any determination about safety, just prior use, and consumers will be even more deeply confused than they are already about whether FDA examines the safety of supplements.

So how do we -- oh, can we get the -- it's not flipping. Oh, there.

So how do we make sure that the effort is worth the payoff both from an industry perspective in terms of patrolling the most dangerous substances that are in food and that give the dietary supplement industry a distraction, a liability, a black eye, however you want to call it, and from an Agency perspective in terms of resources and also from a public-facing perspective in terms of safety?

So here are some propositions that making the

list would be worthwhile if and only if industry is barred from using the existence of the list in labeling or marketing claims. And particularly, I mean with regards to some assertion of safety. And I think the term "safe harbor" is particularly perilous because non-lawyers won't understand that doesn't mean it's safe. That's a legal distinction, not a public-facing or communication distinction that's understood.

Secondly -- and here there's a lot of tension in the room, right -- it requires bona fide, not self-serving or industry-generated evidence of both identity and prior use. I have to say I'm a little puzzled by the fact that companies are saying there isn't this

evidence because if I was a company, if I was a -- I am a lawyer -- if I was advising on compliance and I was saying to the company you have to file an NDI for these things and these things are okay to use because they're pre-'94, I would certainly want to retain some records of that. So I find it very shocking that companies are saying that they haven't retained these records.

How -- that as it may be, if you don't have the evidence, it -- you can't show that it meets the

standard in the law, and that's how it is. So, you know, before '94, you'll have to establish that both the identity and the prior use were according to the law.

Concurrent with developing such a list, FDA should flag pre-'94 ingredients that are known to have safety risks at this time based on the type of safety evaluation outlined in the NDI guidance. And obviously, there's a history of safe use provision as well as a set of more exactly requirements for toxicological testing of novel ingredients. I think both of those things you could apply to the current list and look at the evidence and see -- and say -- and

I think this -- the relationship of this safety evaluation isn't that it's necessarily compelled by statute -- I hear you, Stephen -- but that, you know, the definition of the grandfather clause doesn't necessarily include a provision for safety.

But I do think as a matter of expending public resources on this exercise and in order to ensure that public safety is actually the end result, having a

parallel process that looks at how do we take the most controversial ingredients off the list or include a designation that flags them. And I'm hearing this from industry as well that this is something that they're open to considering, that -- some kind of special designation so that it is not implied that it's a safe list is important.

And then I think the list should uphold many of the key distinctions that were flagged by FDA in the draft NDI guidance, including some that are admittedly controversial. It is sensitive to intake level and population exposures.

And here I want to say reliance on self-affirmed GRAS is particularly problematic for the

reason that the commentator from USP flagged. A GRAS self-affirmation or notification, even, for FDA or even a GRAS-listed substance is based on a risk assessment on food consumption. It doesn't include exposures to dietary supplement in the population.

And so you would need to not only be within the four corners of the GRAS self-affirmation or notification and know that, it's very hard to know that

if something's been self-affirmed GRAS because there's no public record. So this is another way in which the GRAS system being broken actually parts the ability of dietary supplement manufacturers to move forward with regulatory certainty.

It excludes changes to the identity of the source material or meaningful alteration from manufacturing process changes. And here I agree with the panel discussion this morning, the exchange between Duffy and Pieter. If you can show that there's been no meaningful change in the actual consumption by the individual at the endgame, if the manufacturing process has changed, okay, big deal. But you would have to show that, right? That's a -- that -- you have to show

the salience of the manufacturing process changes to what is consumed at the endpoint.

And it excludes excipients and processing aides as well as indirect additives and the other categories that were identified by the FDA in the draft guidance. And here's where I think there's actually a really knotty (ph) problem around combinations, which

is why I was asking Duffy about this this morning.

You know, we have these two standards. We have, first of all, UMPA saying, on average, supplements contain nine ingredients. For an NDI, you have to submit a new proof of safety for that combination of ingredients. And you can argue with the details, and this can get very complicated very quickly. But really, there is a flag that a new combination can exhibit new chemical properties. It's what was misleading about that NutraSweet ad, right? If you've had what's in bananas and milk, you've had NutraSweet? Not really. From a chemistry perspective, we know this is true.

So -- and then with regard to the pre-'94 ingredients, because NDI noticing requirements are not

triggered, you are allowed to market them in any quantity at any potency and in any combination. That creates a problem for public safety that isn't necessarily covered by the NDI guidance because you're not going to -- the Agency is not going to have noticed. It's not going to be the subject of an NDI.

But you're taking older dietary ingredients,

potentially isolating those constituents and putting them in food and putting them in dietary supplements without proof that that combination -- and I think the energy drinks example is actually a great one because, even though it's not a dietary supplement anymore, thanks to FDA's guidance. But in theory, you can have combinations of stimulants in those ingredients that have never been tested in combination. And all you have is the company's assertion that they're safe.

So this is -- I don't know what the plan is here, but we need to -- it's a problem that we would need to grapple with because it seems to me both of the structures that we have from DSHEA don't really deal with how FDA could address that.

Here's my modest proposal, making the drawing

(ph) resources match the game. FDA should first convene a process to examine pre-'94 ingredients and combinations that pose a risk to public health. This is just useful in general, and if you wanted to expand it to any ingredient pre-'94 and post-'94 and just make it a safety evaluation and try to audit essentially

dietary supplements, what I'm told is that yohimbe and yohimbine pose unique risks that dwarf all other kinds of incidents related to dietary supplements.

There may be one or two or three other examples of really high opportunity activities that the Agency could do that would take away a lot of the things that are popping up in the emergency room results and in other sort of concentrate poison control and other sort of data monitoring that we have. And if you focused on those and took action on those, I think the whole political stakes for what is going on with the list activity gets lowered.

Once the status of these ingredients is clear, FDA could then proceed to compile a list based on industry submissions of adequate evidence of prior use. Information of manufacturing process and other aspects

of the products relevant for identity or safety would be made public. This is a key point. If -- we can't really have a list that's produced if the details and manufacturing processes are held proprietary. And this is a flaw in the proposal for a master file that would need to be evaluated and -- vis-a-vis this list.

The list should be -- eventually be made -- eventually, eventually -- be made an exclusive repository for pre-'94 status. It should have some sort of authoritative reassurance to it, or what's the point of the exercise?

So, you know, and new applications could be admitted if there is additional evidence that comes to light down the road. You could leave it open for new processes, but you have to get it on the list as a matter of conferring the status. And it should not perpetuate the GRAS loophole. I've talked about this a little bit. But really, because of self-affirmed GRAS happening in the dark, you can't really do the kind of risk assessment that you should be able to do, and you can't look at population exposure or potency or intake or any of those kinds of assumptions. The consequence

of exclusion from the pre-'94 list merely means the companies have to file an NDI, and there could be a reasonable time for doing so.

So, you know, I think we've got buckets that we need -- that need to be unbroken, essentially. And

I appreciate FDA's ambition in taking this on. I want to assure that the eye doesn't get off the ball, and the ball really is public safety and a vibrant marketplace -- both. And so finding ways to reconcile those with this process I think is the imperative.

Thank you.

And I'll call up Jay, who's coming to speak next.

(Applause.)

DR. SIROIS: Good afternoon, everyone. My name is Jay Sirois. I'm a senior director of Regulatory and Scientific Affairs at the Consumer Healthcare Products Association -- excuse me for that -- the 136-year-old trade association representing manufacturers of OTC medicines and dietary supplements.

I'd like to thank the FDA for allowing CHPA to present at today's meeting and look forward to an

informed discussion regarding the creation of a list of pre-DSHEA dietary ingredients, specifically in regards to the process used to nominate and evaluate dietary ingredients for possible inclusion onto such a list.

A few brief remarks about CHPA. This slide

depicts our overall mission and vision statements both for the association as well as our educational foundation, which promotes safe, responsible use of OTC medicines and dietary supplements. We are here today on behalf of the approximately 30 CHPA members in the dietary supplement space.

In the Federal Register Notice announcing this meeting, FDA noted the discussion during the second panel for the meeting would include topics such as how dietary ingredients should be nominated and reviewed, whether or not an outside panel should be convened and how it should be composed, how confidential information should be handled, and what the ultimate list should look like. I will touch briefly on each of these topics today.

The Agency also felt it would be helpful for CHPA to present in today's session on any lessons

learned from the OTC drug review, a process initiated in 1972 to evaluate the safety and efficacy of over-the-counter ingredients. I'll provide a history of that review briefly discussing the format FDA employed

as well as some of the reasons why they did it the way they did. I will also discuss the formation and composition of the expert panels who carried out the work of the OTC drug review evaluating evidence and providing recommendations to FDA.

In our December 2016 comments to the FDA on a new dietary ingredient draft guidance, CHPA provided a brief outline for a pre-DSHEA ingredient review process. Today in the second part of my talk, I will cover several key aspects to consider as we begin to discuss how to accomplish this type of a review.

So before I cover the OTC drug review and how that process could potentially inform a review of pre-DSHEA dietary ingredients, a little history lesson is necessary for context. In 1938, Congress passed the Food, Drug, and Cosmetic Act requiring drugs to be evaluated by the Agency for safety only.

In 1962, Kefauver-Harris amendments to the act

required FDA to evaluate the effectiveness of new drugs prior to their marketing. In addition, they required the Agency to go back and review all the drugs approved on the basis of safety alone during the 1938-to-1962

period for effectiveness. This ultimately became known as the DESI review, short for drug efficacy study implementation.

FDA contracted with the National Academy of Sciences to perform this review of the approximately 7,000 drugs approved between 1938 and 1962. Most of these were prescription drugs, and in total, about 300 chemical ingredients were involved.

In general, there were a couple of lessons that were learned by FDA during the DESI review which informed the OTC drug review. The first was to make the process more open. For their deliberations, the NAS committees met behind closed doors, and there was no consumer or industry representation or even FDA representation, for that matter.

Another was to issue a more comprehensive report of the decision-making process. NAS reports were typically about a page long, and this later became

an issue under certain circumstances.

And lastly, FDA learned of the drug-by-drug evaluation, as was done during the DESI review, was not

feasible due to limited resources in the vast number of OTC drugs on the market. This led FDA to analyze therapeutic classes of ingredients during the OTC drug review.

The OTC -- excuse me -- the OTC -- yes, that's the one. The OTC drug review was begun in 1972. It's an ongoing process by which the safety and efficacy of OTC ingredients is assessed. Data relating to claims and active ingredients for different therapeutic classes was reviewed by an expert advisory panel. The FDA eventually convened 17 expert panels to review over 60 classes of ingredients. Expert panels were composed of physicians, pharmacists, toxicologists, and industry and consumer representatives.

For each reviewed therapeutic class of OTC drugs -- for example, antacids or analgesics -- a total of seven expert panel members recommended by organizations representing professional, consumer, and industry interest and who had experience with OTC drugs

in some way were chosen by the FDA commissioner. FDA did their best to ensure that individuals did not have any conflicts of interest.

Consumers and industry had a designated liaison member, both of which were nonvoting. Expert panel members reviewed submitted evidence and provided a report to FDA. Panel recommendations became mandated in an official OTC monograph through a three-step public rulemaking process.

Expert panel reports were published in the Federal Register as an advanced notice of published -- proposed rulemaking, which provided preliminary assignments of ingredients in regards to their safety and efficacy. As many of you know, Category 1 was generally recognized as safe and effective for their intended use; Category 2, not generally recognized as safe and effective; Category 3, more data was needed in order to classify the ingredient.

Following FDA review and public comments, a tentative final monograph would be published, proposing approved ingredients, uses, doses, appropriate claims, and required warnings. Following review of an

additional set of comments, FDA would publish a final monograph ultimately codifying allowable claims

labeling inactive ingredients.

There were a number of benefits to the way this process unfolded. By performing the review according to therapeutic classes, it allowed a more effective analysis of the large number of OTC products on the market. Key stakeholders with knowledge of specific therapeutic classes were involved, allowing a very thorough review of the evidence. And importantly, the public was allowed to comment on the process at multiple points.

As to drawbacks, it's been noted that the process tended to be very lengthy, and to this day, some monographs still exist in the tentative final stage. In part because of this, for the past few years, industry has been in negotiations with FDA to add some much needed reforms to the monograph process in order to make it run more efficiently. Under the proposed plan, the Agency would replace notice and comment rulemaking with an administrative order process.

I'd like to transition now to discussion of several key points to consider when developing a

process to determine whether a dietary ingredient was marketed pre-DSHEA. These focused solely on the process and do not consider the types of evidence for review, as discussed during the morning session.

We look forward to input from the Agency and other interested stakeholders on these topics as well as others which we may not have considered. Very briefly, as I'll cover each of the main points in a little more detail in the upcoming slides, the first step in the process would involve the FDA convening an expert panel, followed by a public call for evidence regarding pre-DSHEA marketing of dietary ingredients.

The expert panel then working with FDA would designate a list of dietary ingredients for review of evidence for pre-DSHEA marketing. The expert panel would then review the evidence and issue a determination of the pre-DSHEA marketing status. FDA would publish this determination in the Federal Register and invite public comment. Lastly, FDA would finalize the process by either declaring the ingredient

as pre-DSHEA or that there is insufficient evidence for

pre-DSHEA marketing.

The first step in the process would be the formation of an expert panel. What we envision is a seven-member voting panel made up of three FDA and three industry members as well as an additional member agreed upon by both FDA and industry. Nonvoting members would include a consumer representative as well as an industry representative. All participants would be chosen by the FDA commissioner.

Prior to the commencement of the review process, we feel that FDA should issue a notice of enforcement discretion based on an updated version of the ODI list previously submitted by the dietary -- several of the dietary supplement trade associations.

Subsequent to this, FDA would issue a call for evidence in the Federal Register, asking interested parties to submit proof of pre-DSHEA marketing. Individuals submitting data should be allowed to claim that their information is confidential.

The FDA, in conjunction with the expert panel, would then designate a list of dietary ingredients for

review. This could be based, for example, on the type

of dietary ingredients identified in DSHEA -- for example, vitamins or minerals, herbs or other botanicals or amino acids.

The dietary ingredient expert panel would then review the submitted evidence using agree-upon criteria to determine if the dietary ingredient was marketed in the supplement pre-DSHEA. The expert panel would issue a report to FDA on the ingredient status if one of two findings -- the ingredient under review would either be confirmed as a pre-DSHEA ingredient, or the decision would be that there is insufficient evidence for pre-DSHEA marketing.

FDA would publish this decision in the Federal Register and invite interested parties to comment. Or if we move to the administrative order process, the decision would be posted on the FDA website. FDA would then issue a final decision on the status of the dietary ingredient and maintain an active list of those ingredients found to be marketed pre-DSHEA as well as those for which there is insufficient evidence for this.

A few things to consider. We suggested a defined time frame be allowed for industry to address a finding of insufficient evidence for pre-DSHEA marketing. We would also suggest that a finding of insufficient evidence should not necessarily preclude an ingredient from being marketed. And lastly, we recommend that there be some type of reasonable arbitration process built in for cases in which there is disagreement between the panel and industry on the classification of a dietary ingredient.

My last slide here is just a side-by-side of several of the key considerations I've discussed for the pre-DSHEA ingredient review process alongside similar aspects of the OTC drug review. FDA has previously noted -- and we agree -- that the development of an authoritative list of pre-DSHEA ingredients would benefit both industry and the Agency by enhancing clarity around the status of a dietary ingredient, eliminating unnecessary notifications, and allowing a greater focus of Agency enforcement efforts.

We look forward to continued discussion with the Agency and other stakeholders surrounding this

process.

Thank you. And I'd like to --

(Applause.)

DR. SIROIS: Thank you. I'd like to now invite Chuck Bell to the podium.

MR. BELL: Thank you, Jay.

So I'm Chuck Bell. I am the programs director for Consumers Union. We are the policy and mobilization arm of Consumer Reports.

I wanted to echo the point that Laura brought up and about the safe harbor terminology. We're concerned that statements in the trade press about this issue, about the safe harbor, implies that the ingredients themselves are presumably safe. And I found evidence for this message being received by industry in examining a couple websites of a law firm and a trade association where it stated that these grandfathered ingredients are considered safe for continued consumer use.

So we think that this terminology potentially sends the wrong message to manufacturers. You have a very large and heterogeneous industry with varying

levels of staff and legal capacity. And for the pre-1994 ingredients, there is no pre-market safety review. The only real line of defense for consumers is the voluntary safety review by manufacturers and then the FDA adulteration standard that if the product poses a significant and unreasonable risk under conditions of use it can be removed. But that's been rarely used.

And the voluntary safety review by manufacturers has been shown to be a weak and ineffective control in many circumstances, although we certainly appreciate the industry's efforts in this regard. And in some instances, it has been very important and effective.

So we at Consumer Reports have published lists of dangerous supplements since DSHEA was passed in 1995, 2004, 2008, 2010, and 2016. And some of the ingredients that we believe were unsafe and that we urged consumers to avoid have remained on the list during the entire 23-year period. So what we have noticed is that unsafe supplements can remain on the marketplace for quite a long time. And the inadequate safety system we have that's largely based on post-

marketing surveillance with rarely used procedures to remove products has led to long delays in removing dangerous ingredients.

So these are some of the risky ingredients that have been on the Consumer Reports list. They include ingredients that have been linked to serious adverse events, including some that cause organ damage, strokes, and deaths.

This recent paper from the Journal of Hepatology reports that herbal dietary supplements induced liver injury now accounts for 20 percent of cases in a subset that was collected by the authors through the drug-induced liver injury network. And these are cases of hepatotoxy (sic) in the United States based on research data. And the major implicated agents included anabolic steroids, green tea extract, and multi-ingredient nutritional supplements. And in the pie chart, you can see there's a range of supplements that have been implicated in these reports.

The paper says we need improvements in regulatory oversight. And the ultimate goal should be to prohibit or more closely regulate potentially

injurious ingredients, then thus promote public safety.

So a consumer who goes to the liver tox page at the National Library of Medicine sees this entry for green tea extract. And it says, "Green tea extract and concentrated infusions of green tea have been implicated in many cases of clinically apparent acute liver injury, including instances of acute liver failure and death." This is not an outcome many consumers would expect for a product marketed to enhance health and wellbeing, and this deserves our attention and investigation. We should not want to have dangerous ingredients that pose unreasonable risks to consumers on store shelves, regardless of the legislative language that was written in 1994.

And so beyond the ingredients we have identified, there are potentially many others where the safety profiles of those ingredients are not that well understood at pose -- could pose similar risks to coronary or kidney health or liver health or have other serious side effects.

And so, so far in terms of old dietary ingredients, FDA has basically removed one unsafe old

dietary ingredient, which was ephedra. I realize that the -- this is a slightly more nuanced and complex situation because there has been action taken against a variety of other substances and other specific products removed, but it took 10 years for ephedra to be removed after issuing a safety alert about ephedra beginning in 1994.

And under the law, it is quite difficult for FDA to remove unsafe ingredients from the marketplace because of the high standard of proof that is needed.

Also, as noted by some other speakers, FDA's funding and staff resources have not kept pace with the explosive growth in the marketplace, with 1,000 new products added every year. And that also limits the effectiveness of public oversight for removing unsafe ingredients.

It is more common for FDA to issue warnings, and so we have this webpage here with a number of warnings about supplements. But warnings in a doctrine of let the buyer be aware are inadequate to protect the public. And many people will never see these warnings, and they're not expecting a product advertised to

improve health would have such severe adverse effects.

And this picture is of a young man named Peter Schlendorf, who died after taking the product Ultimate Xphoria on spring break in 1996 that contained ephedra. It took eight years after Peter's death to get ephedra out of the marketplace. Peter's parents very much wish that the Congress and the FDA had taken the time to investigate the safety of ephedra and the other old dietary ingredients before allowing it to go on sale throughout the country.

In some market research we have done at Consumer Reports in a poll that we published, we have found that consumers generally assume that products that are sold at retail and over the internet will be safe and effective for their intended use. They tend to believe that if the product wasn't safe, the government would intervene to do something about it. If they weren't safe, they think the CVS, Walgreens, and the GNC wouldn't put it on the shelf.

Consumers do not expect the situation where there's little or no safety vetting of individual ingredients or that that safety vetting is done only at

the discretion of the manufacturer.

We have a safety system, as I mentioned, that's largely based on post-marketing surveillance. One key problem with using adverse events to track signals with possible safety problems is that people are on the other side of that adverse events. And if the consequence is a severe liver or kidney injury or a seizure or a stroke or a death, it's a really big deal. And in a significant number of these cases, we see people who are otherwise healthy who were made gravely ill by a supplement that they purchased.

So if we have old dietary ingredients where the safety has not been adequately substantiated -- and I think a number of speakers today would stipulate that could be the case at least for several ingredients, if not dozens or hundreds -- we need a process to ensure that they will be safe under expected conditions of use before putting them on a validated list and inviting manufacturers to use them. And I just don't think this process will have credibility with consumers if we can't address that glaring contradiction.

So our recommendation would be that we need a

process to delist unsafe pre-1994 supplement ingredients either through FDA action, voluntary agreement with industry, and/or changes in the law. The current safety and oversight system has not addressed this priority concern of consumers, and we would be very concerned and alarmed if FDA specifically were to accept specific ODIs that are toxic to the liver and kidneys or that caused cardiovascular problems.

And we had some hope in -- right after ephedra was banned in late 2004 when the secretary of HHS Mark McClellan indicated that he would be investigating products like bitter orange and kava and a number of others. But 13 years later, we haven't seen action on that commitment.

We believe the U.S. needs to move to a system where there's universal substantiation of safety for all ingredients and dietary supplements, and we look through -- at this process through that lens. We believe there should be a more effective use of regulatory resources and public funding. It would be for the FDA to set a deadline for manufacturers to

submit NDI applications for products that are currently in the market that have not been declared yet.

Now that the NDI guidance has been further refined, the rules of the road should be clear. And we would argue it's a better use of FDA's resources and staff time to address the proliferation of NDIs that were never declared because this will reduce the number of unauthorized and inadequately reviewed ingredients in the marketplace.

And in that light, I wanted to just acknowledge the point that Duffy made this morning about that if you have a constituent like the example of the bromelain from the pineapple that that would require an NDI or some different notification. We are supportive of that concept.

All right. And finally, we think that consumers and public health is well served by presumption toward openness in supplement regulation and that there should be wide sharing of information about which ingredients are contained in the supplements that consumers are buying and using. And so if manufacturers were allowed to make extensive use

of confidentiality and proprietary claims in this process if it moves forward, it would frustrate the public's right to know what is in supplements and any known shortcomings, side effects, and risks that they may have. So we favor a presumption towards openness in the process.

Thank you.

(Applause.)

DR. WELCH: All right. Thank you to our panel.

Now is the time when we can entertain some questions for our panelists. If there are any questions, I would encourage you to come to one of the two mics on either side of the room. Please speak your question into the microphone and start with your name and affiliation first. We'll also be monitoring questions on webcast. If any come through, we'll ask on their behalf.

Any questions for our panelists? Boy you guys really set it off well.

I do have one question, Jay. When you were getting into the process that -- the suggested process

that was laid out, you suggested -- and I apologize if I noted it wrong -- but essentially convening a panel, reviewing information that had been submitted, and published the determination, I assume, in the docket. I didn't note that, actually.

You were comparing it to the DESI review, if I remember correctly. Were you envisioning for dietary ingredients, not necessarily looking at efficacy, to have one panel for dietary ingredients or differentiating by any particular differentiation, a therapeutic class, or otherwise?

DR. SIROIS: Well, I think -- this is Jay Sirois with the Consumer Healthcare Products Association.

I think, you know, I -- when we look at this, we want to try to make it as simple as possible because, on the one hand, we're looking at evidence of marketing, which you don't have to be a PhD in chemistry to understand that something was --

DR. WELCH: I hope not.

DR. SIROIS: Yeah. And I wasn't singling you out, Cara.

So you don't need that understanding. But I could envision the product -- you know, you -- there are some -- you know, when you get into the manufacturing changes and things like that and you're talking about probiotics versus amino acids versus vitamins and minerals, there may be some benefit to having some of that expertise on a particular panel for each of those classes.

So I think at the end of the day you want to try to keep it as simple as possible, you know, because obviously we learned some lessons from both the DESI review and the OTC drug review that, you know, that can go on for a very long time. But it's a different standard here that we're talking about. We're not reviewing for safety and efficacy. We're reviewing for proof of marketing. So …

DR. WELCH: I -- Dan, were you going to say something?

DR. FABRICANT: Yeah. I'm always interested when people talk about Agency resources, just given my life expectancy, what have you.

(Laughter.)

DR. FABRICANT: I think that, you know, people are talking about setting up processes. And we can just say look, there's not a reg; there's not a statute. But not having a processes -- not having a clear process and just presenting data to the Agency that gets protected by CCI and FOIA rights that people already have, that's pretty -- is non-process and non-burdensome to the Agency as I get you think.

You know, but I mean, I'd love to hear the Agency's perspective, not to put you guys on the spot. But you know, that would seem to be the easiest. People dump data on you guys that has references behind it that would seem to be the no-muss-no-fuss way. But I'm not going to claim to know anything about the FDA's inner workings.

DR. WELCH: Just because I'm standing behind the podium does not mean I'm going to answer that question.

DR. FABRICANT: I did not expect you to, no.

DR. WELCH: And Stephanie, going back to your presentation, at one point, you discussed making sure

you have the right expertise. Technically, I think you

talking about an advisory committee or special government employee. Playing off what Jay was just talking about, about hopefully not needing a PhD in chemistry to determine marketing, what is sort of the expertise that you were envisioning when you commented on that?

DR. SCARMO: So for that, we were thinking about technical issues that would affect an ingredient's identity, so manufacturing changes, chemical alterations. Likely, FDA would have that expertise in-house. But if they don't, and to prioritize their limited resources, they could hire a special government employee or could seek the help of an advisory committee for some of those debated issues.

DR. WELCH: Thank you.

Steve?

MR. TAVE: Steve Tave, FDA. Is this on?

DR. WELCH: I'm not sure it's on.

MR. TAVE: No? Okay.

Steve Tave from FDA. And I think I'm just

enjoying the opportunity to ask questions because usually I'm the one who's up there being asked.

I'm -- first, I just want to thank this panel like I thank the previous panel for coming here. I think you all present --

DR. WELCH: Steve, we're not totally sure you're on, actually.

MR. TAVE: Okay.

DR. WELCH: People behind you don't seem to be hearing you.

MR. TAVE: Okay.

DR. WELCH: So if you could push the button or just hold it.

MR. TAVE: Better?

DR. WELCH: Yes. Thank you.

MR. TAVE: All right. So for those virtual, Steve Tave from FDA. And I'll repeat this because it's important. I want to thank this group of panelists, just like the first panelists, for coming today and sharing their thoughts and views. Again, I think you've all done a great job of just laying out what the issues are that we have to grapple with and different

ways to look at them.

One thing I wanted to follow up on, we heard a

lot about safety, and we heard a lot about process. And I think those two intersect in obvious ways. One suggestion that I think we heard from more than one panelist here and possibly even from folks earlier in the day was that FDA should prioritize looking at ingredients where there is evidence that they're unsafe or they may pose a safety problem.

And I'm curious for any thoughts on how we might identify those first. Would there be a nomination process for those? And the reason I'm asking is, you know, there's utility to you industry and stakeholders in having a list of pre-'94 ingredients. When industry and stakeholder are going to benefit from that list, they're more incentivized to nominate ingredients to be on it. But if the outcome of nominating something is that your ingredient might be identified as unsafe that's potentially contrary of your business interest, how would you suggest we go about that process?

DR. FABRICANT: I thought you were already doing that via the AERs. I mean, that's -- you know, you get safety signals. You investigate safety signals

or other sources of data. That's being done. I mean, everyone can sit around and move molecules around and say this is dangerous, that's dangerous.

But I think that, you know, in a sentinel environment, what you have to deal with at the Agency, a post-market environment -- and it's not just this product center; I mean, it's the same MedWatch system, devices, drugs, what have you -- that's your -- you know, that's your telltale if there's evidence on the market.

I think the Agency has a pretty good handle, you know, despite -- and I appreciate the CSPI folks and then Consumers Union. You know, we know where you guys are coming from. At the same time, you're not walking into any health food store and buying an aristolochic acid supplement. And yet that story has been in 2004, 2008, 2012, 2014, 2016 in Consumer Union's supplements you should avoid. And the Agency's been pretty clear on that as well. They've made it

clear that that's an adulterated ingredient and adulterates the product and stay the hell away from it.

So again, I think a lot of this is much ado

about nothing. I share the point that, yeah, safe harbor probably is the wrong language. But with respect to old ingredients, one, you have to develop a list. And then if anything on that list that are current AERs that are indicating hey, there may be a there there -- look vitamin D is going to be on the list. Guess what? You get too much vitamin D; you got a problem. Calcium -- I mean, we can stay away from swimming pools, too. Water -- you know, there is water toxicity, too.

So I think that these are all things that they fairly well wrote. I don't there should be a nomination process, if you will, because, again, all due respect to everyone in the room, you guys are the food safety authority. So I think that -- I mean, I paid my taxes this year, so I've got faith in you guys.

DR. SCARMO: Unsurprisingly, I disagree.

(Laughter.)

DR. FABRICANT: (inaudible - off mic).

DR. SCARMO: You know, I think it's a great question. One aspect that's a serious shortcoming of the AER system that is -- that it's reasonably decent

at raising an initial red flag but very poor at showing causation. And we've seen this with energy drinks. For example, when I looked at the AER reports, it's over-inclusive and probably grossly under-inclusive in terms of the reports that actually show up in the system.

So I do think there is a need for a much more textured and rich kind of system for developing a rapid response muscle around threats. And I'll just point to, you know, there is an imminent hazard provision in DSHEA that has never been used, so even in the case of ephedra. Certainly, you know, in our view, if there is an opportunity -- if there is a situation that calls for it, it would be powdered caffeine or maybe kratom.

So, you know, those are the kinds of places where we think the system demonstrates its brokenness. And what you could do about that is essentially try to address, I think, to the industry's benefit as well as

the public health the most risky substances that are currently showing up in dietary supplements, be they pre-'94 or post-'94. And maybe they've gone through an NDI process, or maybe they were put into dietary

supplements through a GRAS -- through the GRAS -- what I call the GRAS loophole other people might call the GRAS system -- so that you clear the decks, as it were, and made possible the development of a much less controversial process and list and lower the stakes.

And I think that would beg the question, of course, of how the Agency prioritizes its enforcement resources and how you take action, but it's not necessary that you have developed a full plan to just begin to name the dietary ingredients that are most problematic.

There is in-depth research by Dr. Cohen as well as by others in the field that isn't going to show up in an AER. There is the integration of poison control center data with the AER findings. There's a lot of data streams that need to be talked about -- that should be talked about publically that should

inform all of us so that we all have a shared list of priorities for what are actually posing risks to public health in the supplement area.

DR. FABRICANT: And I'm going to disagree with you, given that I was one of the first people to use

mandatory recall on human food, a dietary supplement. We did that during the furlough when there was nobody in this building four years ago. I don't think you're well aware of all the legal authority the Agency has or of that particular instance.

Mandatory recall is a pretty good stick. It got a product off the shelves after less than 40 AERs in Hawaii. I know Bill also got a complete recall -- and this was voluntary recall -- of Hydroxycut for liver injury after 23 AERs. So again, I don't think that your statement's accurate.

And also, other data points, all due respect to people at poison control, that data is -- it's not very informative. The MedWatch system -- I'm not going to tell you it's perfect, but if you can design something better, great. But again, the system does alert the Agency of where the challenges are,

especially with a liver signal, cardiac signal. And I do trust that they are -- that the folks here at FDA are actively searching that.

DR. WELCH: Brian?

MR. FRISBY: Brian Frisby with KGK and other

places.

I wanted to kind of reiterate but also to ask a question, kind of go back to what Steve was just saying, is I have watched every one of these presentations now and the products that kept coming up as far as issues with them. I think everybody in this room knows what these products are. We're all aware of them. They've been out there. In some cases, as Dan said, we've had reports and reports and reports for, literally, 20 years on these.

Now, the obvious question is how do we move those, get those off the market or make them so that they're safe. I'm not sure. The thing is, is I look around at this room here, and the people that are here are not making those products. Those products are not made by people that are responsible. They're made by

people that want to just make a lot of money real quick in the dietary supplement business and then get out.

And so I think the point of it is, is that we're not here to make poison. We're not here to kill people. We're here to make products that actually help people. And that's why I've been in this business for

over 30 years to do.

With that being said, I want to go back to what Steve asked and what Dan and Laura were talking about. Perhaps there is someplace where there's a threshold, or whatever, that if you get enough reports -- and obviously, the SAER is a system that we should depend on, but I don't know how many people adhere to that the way they should. And I can tell you that I have never been audited in a facility where someone's come in and said let me look at your customer complaints and your AERs. I think it should be done, but it hasn't been done. You know, again, we just don't have the bandwidth on the Agency side, I mean.

But where I'm going with that is that, you know, again, every one of those products we saw up here today are things that have come up and up and up. How

many times do they come up before we finally move on them? And a good -- you pointed out several opportunities, or two opportunities, where we did move things off of it. So I'll leave it to you for that in the comments.

DR. FABRICANT: As far as I know on AERs, it's

-- it used to be part of the turbo AER on the inspection pack that you could look at 761 compliance and things like that. I don't know if that currently is, but I believe it is. So -- but I'll leave that to you guys to discuss.

DR. SCARMO: Well, I would just say, you know, that reflects a level of, I think, candor and shared frustration that is a common ground, I would imagine, for the more responsible aspects of the industry in this room and the consumer community. We're all tired of seeing the same ingredients be cited in public health-related reporting. And we're all tired of an -- a system that doesn't adequately police the safety of the public and put that first.

So I do think that there is the ability at

this point with the maturity in the industry and the concentration of better actors among many of the companies and producers that we could get together and decide we're going to take action in a concerted fashion against those things that pose the most serious risk to public health and not only now, but set up a system that is capable of taking action when the next

threat comes down the pike and is a kind of rapid response.

You know, those aren't the only concerns that the consumer advocacy community has. We also have concerns about efficacy, what's in the bottle is what's on the box, all of that.

But really, the most pressing public health-related concern that I hear from advocacy organizations has to do with the risk and threat to public health. And so I think there's an opportunity here. I'm not sure making a list of grandfathered ingredients is a mechanism by which to do it. In fact, the safe harbor would be the only things that aren't evaluated for safety.

And so for me, it's particularly inept

terminology, and maybe the task is something else. Maybe the task is trying to get together to try to pull together a list of -- that's an action list, frankly, and shared by, you know, voluntary action from the industry and enforcement action from the Agency.

DR. SIROIS: This is Jay Sirois with the Consumer Healthcare Products Association. I just want

to echo a couple points that have been made, one by the commenter that the associations represented here are not the folks that are manufacturing some of these ingredients. I think that's an important point to make. I think it's also important to point out that what Dan mentioned, that the Agency has adequate abilities to enforce under -- for safety issues.

And I also want to point out that all of the trade associations here that are represented are part of advocacy efforts to promote safe responsible use and the production of high-quality dietary supplements. I mean, you all know the efforts. There's the Dietary Supplement Quality Collaborative. There's the SSCI. There's the Botanical Adulterants Program. There's the

OWL database. There's the Good Agricultural Clinical Practices.

So it's -- you know, we want to make sure that the efforts here are focused on the right area, right? I mean, we want -- we don't want unsafe products on the market. We are all about informing consumers about what is safe to use, don't believe outlandish claims, and things like that. So we want to make sure the

efforts are tightly focused, and we do think the FDA has adequate safety resources.

DR. WELCH: Michael.

MR. MCGUFFIN: Michael McGuffin, American Herbal Products Association.

And you know, I appreciate, Laura, the call for we can all get along; we can work together. But to do that, we have to get beyond the myth of -- that there's only one ingredient that the Food and Drug Administration has ever removed. It's simply not accurate.

There's one ingredient that they removed through that mechanism. As Dr. Fabricant pointed out, I can't buy aristolochic acid, as the Food and Drug

Administration issued an import alert one afternoon, not 10 years. One afternoon they issued an import alert. You can't get aristolochic acid into this country. Does that mean there's none? No. Is it broad -- as Dan said it -- can I get it in Whole Foods? No. Can I get aconite in Whole Foods? No. And that is actually an industry self-control mechanism.

The Agency did act on kava. They didn't act

to ban it because the evidence didn't support banning it. They issued a consumer advisory that said you should be informed about your use of kava. If you're going to use it, you should be aware of the symptoms of liver disease in case that comes up. The last time I checked, that warning was on every kava product that I can find in the marketplace.

And they -- the same thing happened with chaparral when the Agency said we're concerned about some safety issues. But they did not say therefore, it should be banned. They said therefore, there should be cautionary language on chaparral products. And as I pointed out earlier, we have an affirmative obligation

to provide material information.

Citacortopholia (ph) on Consumer Reports list, Chuck, that was a mistake that the Food and Drug Administration made -- I apologize -- where they identified that as a good source of ephedrine. In fact, it's not. There might be a little bitty bit, and we do know that some companies were spiking ingredients identified as citacortopholia with ephedrine for a week or two or a month or two. I don't know what. But it

shouldn't still be on your list, Chuck.

And so if we're going to have the conversation about how we can work together to resolve where there are cases where there's true safety, then we need to be very truthful in all of our communications about these issues and not continue to tell the story that it takes 10 years. It doesn't take 10 years when FDA chooses to use other mechanisms.

MR. BELL: Well, so I helped -- or organization helped get ephedra off the market by working with the Schlendorf family to ban it in Suffolk County and then Westchester County and then New York State and then California. So I've -- I think it's a

little hard to accept people telling us that FDA has the authority to remove dangerous ingredients. There's a lot more items on our list besides the handful that you mentioned.

You know, to mention the aristolochic acid as something that's already been dealt with, you know -- and we're often given this point that, you know, the products you're talking about are not in the mainstream of the marketplace. But whether it's a niche product

or not, manufacturers around the country have the freedom to reintroduce these ingredients if they're on a list of old dietary ingredients and wait for FDA to take action after the fact. And so we just -- we don't -- we disagree that that is adequately protective of the public.

And also, on the paper about the liver injuries, it's mentioned that quite a number of those cases involve multi-ingredients weight loss products.

So there's a lot of safety issues here. And you can hide behind this idea that FDA has this authority to address them. We haven't seen that

authority used that much. And so it's a disagreement that we have and I think we're going to continue to have.

DR. WELCH: While I always appreciate spirited discussion, I do think we're straying a bit away from the list that we were -- actually came here today to talk about, which we be an ODI list, though I do appreciate the points that were made in the presentations.

To bring -- come back to that, that topic, I

was wondering, Chuck, if I had a question for you. You started off talking about terminology is very important and communication and rolling out that list. You also, of course, mentioned that one poll from Consumers Union history. I'm not sure when it was taken. But consumer education is always a real interest at FDA. It's expensive, and we don't always have the money or the resources to do that.

I'm just curious. You -- the question that you discussed was -- or the answer that you discussed was that consumers generally believe the marketed products are safe and effective. I'm curious if --

starting off with your first point about the terminology in safe harbor, the -- what sort of communication or terminology do you think is important when we theoretically put together the final product? So what -- the end list, is there something important that we need to make known in this end product to give that message of what it truly is, a list of ingredients that were marketed prior to October 15, 1994?

MR. BELL: I mean, I would say, for one thing, like, let's not call it the safe harbor. You know,

let's call it a list of dietary ingredients that the Congress -- I mean, I don't know what the correct title would be. But --

DR. WELCH: Not to put you on the spot.

MR. BELL: -- I have a concern that, no matter what type of disclaimer that you put on it, a large block of consumers is still going to believe that these have been subject to pre-market safety review. People do not expect that with the government we have and the FDA that we have that such ingredients can be put into the marketplace with only the word of the manufacturer

behind them. So I think you have an inherently difficult thing to communicate.

That poll is from 2015. And we also found that 50 percent of consumers thought that products have been tested to be effective by their manufacturer prior to marketing.

And so there's also a question about sort of the risk-benefit arrangement. We have products that are not shown to be effective or which there is scant evidence that they're effective. They pose, you know, a rare but significant risk of liver injury. Is it a

good thing to have a product like that on the marketplace where one of the consequences is just economic fraud that consumers are essentially throwing away their money on the product and then put -- being put at risk of a rare event of liver injury? We would say take something like that off the market.

MR. FRANKOS: Bill Frankos with Herbalife.

To get back to the question of prioritizing a list, I think there is a simple list of priorities. The first to me is let's take all of the 21 CFR direct food additives, the GRAS ingredients that are listed

there, the flavor ingredients, the -- let's see. There are also some other ingredients, processing aides, and things like that that are listed. Nobody has to submit those. Just take them and either through some kind of a -- either put them all on a list or reference the CFR so that everybody knows what they are.

There is a list of spices. The list of spices also would be included in the industry's list. So let's cross off the ones that are on the spice list for GRAS and get them off the industry list so we've now gotten all of those down.

There's a list of GRAS ingredients. There's a published list in 21 CFR. There's a self -- I mean, there's a no-objection list of GRAS ingredients. Go through that. Put it into the list.

That leaves you now the industry list minus any of the ones that are crossing over. Now let's take the industry list and, through a group, before any data is submitted, get the crazy outliers off. I mean, there is acetaminophen in there. There are -- there is aspirin. There's stuff that just shouldn't be in

there. Let's get rid of that.

And now we're down to something where probably 50 percent of the industry list everybody in the room will agree with very little data. I mean, I'm sure that we can find very simple references in cookbooks, magazines, whatever.

And then we have the more difficult ones. Now industry is going to have to really work to get those in.

But I do think we can start this process very quickly. We all agree how to do it. So that's my suggestion.

DR. SCARMO: Can I comment on that?

DR. WELCH: Please do.

DR. SCARMO: So I don't think -- I think there's three issues with using the GRAS listings. They're not insurmountable, but they require some thinking through. One is that, obviously, there's three pots. There's the GRAS-listed ingredients that FDA created in a list. There's GRAS notifications, and then there's self-affirmations by companies. And those self-affirmations are not public unless they were later

submitted to FDA and they're in the notifications bucket.

So the -- so you don't have any public record of the third category, so I would exclude those, a GRAS self-affirmation, which shouldn't be usable for this process. You don't know the assumptions on which the risk assessment was made, essentially.

Second, GRAS -- even the GRAS listed and the notifications include an embedded consideration of conditions of use. Those may or may not apply to the dietary supplement. And an example of that outside of this context is that my understanding is that some of

the companies in the e-cigarette and vaping world are using GRAS notifications on flavors as the regulatory authority for using those things when they're inhaled. But the route of ingestion is very different when you eat something versus when you're breathing it into your lungs. And so you have this sort of problem where a particular condition of use is not a blank check. You know, it has to be sensitive to how you intend to use the product.

And third, the point that was made this morning is that the assumptions in the risk assessment on the GRAS food side are exposures that are then the uses in -- for that ingredient in food, not including dietary supplement uses. So depending on how sensitive the overall exposure analysis is to the risk, if there's some problems there, then you would have to make sure that you're within the four corners of the exposure under current conditions of use for the food ingredient as well.

The -- I think there's a one -- fourth problem, which is that there's some dead letter in the way that the Agency has evaluated the GRAS safety

standard. There's some -- GRAS notifications and self-affirmations under the regulation are supposed to include consideration of chemically similar and pharmacologically similar ingredients that are already approved and then used in food. They usually exclude that. That is being litigated right now in Federal Court in our challenge to the final rulemaking on GRAS as one of the problems with the way that the GRAS loophole allows for a lack of attention to the

regulatory standard on safety.

So I think, you know, it sounds plausible as a starting point, but you really have to understand the flaws from a safety analysis perspective that are in the GRAS program.

MR. FRANKOS: Yes. I want to make sure I separate safety assessment from the regulatory listing. There are two processes. I completely agree that you have to consider all -- everything you've said from a safety standpoint, but that burden is on the manufacturer of that product. So they have to look at the GRAS review, see what the acceptable daily intake was in that document and then look at the margin of

safety between how they're using the product versus what was anticipated in the GRAS notification.

All of that, I think there has to be a whole another meeting to discuss how to use the data to do your own safety review. But the process of listing I think can be started right now. We've got some very easy things. And then we start down and get to the more difficult ones over time.

DR. WELCH: Thank you.

We actually have a couple webcast questions. So I'm going to turn it over to Sibyl Swift to read the questions.

MS. SWIFT: The first one is, "Recognizing that this would require funding, has what EPA done with ToxCast prioritized chemicals for in vivo safety testing by using in vitro screens and computational models been considered at all, or could it be? This approach looks for signals of toxicity as a starting point. Perhaps the ingredients of most concern could be screened and then tested."

DR. FABRICANT: Is there a wrong buzzer? This is about a pre-DSHEA list and the Agency establishing

that. I think these folks on the -- you know, I know the safety talk has been -- it's certainly scandalous and always delicious. But I think that it's getting back to that's the point, is why are we here.

The Agency is trying to move further on NDI enforcement, which I applaud, and they have tough jobs. And so part of that is getting some closure here on what a pre-DSHEA list is that will help, I think,

everyone prioritize. So they're benefitting, and the Agency's benefitting by not establishing a safe harbor. But let's call it a tranquil harbor. I think there's a town in Maine that's called that, right? Tranquil Harbor?

So that's really the point here. All this computational EPA program nonsense is not relatable here. There is a date in statute that says if it's on the market. And pre-19- -- October 15th, pre-1994, it gets around that adulteration clause. It's a technical adulteration clause. And that's really where I think - - and I'm not going to put words in any of your mouths from the Agency, but I think that's the issue that's on the table here, not setting up a brand new, you know,

super regulatory fire truck while this is a fire that could be put out with a garden hose.

DR. WELCH: Go ahead and go to the next one.

MS. SWIFT: "Has the FDA considered NHANES data from 1988 to 1994 or the President's Commission on Dietary Supplements Report in 1997 for establishing pre-1994 dietary ingredients as 'authoritative?'"

DR. WELCH: So since that was apparently directed at FDA, I will just say that I think there's a lot of sources of evidence that are out there. Our first panel certainly brought forward some more creative ways to think about it. But I think it's important as we move forward on this process to be transparent with whatever we do consider being appropriate standards of evidence moving forward.

So I think comments like these are important to us because we can then note them down and, as we move forward, make sure we're clear as to what we consider authoritative all on its own or, you know, in conjunction with other pieces of evidence. So thank you to that.

But if anyone else on the panel actually would

like to comment, you can certainly go ahead.

DR. FABRICANT: Is NHANES independent and verifiable?

DR. WELCH: I --

DR. FABRICANT: You have -- the labels would have to be into (ph) things like that. So that would be -- it would be the same standard, right?

DR. WELCH: Duffy?

MR. MACKAY: I'm just curious. On the consumer group side, absence of safety evaluation, the idea that a magazine ad might not tell us the plant part, how comfortable are you with experts, independent experts, saying yeah, everyone uses chamomile flower; we've know that for hundreds of years; it's not the root; it's not the stem? Are you guys going to feel well, wait, that's not good enough evidence, or is that something you're willing to meet halfway on?

DR. SCARMO: I thought the response on that this morning from FDA was quite sensible, that you look at the whole body of evidence. I'm usually, as a consumer advocate, a little bit wary of multi-factor weighing tests because there is so much room for

discretion.

On the other hand, I understand we're constructing a record that may or may not be complete. I think, you know, you -- if you were to -- if FDA embarks on this path, they would need to develop a set of criteria for what the evidence would be and what it

looks like in toto and when it's convincing or not convincing and have a set of practices around that and just kind of regularize what is the body of evidence.

I do think, however, that the consequence is not as drastic of not having an ingredient grandfathered. It -- though there may be some cost, there is probably a safe history of use for NDI purposes. And so it's not the wholly weighty categorization that it is sometimes painted to be.

I also just -- I'll just say this. I -- the reason why the safety conversation comes up is because if the safe -- if safety is set aside, I agree with Pew that then the criteria need to be more stringent and we should just have a much more conservative classification system for what gets grandfathered in because those substances will lack any kind of safety

review.

So that's why -- I mean, you know, structurally, that's why I'm saying if you address the issue of safety at the forefront and we can all get together on that -- it's not a Kumbaya moment; it's in everyone's best interests -- then it's much less

important what criteria are used to keep or -- you know, on or exclude from an ingredient on the pre-'94 list.

MR. MACKAY: And that makes sense. But then there's also the issue that if we are presenting a very limited and rigorous sort of it's got to have a description, it's got to talk about the manufacturing method for it to be on this list, then industry might just say we'll just hold all this evidence and we'll just hold it. And we'll be exactly where we are today. And that's one outcome of this meeting.

DR. SCARMO: Agreed. But without an assurance that there is a public safety function that's being developed that comes out of this kind of investment of FDA resources -- and, you know, the kind of counsel process, I noticed the consumer representatives were

non-voting. Regardless, there's, like, four of us. And the kind of time involved with participating from a consumer perspective in this process involves a significant resource investment on our side either, and we don't sit where the industry sits and have a benefit

that's going to be industry-wide.

So agreed. But you know, we're in it for what -- for public health reasons.

DR. WELCH: All right. Thank you all.

I didn't actually expect it to, but we went ahead and filled up the extra time. So we're at our typical break time. You have about 20 minutes for break. We'll reconvene, and we'll start off with our afternoon public comments session at 3:15.

Again, if you want to give public comments, please check in with Juanita Yates at the registration desk.

Thank you.

(Break.)

DR. WELCH: All right. We will get started on our afternoon comments session.

Just a reminder for our commenters, you can

step up to the microphone. Assuming it's the same as before, you'll probably have to turn it on. So we'll -- we will not count that against your five minutes.

Please speak your name and affiliation when you start your comments, and you have five minutes.

I will start with Ashish Talati.

MR. TALATI: Good afternoon. Thank you so much. I just want to thank the leadership at the FDA for arranging this public comment. I think it's an important step.

I support the development of an ODI list and believe it is an important step for the industry, FDA, and consumers. However, it is important to clearly define the scope or understand the scope. FDA is proposing to create a list of ingredients marketed before October 15, 1994, and not proposing to conduct a safety review of those ingredients. If an ingredient is on the list, it does not automatically mean that it is safe and no action can be taken by the Agency.

In 1994, DSHEA created the regulatory framework for dietary supplements in the U.S. Its purpose was to provide consumers access to dietary

supplements and also give FDA the necessary tools to take actions against supplements that are adulterated or misbranded.

The framework -- the regulatory framework for

supplements is primarily a post-market program, as is the case for foods in general. Should safety problems arise after marketing, the adulterations provisions of the statute come into play.

So under DSHEA, the dietary supplement is adulterated if, among other things, it or any of its ingredients presents a significant or unreasonable risk of illness or injury when used as directed on the label or under normal conditions of use if there are no directions. FDA certainly bears the burden of proof to show that a product or ingredient presents such a risk.

I believe we should proceed cautiously and ensure that any process and list created reflects a flexible standard that is not too bulky so as to be prohibitive yet has enough substance so that it is meaningful.

Earlier, we had -- we heard from Chuck, who had a concern that consumers might interpret the list

as a safety list, that the ingredients on that list are considered safe. That is a valid concern. At the same time, it is possible that regulators at various FDA districts, state, county levels, and customs officials

may take the list as an all-inclusive list. I think a strong disclaimer clarifying that the list is not a safety list or an all-inclusive list can minimize the impact.

A fundamental question, though, is whether or not it's even feasible to develop a list 23 years after DSHEA. In my opinion, the answer is yes if we start with the list that is already in place and that has been informally used for nearly 20 years. That is the list of ingredients documented by the various trade associations. That would be a great start, and the list can certainly be further improved.

The ODI list and the procedures for creating and adapting it should be created with an eye towards the future and ensure that sufficient flexibility allows for the continued success of an official ODI list.

Thank you.

DR. WELCH: Thank you.

Next we have Alissa Jijon from USP.

MS. JIJON: Yes, good afternoon. Alissa

Jijon, USP.

So on behalf of USP, I would like to thank the Agency for giving us time to share our thoughts on the process to develop an FDA pre-DSHEA list of ingredients.

Earlier today, my colleague presented USP's remarks on criteria that could be considered for included ingredients. We underscore USP's belief that an authoritative list could be useful for industry and for the advancement of public health if sourced appropriately.

USP is an independent scientific nonprofit public health organization dedicated to improving health through the development of public standards for medicines, foods, and dietary supplements. We are governed by the USP Convention, comprising over 450 academic institutions, healthcare practitioner organizations, industry groups, and governmental organizations.

For nearly 200 years, USP has been building foundations essential for a system aimed at providing quality products to consumers and ensuring

manufacturers have access to reliable information that ensures their products meet the standard of quality that regulators and consumers expect and that industry itself strives to provide.

USP develops public quality standards through an open, transparent process with participation and input from stakeholders, including academic, industry, and government representatives. Particularly relevant to the topic today, USP has a longstanding program of developing identity standards and specifications for dietary ingredients used in dietary supplements.

Because USP has significant experience with administering a collaborative process to set public quality standards, we believe that many of the same principles and operational learnings could prove useful in the creation of an authoritative list. To the extent that FDA and industry would find it beneficial to engage with USP to share learnings about the process, and perhaps even to discuss ways in which

information that USP may already have reviewed, could be brought to bear in establishing such an

authoritative list. USP stands ready to facilitate such dialogue.

USP is committed to its confidentiality policy and would of course consult with industry stakeholders regarding any proposal that involves information sharing.

Consistent with our shared public health mission, USP is ready to engage with FDA and industry and seeks to do this in a way that will have the greatest impact.

Thank you for the opportunity to comment. We look forward to exploring ways to expand our partnership with ODSP and to serve as a resource in new ways as FDA undertakes the development of this important resource.

DR. WELCH: Thank you.

George Paraskevakos.

MR. PARASKEVAKOS: Good afternoon. George Paraskevakos, International Probiotics Association.

Again, we want to thank the FDA for the

opportunity to be present and comment at this very important date both in the morning and the afternoon.

As I discussed this morning, probiotics are a unique category of dietary ingredients with a very long history of safe use both in dietary supplements and in the food supply. Now, in its (ph) comments to the NDI draft guidance, we provided a list of probiotic species that we believe should form the basis for the grandfathered probiotic ingredients.

Whatever process FDA decides to follow to create the list of ingredients that do not need to be subject of notification, FDA should carefully balance the competing needs of openness and confidentiality. The creation of the list should generally be an open process to ensure public confidence in the safety of dietary supplements transparency, which is very important to the public.

However, there may be information that a stakeholder may want to provide that is a proprietary trade secret, manufacturing process, or otherwise commercially confidential. We believe that the FDA should adopt procedures to ensure such information,

when appropriate, is afforded protection from public

disclosure. As an example, the same approach of master files that was presented in the draft guidance for notification can be adopted for grandfathering as well.

This was additional. What about GRAS? We heard a lot about stuff (ph) from GRAS today -- this afternoon, specifically -- what -- about it not being considered. But I would like to remind everyone that GRAS notifications to FDA is a voluntary decision linked to a specific intended use outside the common use for probiotics. Let us not forget the law recognizes self-affirmed GRAS at the same level as a GRAS notification to FDA. In the law, DSHEA has placed the industry as responsible to ensure safety at an international level from an IPA perspective, particularly in probiotics where they are known to be safe at a wide range of doses used by healthy populations.

Finally, while FDA should consider information from all stakeholders, we believe, perhaps selfishly, industry trade associations can have a very meaningful role in the process, a notably IPA for priobiotics, IP

representing large numbers of probiotic industry

stakeholders for the ability to efficiently gather relevant and accurate information for FDA, which can help expedite the creation of these vitally needed lists. Indeed, it is IPA's mission to promote the safe and efficacious use of probiotics globally, and this can be a steppingstone in ensuring probiotics are accurately marketed in the U.S.

Again, on behalf of the International Probiotics Association, I want to thank you very much for the opportunity to present these comments today. And we look forward to continuing to work with FDA and the rest of the dietary supplement industry as the process moves forward.

Thank you.

DR. WELCH: Thank you.

And finally Susan Brienza.

MS. BRIENZA: I had to lower it.

Okay. Cara, thank you and FDA for allowing me to have another five minutes.

This is a rather quirky point that I will make, a point and some questions having to do with

synthetic ingredients in both dietary supplements and in foods.

So again, it's a bit broader, but I think it's all relevant, considering that I agree with about, oh, one-half to two-thirds of this -- of all the speakers today who mentioned that the ODI list, the pre-DSHEA list, does have a presumption of safety. I disagree with the safe harbor phrase -- but presumption of safety. So safety and the list are definitely interrelated.

My information is that there were certainly before 1994, maybe decades before 1994, synthetic vitamins and minerals on the market. And in -- some examples might be some forms of calcium, vitamin C, and taurine as an amino acid -- all synthetic.

What strikes me as strange then, or curious, is that in the 2011 draft guidance, the FDA made the comment that synthetic in dietary ingredients would -- well, synthetic ingredients would be considered not dietary ingredients. And a contrast or -- I'm not sure whether it's a contrast or an analogy or a comparison to think about -- is a novel meat that maybe many of

you have heard about -- it's been in the news quite a bit lately -- which is a synthetic -- well, it's a genetically engineered yeast added to hamburger, well -- or rather, something called the Impossible Burger. It was -- it's an innovative product from a company called Impossible Foods. And this genetically engineered yeast from soy, which has the acronym SLH, has been added such that this veggie burger bleeds and tastes and smells, even fries up like a regular hamburger.

It most recently has been in the news September 20th, internet article in the Wired Magazine. And the problem is that it is a completely novel food. It did not get FDA's blessing. The company filed a GRAS notification either 2014 or 2015, which is very, very odd, and it raises many of the issues we've been talking about today, including food additives.

So the GRAS notice actually, at one point, calls this new ingredient a flavor and, in other points, calls it a component. It seems to me if it's a flavor, then it should have gone through the food additive process, which is more rigorous.

So the -- needless to say, the company did not get a no-objection letter or no-question letter from its GRAS filing. Instead, it got a letter that was filled with objections and filled with questions.

So meanwhile, the New York Times filed a Freedom of Information Act request -- and the New York Times loves filing FOIA requests usually in the more political realm, but everything is political -- and asking for internal Agency documents. And that yielded an internal memo that Agency officials wrote to the company Impossible Foods before a phone call. And I quote, "FDA believes the arguments presented individually and collectively do not establish the safety of soy" -- big long word -- "SLH for consumption, nor do they point to a general recognition of safety."

So it just seems rather curious that we've got this synthetic meat on the market. Of course, the CEO and the New York Times pointed out that there was no requirement, there was no pre-market filing required. But here is this veggie burger on the market, very popular with shish (ph) restaurants from New York to

Los Angeles and with the -- either a synthetic component or flavor and yet synthetic dietary ingredients, apparently.

But maybe we should hear from this expert Agency panel what the connection is going back to dietary ingredients between old and new synthetic dietary ingredients. Maybe you can comment on that.

And I'll just end there.

DR. WELCH: Thank you.

MR. TAVE: We appreciate the comment. And personally, I -- once you started talking about impossible meat, I thought you were going to go down a path of saying that we had an impossible task ahead of us. So thank you for not doing that.

(Laughter.)

MR. TAVE: Synthetics are a complicated nuanced issue, and I don't know that we can do them justice here. And that's, you know, candidly, not the reason that we gathered here today. I mean, I think it has relevance to the questions we've discussed in terms of how to compile a pre-DSHEA lists. But I don't know that we can really do them justice in this Q&A comment

period right now.

I know you promised earlier that you would submit written comments on the docket, and I encourage you to do so. And it sounds like there's a lot for all of us to think about. But that's going to be a polite non-answer.

DR. WELCH: And that actually concludes our afternoon comment session. So at that point, I actually turn the mic over to Steve for some final comments.

MR. TAVE: Okay. Is my mic on?

DR. WELCH: It should be, yes.

MR. TAVE: Can people in the back hear me? Can people on the -- no, not so much. Okay.

Can people in the back hear me now? All right.

So we have the room until 5:00. So Cara has informed me that I need to speak for an hour and 28 minutes.

(Laughter.)

MR. TAVE: So I'm going to apologize.

No, I don't know that I have anything really

useful to add to what's been said today. You know, I think we've accomplished initially what we set out to do, which was to get people together, again, both in person and virtually. And I appreciate the fact that folks on the webcast contributed questions because I know it's hard to feel connected that way.

But we had people in a big room, in a virtual room, talking about important issues and talking openly. And I think it's fair to say, especially after our afternoon panel, nobody held anything back. And that's the way we have to do it if we're going to make progress on this issue.

You know, nobody said these are easy questions. They would have been answered a long time ago if they were. But we're not going to avoid them just because of that.

You know, I want to start quickly with -- just with some thank you's. There were a lot of FDA staff who none of you met or heard of or will ever see who spent a lot of time and effort making sure that this event went off flawlessly. And notwithstanding one or two, you know, audio glitches, which are inevitable, I

think everything went really well. And it's a credit to them. I'm not going to name names just because I don't want to -- this isn't an Oscar speech, although someday I will win one.

(Laughter.)

MR. TAVE: But you know, I just -- I think I want to make a point of thanking all the people at FDA who spent a lot of time working to make sure that this happened. I want to thank Cara and Bob especially for standing in the line of fire and helping keep things going.

And I want to thank all of our panelists who came from near and far and put a lot of thought and time into being here and, you know, I think really approached this with the right attitude, which is let's talk about these issues, let's ask the right questions, and let's try to find common ground so that we can all move forward together in a way that benefits everybody.

And then finally, I want to thank all of our participants for -- you know, for being here. This needs to be a participatory process. We need to have engagement. We've got that. I think this is a model

for how we can do things in the future. And to me, that's just really gratifying.

You know, we said it before. I'll repeat it again. If you didn't speak today, if you spoke today and you have additional thoughts, if you know somebody who has additional thoughts and couldn't be here, we have a docket open on regulations.gov. We are accepting comments through December 4th, 2017. There is no five-minute limit on comments. Whatever you want to tell us, you know, I promise you we read them.

And I would encourage you by the same token to read the comments that other people submit, too, because it's very easy to look at something, especially something as complicate as this, from the perspective in which you go about your business every day. Whether it's, you know, as a manufacturer or a distributor or trade association or consumer advocacy group or a regulator, we all tend to approach the world through our normal lens. And so it's a very good use of time, I think, to step back and try to take an open mind into reading the comments that others submit.

And I think especially when -- you know, I

know when I do that, that's when I start to notice the kinds of things like common ground. I notice consumer advocates and trade associations saying the same thing in different words. And that's when I see that there's opportunity for us to really work together and make progress.

The meeting was transcribed. I tried to speak slowly so that hopefully the transcription will capture everything that I've said. I know others did a better job than I did, but we'll do the best we can.

I don't have a date for you in terms of when the transcription will be available, but when it is available, it will be on our website on the Meeting Notice page. And if you're not sure, you know, just feel free to check there. If a lot of time has passed and you haven't seen it, feel free to, you know, check in with us and ask us what's going on.

You know, with that said, I think -- you know, the work lies ahead of us. So we accomplished a lot today. I'm really looking forward to seeing the comments that we receive. I think there is an opportunity to move forward here.

And again, you know, just as we have been transparent leading up to today -- we had a transparent process today -- the process will continue to be transparent. So as we figure out what the next steps are, it will be inclusive. I anticipate that we will be reaching out to all of you. We will be taking feedback from all of you. And we will let you know what's going to happen next so there won't be surprises. That's how we do business, and that's how we'll continue to do business.

So I think on that note I will say thank you and adjourn one final time. Thank you all very much.

(Applause.)

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I, Natalia Thomas, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

Natalia Thomas

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10/16/2017

DATE Karynn Willman