DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

DIETARY SUPPLEMENTS PUBLIC MEETING

PRE-MARKET NOTIFICATION PROGRAM FOR

NEW DIETARY INGREDIENTS

Monday, November 15, 2004

9:04 a.m.

Harvey W. Wiley Building
5100 Paint Branch Parkway
College Park, Maryland 20740

C O N T E N T S

P R O C E E D I N G S

DR. SCHNEEMAN: Good morning. If I could get everyone to please take their seats, I think we'd like to get started. We know we have a full program, and we want to give as much time as possible for our presenters and commenters so that FDA has an opportunity to hear what it is you have to say.

My name is Barbara Schneeman. I'm the Director of the Office of Nutritional Products, Labeling and Dietary Supplements. That is one of the offices in the Center for Food Safety and Applied Nutrition, and we are definitely pleased to welcome you out here to College Park for this meeting on new dietary ingredients.

As the meeting has been set up, FDA is here to listen. We'll be gathering comments and analyzing those over the next few weeks, and we know that many of you also plan to submit written comments, and we're looking forward to those written comments as well.

Without further, I want to introduce

someone from the Center Director's office, who is also relatively new to our office, Mike Landa, who has been with FDA for quite a number of years but has just recently taken the position of Deputy Director for Regulatory Affairs in the Center for Food Safety and Applied Nutrition. And so I'd like to ask Mike to make a few opening comments.

Thank you.

MR. LANDA: Thank you. Thanks, Barbara.

First, let me welcome everyone. Thank you for coming today to share your views with us. We hope and expect this meeting will be instructive for us, but let me add we don't anticipate that it will be interactive; that is, what we expect it to be is in what's called listening mode. The "we," as you will learn later this morning, will consist of sort of a listening panel, including myself, Dr. Schneeman, and several others.

With respect to the NDI notice itself, let me just say we know there have been requests for an extension of the comment period. We know it's a long-ish notice, at least in terms of the number of

questions we've asked and areas we've asked for comment on. We will be making a decision shortly on the request for extension, and we'll let you know once the decision has been made.

The purpose of the meeting today, as Barbara mentioned, is for us to hear presentations on the Pre-Market Notification Program for NDIs. We're soliciting comments from all interested persons, from consumers, from industry, from others, concerning the content and requirements, format requirements for notifications made under the statute and in the agency's regulations. The Federal Register notice announcing this meeting sets out the questions we're most interested in hearing your comments on in great detail. Copies of the notice, by the way, are on the registration table outside the auditorium.

We'll consider the presentations we hear today and any comments we get to the docket in deciding what our next step or steps will be. That makes it, of course, extremely important that you make sure to get your comments to the

docket--closer? Okay. Is that better? Is that worse?

[Laughter.]

MR. LANDA: To briefly recap what I was saying, but apparently no one heard, a couple of points. One, we're going to be--"we" meaning the agency folks here--we'll be in listening mode today. We may ask clarifying questions of the speakers, but we are here primarily to listen. In that sense, we don't expect the meeting to be interactive.

The second point I made was that we know we have requests for extension of the comment period in-house. The agency has not yet decided whether to grant that request. We'll let you know as soon as a decision is made.

The third point was that there are copies of the notice available at the registration desk. For those of you who don't have a copy with you, perhaps during a break you can grab one out there. We will, of course, take into accounts presentations we hear today and any comments we received

on the docket in deciding what the next step or steps will be in relation to new dietary ingredient notifications. It makes it all the more important that people make sure to get comments to the docket. If they are sent elsewhere in the agency, they may or may not work themselves to the docket, so please send them there.

In just a minute, I'll turn the program over to Dr. Susan Walker, who is in what we call ONPLDS, with affection. Susan is Director of the Division of Dietary Supplement Programs in ONPLDS. But just before I turn the meeting over to her, I'd like to publicly acknowledge the work of the division in making this meeting happen. I think ONPLDS certainly in general but the division in particular really drove this meeting. I'd also like to acknowledge the work of a couple of lawyers in the Office of Chief Counsel who do foods work for us: Irene Chen and Louisa Nickerson.

I think with that I'll just turn the meeting over to Susan.

DR. WALKER: Thank you, Mike, and thank

you all very much for coming. We're truly glad that you're all here today, and we've been looking forward to this meeting. Let me see if I can actually remember how to do this audiovisual piece.

Well, maybe we need an AV person. Oh, there we go.

What I'm going to do is very briefly just introduce the members of our panel today, and then I'll give a very short background about how we got to where we are today and why we're having this meeting. And I'd actually like these folks to stand up because they've done so much work in getting us to this point. As Mike said, the division is within the Office of Nutritional Products, Labeling and Dietary Supplements. Our Office Director, Dr. Barbara Schneeman, has been extremely supportive and completely behind our efforts, and we really thank her for that.

There are three branches in the division, and we've got Dr. Bob Moore, Compliance. I think you're all pretty familiar with Bob. And then Dr. Linda Pellicore, Regulations and Review, and Linda

is really the person you have to get through if you're going to get through the NDI program. So I'd like to introduce Linda especially. And then Dr. Jason Woo, who's our Clinical Team Leader. Also we have Dr. Bill Frankos, Special Assistant for Science Review, and Bill has recently come to the agency, about a year ago, and he will be moderating our session. And we'll talk more about that in a bit.

Now, I'd like to acknowledge Dr. Kelly Williams-Randolph, who was very instrumental in setting up our meeting and making sure this happened today.

Other members of our panel I'd like to introduce: Mike Landa, who you just met; Barbara Schneeman; and then Dr. Jeanne Rader, who is Division Director for the Research and Applied Technology Division; and then Dr. Alan Rulis, who I'm sure you all know, who is currently the Senior Advisor for Special Projects.

Now, in our new dietary ingredient program, basically we have a variety of ingredients

that are notified to us, but this is our recent history, which is predominantly botanicals and botanically derived substances. So as we move forward, it's important to remember this is a very large part of what we're receiving in our notification process, and this probably reflects the fact that the complexity of this area really drives some of the complexity of this entire process. And we really have to be aware of these substances as we move forward.

Now, in looking at our notification program over the past few years, we've noticed that there have been many more notifications and that FDA has been objecting to a larger percentage of these notifications. And looking at these, we wanted to determine why is this happening, and we've identified several factors. These are not all the factors, but basically they're issues about describing the new dietary ingredient. We need to know what it is, and that actually sounds like a very simple question, but it's a very complex issue, particularly with botanicals.

We need to understand how and why it's eligible to be a new dietary ingredient. We need to understand what's an adequate amount of safety information for the statutory bar in the law which is establishing reasonable expectation of safety. And then we've noticed there's other necessary information that's frequently not there, just general identifying information.

All of these are in dockets and they're publicly available. Anybody can go in there, can see all the notifications and see all the responses from FDA.

So this is the history in the past ten years. The notifications, obviously we're getting more and more, and there's a higher and higher objection rate. Some folks have pointed out that it's likely that there are notifications in here that may not be new dietary ingredients.

So what's really the key to the issue today? It can be summarized in two slides that I'm going to put up here. And this is the discussion we really need to have over the next few weeks and

months.

The first piece is when is a substance an eligible dietary ingredient under the statute, under 201(ff), which has three sections, so it's going to be very important to look at the basic eligibility of a substance to be a dietary ingredient.

So once this gate has been opened and gone through, the next question is: Was the dietary ingredient marketed in the U.S. prior to October 15, 1994? Because this is the actual statutory definition of a new dietary ingredient in DSHEA, and there are really only two answers. It's yes or no. If it was not, then that substance is a new dietary ingredient. If it was, then it's not a new dietary ingredient.

The ramifications of this are large because if you're a new dietary ingredient, not all new dietary ingredients have to notify. A subset of new dietary ingredients has to notify. So the next question that's going to be very important is: What is the group of substances that does not have

to notify? The third important question is: For those that do have to notify, how do we fulfill both parts of the notification requirement such that we don't reach a status where that product is adulterated? Because if there exists a history of use or other evidence of safety, basically establishing this reasonable expectation of safety and FDA has been notified, then that's a lawfully marketed product. If either of these is not met, that product on its face is adulterated.

So the scope of this meeting clearly is to discuss and receive comments on the status of substances as new dietary ingredients; questions about the chemical identity of a new dietary ingredient; when and under what circumstances does an ingredient that may have been available prior to 1994, is there a point at which it becomes new because it's been transformed, there's been a chemical alteration, there's been a different extraction process? We've really got to develop an understanding of what "marketed prior to 1994" really means in terms of safety because we really

have to bring this all back to safety. The intent of that section of DSHEA I would imagine--this is me speaking personally, but it's the safety gatekeeper. And if we look at 201(ff), the identity section, and we look at 413, the new dietary ingredients section, those two pieces taken together are a very powerful safety tool.

So we need to look at the standard for establishing a reasonable expectation of safety, what type of information should be provided. We need to look at some of the definitions for new dietary ingredients. And when we look at all this, as we said in the notice, we'll determine if there's a need for guidance or amending the regulations.

So in order to proceed with this actually complicated task, we're having this public meeting today to get started. We'll receive the comments to the docket. We'll look at those and then determine next steps. And for today's meeting, I'd like to actually introduce Dr. Bill Frankos, who's going to serve as our moderator. Bill is a Special

Assistant for Science Review within the division, and he received his Ph.D. in pharmacology and toxicology from the University of Maryland Pharmacy School. He has over 30 years' experience in the toxicological and pharmacological evaluation of data used to assess the safety of nutritional supplements, foods and food additives, drugs, medical devices, cosmetics, pesticides, and environmental and occupational exposures. And prior to joining FDA, Bill was a principal in Environ Corporation and Associate Director, Life Sciences Division, at Clement Associates.

Previous to joining the private sector, he was with us in FDA in the Office of the Commissioner as a senior toxicologist, and previous to that at the Office of Food Additive Safety, I believe. So Bill obviously has a lot of experience. He's going to be very helpful in moving this process along, and I'd like to introduce him today as moderator for our session. Thank you.

DR. FRANKOS: Thank you. I'm quite

excited at the prospect of starting to deal with some of the issues that have been presented in the Federal Register notice. The list of questions that you've all seen is a list that was developed after the whole division went back and carefully looked at the process of NDI review and the problems that occurred. We felt that there were so many issues that we needed to deal with that we needed to open this up to the public, get input, and start a process that is certainly going to take several months, and we feel that it needs to be a public process. This meeting is the first of what I think will be other meetings that may have to occur in order to bring this together.

The panel that Susan introduced is here to really listen, but if clarification is needed, they certainly will ask questions. The ground rules for the questioning is that we will only be asking questions that are clarifying questions.

Now, if any members of the audience have a specific question, a clarifying question they would like to ask, if you come to one of these mikes here

and introduce yourselves, we can recognize you. But I would like those questions to be clarifying questions, not going into areas that have not been addressed by the speakers.

I'd like to introduce Kelly Williams-Randolph. She's been doing a great job coordinating this notice, and she wants to go through a little bit of the housekeeping, and then after that we'll start with the speakers. Thank you.

DR. WILLIAMS-RANDOLPH: Thanks, Bill. Good morning. I'd like to start off with a welcome to the members of the FDA panel, the folks from industry, consumers, health professionals, and everybody that's here in the audience. I'd like to go over some meeting logistics with you, starting with today's agenda.

This morning we will spend with introductory remarks and one speaker group session. There will be a morning break at 10:30 a.m. for 15 minutes, and then another speaker group session. After the second speaker group session, we will

have another 15-minute break, scheduled for 11:45 a.m., and then have our final speaker group session. Bill Frankos will then give closing remarks.

In addition, I would also like to go over the speaker group session presentation time limits and time limits for clarification questions from FDA panel and audience members. Each speaker will have 15 minutes to present, with a five-minute follow-up period for clarification questions regarding the presentation. We will be using a color card timing formula for keeping speaker presentations on schedule. A green card will signal the speaker that they have five remaining minutes. A yellow card will indicate the speaker has one remaining minute. And the red card will indicate that the speaker should finish his or her sentence.

In closing, you can find bathrooms located midway between the front entrance of the building and the registration tables. Signs are also posted indicating the location of the restrooms, and on

the back of your agendas you'll find a floor plan.

Thank you, and I hope you will find today useful. Now I'll give the floor back to Bill.

DR. FRANKOS: Thank you.

Our first speaker will be Michael McGuffin, who is president of the American Herbal Products Association. Michael, can you come up?

MR. McGUFFIN: Thanks, Bill. How do I get to my presentation here?

[Pause.]

MR. McGUFFIN: Good morning. It's a pleasure to be here, and I appreciate the opportunity to address you all. I really appreciate the people from FDA inviting me.

I already tried to negotiate an extra five minutes from Bill, so I hope we can tolerate. I've got a pretty packed presentation here.

AHPA represents about 200 companies that sell herbal products, almost exclusively as dietary supplements, and my primary comments are going to be the impact of this rule on herbal products. AHPA will submit substantive comments to the

docket, and just for the record, we would really appreciate those extra 60 days. This is a knotty issue, as you all know, and anything you can do to give us the time extension will be appreciated.

I'm going to just move into this in the interest of trying to get through this in 15 or maybe 18 minutes, and I want to start with the definition if a dietary ingredient, specifically as that applies to botanicals, and I'm emphasizing here with these bold lines that there are really two different classes of botanical ingredients: the 321(ff)(1)(C), which is an herb or other botanical, it's an unprocessed herbal ingredient; and then (F) can be a concentrate, a metabolite, a constituent, an extract, or a combination of any of the above. And I think it's important to think of these separately. Although much of the information that's required for a new raw material herb or a new constituent or concentrate or extract are the same, there are some differences that I'm going to point out that I think are important to keep in mind.

I'll get back to this a little later, but I want to look, too, at just an overview of what's required in a new dietary ingredient notification. If you go to 21 CFR 190.6, that's where the reg is written, and I class five different pieces of information that are required there if you break down the various subparagraphs. And I don't need to say much about the first or the last. Almost everybody knows their name and address and remembers to sign it. But each of these other things needs some attention: the name of the ingredient, which with an herb must include the Latin name; a description of the supplement that contains the ingredient, including, of course, the level of use and conditions of use; and the big deal, the thing that we're really after, the evidence on which a reasonable expectation of safety is based.

I want to point out something that's not here. It does not specifically state in 190.6 that you need to identify the dietary ingredient. There's a requirement for a description of the

supplement. There is not a specified requirement for a description of the ingredient. I'm going to again come back to that later because it's something that we need to pay attention to.

A quick review. As of last week, there are 249 notices on the docket. Fifteen of these are for dietary supplements. They don't belong here. There should not be submissions for new dietary supplements. It's not required. It confuses the system. But where we end up was 194 unique dietary ingredient submissions. There are also a number of duplicates, a few withdrawn, but this 249 comes down to 194. And of those 194, I get slightly different numbers than Susan did, I think. I count 83 non-herbal dietary ingredients and 111 herbal. And then the herbal breakdown into that subparagraph (C), the unprocessed herbs, there are 33 of those; herbal constituents, which is one of the words used in subparagraph (F), there are 26 of those, and then there are 52 herbal extracts, or concentrates or oils or things that aren't just the herb but neither are they constituents.

I don't do as good a job of drawing these pretty pictures as Susan also, but here's just a pie graph of--again, you can see over half of these are botanicals, and they're kind of split between these three subclasses of botanicals.

Then here's the outcome, here's what happens if you look at these different subclasses with regard to the number of notifications, the number that are filed. And "filed" is as close as FDA gets to "accepted." It means they didn't object to. It means they didn't send you back a letter with the word "adulterated" in the letter. So of the non-herbal ingredients, you can see 63 percent of those are being filed; 65 percent of the herbal constituents; but the unprocessed herbs, only one out of five is making it through the process. And the extracts, it's a little greater than one out of three. So there's clearly the herbal constituents, things like sesamin from sesame seed, vinpocetine, those are getting through; whereas, the herbs themselves tend not to.

Now, my interest is herbs, so I'm, of

course, concerned about what is it that's making it so that the herbs don't get through, and so I've looked at why FDA refuses to file so many of these.

Some of the issues are very specific to herbs: plant part not named. Again, though, 190.6 does not specify tell us the part of the plant. One of the suggestions that AHPA will make, 190.6 should specify name the part of the plant if your ingredient is a botanical. It's obvious. You don't have an ingredient that's a botanical without also naming the part. But it's not stated. Some companies miss that, and we'd like to help them address that. This No. 247, that's a mushroom, and FDA said we don't know what part of the mushroom. So those were both objected to or rejected. There's confused nomenclature in the last one filed, this plum extract, where the filing company said we're not sure if it's Terminalia ferdinandiana or lapides. FDA said, well, if you don't know, then we don't know. It turns out those are two different names for the same plant. They should have called me and I could have helped them

with that. But, nonetheless, that kind of confusion gets an objection notice. Or in the case of freeze-dried kimchi--I love it. Somebody wants to sell us freeze-dried kimchi, but they didn't tell us that it was Brassica, so FDA said we don't know what to do with that.

Many of the other reasons that FDA objects to herbal filings, though, are the same that they object to the non-herbal filings, and Susan pointed out some of these. I've quoted from some specific notices. "It is unclear...whether the test substances used in the referenced studies are qualitatively or quantitatively similar to" to your new dietary ingredient. So somebody says I want my ganiderma product to come to market, and here's a whole lot of information about ganiderma extract, but they don't clarify that it's, in fact, their ganiderma extract. FDA says we don't have any information that's a basis for knowing that your ingredient is safe. I've seen that one over and over and over. And then as Susan also mentioned, inadequate information to clearly identify the

ingredient.

There have been other issues. Things have been rejected just because they're frank toxins, things like extract of oleander--thank you for rejecting that one--pokeweed lectins, illegal substances like GBL, and then sometimes because the described dietary supplement is in a form that doesn't fit the definition. My favorite one is an herbal eyepatch which FDA wisely chose to reject.

With regard to this second point here, though, the inadequate information presented to identify the ingredient, I want to repeat, 190.6 does not specifically state identify the ingredient. Again, it's an obvious recommendation that AHPA will make that 190.6 should, in fact, state that the identification of the ingredient must be included.

The next two slides are looking at the requirements set in 190.6 and breaking it down into the identity, the description of the supplement in which the product goes, and the evidence of safety. And I have two slides here. This one is for

subparagraph (C), which is herb or other botanical. And my position is that all you need to identify an herb is the name of the herb and the part. You don't need chemistry. You don't need anything that goes further than that because peppermint leaf is peppermint leaf if that's what I'm selling. Now, that's an old ingredient, but just to make the impression. Whereas, if it's anything in (F), if it's an extract, if it's a concentrate, clearly you need a lot more information, and all of these points are actually from a document that AHPA produced a couple of years ago, a guidance on manufacturing of extracts that I will leave a copy into the record here.

You have to disclose the solvents, the ratios, all other ingredients. You need to describe the process. Is it a liquid product or a solid product? And then these bracketed items--the markers, characterization, and purity--are often but not always relevant. It's a much more dense process once it moves from an unprocessed herb. Whereas the dietary supplement description, it's

not any different for the subclass (F), which are the extracts and concentrates, than it is for the raw herbs. And the only difference that I have on evidence is that the evidence of the herb would be history of use and other evidence, whereas the extract you can argue that the history of use of similar dietary ingredients, like the raw herb, has relevance.

I also want to point out that in the description I've made a pointed statement that there is not a requirement to identify the other dietary ingredients. Most companies want to say, "My new dietary ingredient is this ingredient, and the use is 50 milligrams in a dietary supplement." Most of those submissions have gone through. Most recently, FDA in one letter said, well, we don't know what the other ingredients are, so how would we know that the supplement is safe? We want to argue against FDA taking that any further.

Old versus new, again, the class (C) and the class (F) are different. With regard to just herbs--roots and leaves and seeds and things that

are just parts of plants--AHPA in 1995 sent out a call to industry to identify old herbal dietary ingredients. The next year we submitted a list of over 1,600 herbs to FDA, identified those as believed to be in commerce prior to the date, and in 2000 we published "Herbs of Commerce," 2nd edition. We added about 400 other plants in the meantime, numerous Chinese plants, numerous Ayurvedic plants, fungi, algaes. It's a very thorough document.

We also disclaimed it in two different ways. The first disclaimer says just because it's here doesn't mean it was marketed prior to the date. And the second one says just because it's not doesn't mean it wasn't.

Our thinking here was we accepted submissions honorably. We believed that they were submitted honorably. But we didn't go out and double-check or prove that chamomile had, in fact, been marketed prior to the date. Nonetheless, it is AHPA's position that even though "Herbs of Commerce" may not be authoritative, this disclaimer

should not be read as a reason to abandon our text. It should not be seen as assuming that there is no relationship whatsoever between the listing of an herb in "Herbs of Commerce" and its marketing prior to the date. That is what we asked people to tell us. We think it has relevance. We think it does create a presumption of presence in the marketplace.

If the agency wants to take it further and get to something like an authoritative reference, AHPA is uniquely positioned. We would be happy to discuss being actively involved in a process or being contracted for a process to do an old dietary ingredient substantiation for botanicals. We know a lot about this issue.

Then with regard to old herb extracts--and by extracts I mean everything in (F)--we didn't go out and say tell us all of the extracts. We didn't ask that kind of thing a decade ago. But there are standard accepted extract forms: decoctions, liquid extracts, dry extracts, tinctures. There are long accepted food-grade solvents, and I've

listed numerous of those here; established extraction processes. And there is a reason to think that all of the common herbs were manufactured by all of these common processes with all of these common solvents. And if I've got a 32-percent ethanol chamomile, I shouldn't have to prove that a 32-percent ethanolic extract of chamomile was marketed because it's in the range of reasonableness that it was marketed.

I also want to point out there are other solvents that I didn't list here and other extraction processes that had come into the marketplace, not as extensively, things like hexane and acetone, super-critical gases and super-critical extraction.

Let me move then to suggestions, and the first few here I'm just repeating, modifications to 190.6, and an assumption that "Herbs of Commerce" herbs are "old," as are extracts by common processes. I'm repeating, we'd really like to see the agency just not accept filings for new dietary supplements. Those are wrong. They create a

bizarre record where now there's a document that says that licorice root and ginseng aren't allowed to be sold because somebody submitted--actually, they don't say that. They say your product may be adulterated which contains this ingredient. There are these lawyers in California that will make lots out of that. We'd really like to see that stop.

We'd also like to see the agency refuse filings for obvious old dietary ingredients, and I've listed a number of them here.

With regard to enforcement, I think it's obvious that enforcement needs to be prioritized based on safety concerns, and one point in passing, Susan mentioned the food exemption if it's present in the food supply and not chemically altered, and we want to make sure that the agency thinks what we think, that international food supply counts against that clause.

We'd like to see restraint from overly broad or maybe I mean overly narrow interpretations, but I've given some examples. For an herb, for the agency to say you didn't give us

specifications on purity, that's a GMP issue, not a new dietary ingredient issue. Compositional analysis, I've made my pitch that I don't believe compositional analysis of chamomile flowers is warranted; whereas, chamomile extract in a new solvent and a new extraction method may be. And, also, this issue about I really strongly argue against any requirement that the only way I can get my new dietary ingredient approved is to disclose every other ingredient that it may ever be marketed with. That puts an unfair burden on every product that has a single new dietary ingredient versus the whole world of products that have only old dietary ingredients. And we would oppose that.

There's a tendency for companies to resubmit when they change the dose and that I think is wise, but we'd like some guidance on that. There ought to be minimum criteria for FDA to review a submission. I'm not sure what those are, but I'm sure that they do include all of the administrative parts of 190.6, if it's not in triplicate, if it's not signed, if it didn't

disclose the plant part, those kinds of what I called here administrative or technical issues. And then, of course, the identity of the new dietary ingredient, if it's not identified I don't think the agency should go through that whole process of sending it back saying your ingredient is adulterated. I think the agency ought to not accept it, and I know that the record shows the agency does go back and ask for more information. We encourage that. We'd love to see more timely access at FDA's docket. I notice today it's really up to date. We appreciate that. But I also know that you pushed a bunch of stuff through in the last few weeks. We appreciate that.

In closing, AHPA and another organization, NPI, we're in the middle of creating a searchable database. We're going to make it so that you can go in and search for astaxanthin or licorice or whatever and find every submission that mentioned that. We'll also search--we'll provide a summary outcome statement of what happened, was it filed or was it objected to.

A couple things that I didn't get on here, we'd love to see an opportunity to withdraw that's very similar to what happens in a GRAS notice. There have been three or four withdrawals, one of which the agency refused to allow. We think that it ought to have rules that are a very similar to the GRAS withdrawal process.

We need to see consistency. I know that FDA intends to be consistent, but I can find examples. Astaxanthin, there have been five submissions--the three that were submitted prior to 2002, those were accepted; the two that were submitted this summer were not. I don't know that they were markedly different, those ingredients. If they were not, we'd need to understand did something change in the policy, because it needs to be very consistent, and I think you understand that.

I know that there's a new emphasis now on the agency saying exactly which subparagraph of a dietary ingredient is it in. I think that's a good question. But I also don't think that when

the--that's not a reason to object to a filing just because somebody didn't tell you that they believe that deer antler is in subparagraph (E) or that carnitine is also in subparagraph (E).

Maybe my last statement. The industry needs to see the whole process of the new dietary ingredient notification as a gate through which new ingredients can come, not as a barrier that refuses to allow new ingredients into the marketplace. And we really look forward to working with the agency. Guidance is definitely needed.

One point I forgot to make, some of these submissions are just a mess, and that needs to be acknowledged. Some of them don't deserve to be filed. They're embarrassingly narrow in the information that's submitted, and I think I can close it there.

DR. FRANKOS: Thank you, Mike.

Any questions? Linda.

PARTICIPANT: Mike, I wonder if you could tell us what NPI stands for on that last slide.

MR. McGUFFIN: You know, on the Metro on

the way in, I thought--I'm fairly certain it's the Natural Products Institute. I think that's what it is. They're a publication company in our trade who does a lot of work in communication, and we're partnering with them to put this thing together.

DR. FRANKOS: Mike?

PARTICIPANT: When you compiled "Herbs for Commerce," did you ask for documentation?

MR. McGUFFIN: We did not. We just asked for people to tell us, some companies provided--oh, sorry. Yes, the question was, when we compiled the information for "Herbs of Commerce," did we ask for documentation? No, we did not. We simply asked for people to inform us what they were selling. Some companies provided us with notarized statements. Some companies provided us with copies of their catalogues or advertising. And, also, I'm kind of a pack rat. I've got a whole box of catalogues from '93 and prior.

DR. FRANKOS: I have one question. When you said that whole herbs history of use is relevant for evaluating the safety of extracts, I

was curious how you would use that data when there are so many forms of extracts.

MR. McGUFFIN: I'll tell you what. The question is: How would I use information about whole herbs to evaluate the safety of an extract of that whole herb? What I have done, Bill, is I've looked at all 249 of these. What I haven't done is file one. So I'm not sure. I think some of the toxicologists that are going to talk to us might have more relevant responses to that because I think the way that you would use it, though, is the more that you could show that your extract had a chemical characteristic that was similar to the raw botanical, then I think you're going to be able to use that as information that suggests that we've been using that for some number of years or generations.

DR. FRANKOS: Thank you.

Yes, Jason?

PARTICIPANT: [inaudible, off microphone] you're specifying international use as a food, not as a medicine or--

MR. McGUFFIN: Correct. Yes, the question is with regard to my call for international use, there's that one--I forget. What is it? I forget. The one that says that you're not required to submit a new dietary ingredient that is present in the food supply in a form that's not chemically altered. That's exactly the part I'm saying. If it's present in the food supply in South Africa, that's okay; it doesn't have to have been present in the food supply in South Dakota.

DR. FRANKOS: Okay. Thank you.

MR. McGUFFIN: Thank you.

Our next speaker is Annette Dickinson. She's president of the Council for Responsible Nutrition. Annette?

DR. DICKINSON: Good morning, and thanks to FDA for the opportunity to be here and for beginning this initiative.

The Council for Responsible Nutrition is one of the leading trade associations for the dietary supplement industry. Our members include mainstream manufacturers of dietary ingredients

themselves, as well as manufacturers of both national brand names and private label dietary supplements. And we also have a number of members whose interest is international in scope.

We want to congratulate FDA for the three documents that were issued in the last few months, all of which are intended to move the agency and the industry toward full implementation of DSHEA. We don't believe anything is more important to solidifying the confidence in dietary supplements and the confidence both on the part of the regulators and on the part of Congress as well as consumers than moving to full implementation, and we congratulate the agency over the past couple of years for a number of initiatives toward full implementation and enforcement, which we believe is necessary.

At the same time, we are concerned that that enforcement and implementation be consistent with the intent of DSHEA, and I know that the staff at FDA is determined to make that happen. The purpose of DSHEA was to ensure consumer access to a

wide variety of products and also to provide consumers with more information about the uses of those products. The intent of DSHEA was to affirm the safety of a broad array, a very broad array of existing dietary ingredients and establish a notification process for new ingredients that was distinct from, deliberately distinct from and intended to be less burdensome than the food additive approach that the agency was using at the time.

We have also submitted in conjunction with this meeting a statement prepared by our legal counsel, Peter Barton Hutt, which was prepared at the request of both CRN and one of our sister associations, CHPA, the Consumer Healthcare Products Association, which presents his legal view of the status of dietary ingredients and new dietary ingredients.

The definition of dietary ingredients in the act is extremely broad and was meant to be broad, and any discussion of new dietary ingredients we believe must begin with a discussion

of what fits within the rubric of dietary ingredients in the first place.

While we agree that safety is an important factor in determining whether an ingredient may be marketed and also an important factor in determining whether an NDI notification is adequate for its purpose, safety is not necessarily a factor in defining the category per se, that is, the category of dietary ingredients. And I'll offer a couple of examples of why that must be the case.

One of the categories of dietary ingredients is minerals. Minerals is an extremely broad category. Minerals typically occur naturally, not as elements but as various compounds. Calcium, for example, is an essential nutrient, an essential mineral which occurs naturally as calcium carbonate and some other forms. However, it has been used for many years in dietary supplements and is grandfathered in other forms that actually do not occur naturally, such as calcium citrate. This illustrates a point, which is that we do not believe the inclusion of a

mineral in this category depends on it being in a naturally occurring form. In addition, we do not believe that inclusion in the mineral category is limited to nutrients that are essential. Calcium is certainly an essential mineral. But there are many others, such as tin, vanadium, silicon, and boron, that have for many years been present in very popular national and private brands of multivitamin/multimineral formulations, and we consider all of these to be grandfathered ingredients.

Likewise, the area of botanicals is an extremely broad category. It includes common and generally safe ingredients such as ginseng, garlic, and ginkgo. It also includes ingredients about which some safety concerns have been raised, such as comfrey, chapparal, and kava. The fact that there may be safety concerns that need to be addressed does not mean that the ingredient doesn't fall definitionally into the category. It is an issue that needs to be dealt with separately, and we urge FDA in its proceedings to keep these two

sides of the issue separate, that is, what falls within the category of the definition and where safety issues may arise.

Another category of ingredients in DSHEA is dietary substances. We believe dietary substances is an extraordinarily broad category and must be accepted as broad. There is a colloquy that we refer FDA to in our written comments that occurred during the passage of NLEA, not DSHEA, back in 1990 and that focuses on what might qualify as a nutritional substance. We believe that all of the substances mentioned in that colloquy, which include enzymes, coenzyme Q-10, evening primrose oil, and various other substances, certainly fall within this category of dietary substances.

The next question has to do with if something is an ingredient, is it a grandfathered ingredient? In order to be grandfathered, there are three criteria that must be met: the ingredient must have been on the market in a dietary supplement; it must have been on the market in the U.S.; and it must have been on the market

prior to October 15, 1994.

The vast majority of dietary supplements on the market currently contain grandfathered ingredients, and there is no suggestion in the law itself that there are any circumstances under which an old ingredient would become a new ingredient. This is something that is going to require considerable discussion within FDA, within our various associations, and among us all during this period of comment that we have available to us. We have discovered in our various conference calls leading up to this meeting that we don't necessarily have agreement within our association about the breadth of what might be grandfathered and whether there are conditions under which an old ingredient might become a new ingredient. So this will be, I am sure, a fertile field for further discussion as we move forward here, and it's another reason why we did join with AHPA and NNFA and other associations in requesting an extension of the comment period.

Another issue I'd like to raise is that in

some of FDA's recent enforcement actions, warning letters, FDA has taken the position that certain ingredients were not grandfathered because they were not legally marketed before 1994. The term "legally marketed" does not appear in DSHEA, and we do not believe that necessarily legal marketing is a criteria for what is grandfathered, and I want to give you three examples of why that might be the case.

The first two involve the essential trace minerals selenium and chromium. On several occasions during the decades prior to the passage of DSHEA, FDA took the position that selenium and chromium were not formally recognized as food additives and were not formally approved as GRAS substances and, therefore, were not, technically speaking, legally marketed as dietary supplement ingredients. Nevertheless, as we know, these ingredients were commonly marketed in dietary supplements prior to DSHEA and are still commonly marketed in dietary supplements. And, in fact, FDA has now established an RDI for both of these

minerals. Therefore, it cannot be a criterion chromium and selenium being legitimate ingredients of dietary supplements and being grandfathered that FDA should have viewed them to be legally marketed prior to DSHEA.

Another example is amino acids. Under FDA food additive regulations, there were very limited conditions under which amino acids could be added to conventional foods, and technically FDA viewed them as not being legal ingredients in dietary supplements. Nevertheless, they were widely markets as dietary supplements and still are and, in fact, now have their own subcategory in the definition of dietary supplements. Therefore, we believe this is another illustration that grandfathering cannot be denied based on a narrow interpretation of whether an ingredient was legally marketed prior to DSHEA.

In these comments today, CRN is going to focus really on some very broad issues and not delve into most of the detailed questions that FDA presented in the Federal Register notice, although

we will certainly do that before the end of this process.

In describing the information that should be provided in a new ingredient notification, we're going to skip over most of those questions, but we are going to indicate that one of the concerns that has come through loud and clear from our members is that FDA should be aware that much of the information they have requested, particularly regarding processing, may be proprietary information. And as we move forward, there will be a need to assure that proprietary information can be protected.

In addition to requesting information about the dietary ingredient, FDA requests certain information regarding the dietary supplement, and we believe this is entirely appropriate. DSHEA refers to the new ingredient notification needing to provide information on the basis of which the dietary supplement itself can be expected to be safe. However, as one small part of this section, FDA asks the question whether a label should be required to be submitted at this point. We would

simply note that in many cases the dietary ingredient notification is filed by the ingredient supplier or by a manufacturer during a pre-launch phase of development of the product, and a label simply may not be available at that point, so we do not believe submission of a label should be a critical part of that process.

Really the core question facing all of us here and the core question that will need to be resolved before the end of this process is: What type of information should be included in an NDI notification in order to establish a reasonable expectation of safety? FDA has outlined a number of questions that are very good questions that should be considered by every company submitting an NDI notification. However, we do not believe that the questions posed should be viewed as an absolute requirement or an outline for the information that must be submitted in a notification. We believe it really goes beyond what we see as the intent of DSHEA in establishing this notification process.

In particular, members of our association

who are very familiar with food additive petitions look at this list of questions and they see something very similar to a "Red Book" list of what must be submitted for a food additive. Members of our association who are on the pharmaceutical side look at this list and they see great similarity to what might be required for an NDA filing. And we do not believe either the food additive model or the NDA model was intended to be the basis for describing what needs to be included in a new ingredient notification.

We would request, as we move forward with defining what does need to be included, that FDA express its openness to consultation with companies who are considering an NDI notification in order to help them direct their information in such a way that the NDI notification will include the information FDA expects to see and that the company can improve its chances of having the NDI notification accepted.

Some FDA personnel in the last little while here, the last month or so, have made

presentations in which they have indicated that they really see no difference in the standard of safety that is described in DSHEA and the standard of safety that is expressed for food additives. We cannot agree with this assumption because we believe that when Congress wrote DSHEA, it certainly was aware of the standards of safety that are set for food additives, and it chose to establish a different statement. It indicated that new ingredients should be reasonably expected to be safe. Furthermore, in terms of the process, it did not permit or require FDA to actually approve an NDI; that is, there is no formal approval of the NDI from FDA once the document is submitted.

What is required is that the manufacturer or distributor should have in its holdings and should submit to FDA sufficient information to support the manufacturer's determination that the ingredient and the product are reasonably expected to be safe. We believe those are significant differences from the food additive model and that FDA should clearly incorporate those aspects into

their consideration.

There are other models than the classic food additive model that we believe bear consideration here as FDA looks for a model on which to base the new ingredient notifications. In particular, the GRAS self-determination process we believe is an extremely effective and flexible process. I don't know what's happening to my--it looks fine right here on this screen. I don't know what's happening up there. We believe the GRAS self-determination process is an example of a highly effective and flexible process which allows manufacturers to make a determination of safety, relying heavily on the input of experts or committees of experts to help them make that determination and to help respond to any questions FDA may have.

There are other programs that might be considered. For example, the EPA has a program that it puts new chemicals through when it approves new chemicals for introduction into the environment, which involves a functional analysis,

a functional safety analysis--a structure activity analysis, is what I'm trying to say, of the compound as it relates to other compounds in the same class. And we think this might have some relevance to FDA's review as it pertains to new ingredients that are single chemicals.

Likewise, Canada's Natural Health Products Directorate has recently--is just this year implementing a whole new program of review, including protocols for safety evaluation of natural health products, and we believe there may be some elements of this that would be relevant to this program.

FDA itself has adopted on occasion other methods than the food additive method for looking at safety of various ingredients in evaluating health claims for psyllium and stanol and sterol esters. FDA found that those ingredients did not have official regulatory status at the time the health claim was evaluated and required the companies to submit certain additional information on the safety of those ingredients, and we think

the nature of those submissions may be relevant to this process.

Finally, FDA's guidance on new plant varieties produced through biotechnology also relies heavily on manufacturer determination of safety and on comparability to existing plant varieties with a minimal or no reliance on actual clinical testing to go along with that.

FDA addresses the need for definition of certain other terms that appear in DSHEA, and we will reiterate here the same point that we made with regard to dietary ingredients. All of the terms should be understood broadly and literally, terms such as extract, constituent, metabolite, and the issues having to do with safety or other considerations that arise because of the breadth of some of those definitions we believe should be dealt with directly and separately and not used as reasons for restricting the definition itself.

We do endorse the seven recommendations FDA made in the Federal Register notice for improving the format and content of notifications,

and we will be addressing those in more detail in further iterations of our comments on this issue.

Finally, we congratulate FDA for undertaking this initiative and also for fully involving all stakeholders, which we believe is critical to the successful outcome of this discussion. And we look forward to future opportunities to work with FDA to improve the confidence with which consumers, regulators, and legislators can view this product category.

Thank you very much for this opportunity.

[Applause.]

DR. FRANKOS: Any questions?

[No response.]

DR. FRANKOS: Annette, I have one question. With respect to using a GRAS self-determination process, how would you see that fitting into the NDI notification process?

DR. DICKINSON: I would see that fitting in in a way similar to the current GRAS self-determination process where a company may submit their determination to FDA and request

listing of that GRAS notification. In that process also, FDA does not formally approve the GRAS ingredient, but simply arrives at a point where it has no further questions. But the company would ahead of time do its analysis of the safety, including relevant involvement of experts.

DR. FRANKOS: Thank you.

Okay. Our next speaker is David Seckman, and he is Executive Director and CEO of the National Nutritional Foods Association.

MR. SECKMAN: I'm David Seckman, Executive Director and CEO of the National Nutritional Foods Association. NNFA was founded in 1936 and is the oldest and largest trade association in the natural products industry. We represent the interests of more than 8,000 retailers, manufacturers, suppliers, and distributors of health foods, dietary supplements, and related items. I appreciate being able to submit this testimony in response to the FDA's request for input on pre-market notification for new dietary ingredients. And I think I'm glad I didn't have

slides today.

[Laughter.]

MR. SECKMAN: Just kidding.

NNFA has consistently supported FDA's ability and efforts to enforce the Dietary Supplement Health and Education Act of 1994 and to ensure that dietary supplements continue to be safe. In fact, in May of 2002, we submitted comments to FDA suggesting ways for FDA to enhance the quality, utility, and clarity of the pre-market notification requirements for a new dietary ingredient under Section 413. We continue to believe that FDA could use public comments on Section 413 to provide the industry with much needed guidance on NDI submissions. Of course, any guidance will apply to any company putting dietary ingredients on the market, whether they be the manufacturers of finished products or raw ingredient suppliers who need to guarantee safety to their customers.

What everyone in the industry needs is clear guidance. Specifically, NNFA believes that,

as written, Section 413 is unclear both as to when a new dietary ingredient notification is required and the type of information to be included if a pre-market notification is filed. In light of FDA's November 4th publication of its major initiatives for dietary supplements, NNFA specifically urges FDA to use caution in enforcing on NDI issues before it offers clarification to industry as to when a pre-market submission is required. Although NNFA will be commenting in more detail later, the following are a couple of key issues and comments that we think that need to be addressed in the guidance.

Our first issue concerns the not chemically altered exemption. According to Section 413, a dietary supplement containing an NDI is not adulterated if the dietary supplement contains only dietary ingredients which have been presented in the food supply as an article used for food in the form in which the food has not been chemically altered. Thus, the chemically unaltered ingredients from the food supply does not require

NDI filings to be made before being used in a dietary supplement.

The legislative history of DSHEA offers a small bit of clarification of what is meant by chemically altered, and I quote: "The term `chemically altered' does not include the following physical modifications: minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry powder, or solid in suspension." Clearly, many forms of processing have been left off this list, and FDA has not offered industry guidance of how to determine whether a process would or would not be considered chemically altered.

NNFA takes the position that a dietary ingredient should fall within its not chemically altered exemption as long as the resulting dietary ingredient is found in nature. Supplements are a subset of food. They need to be regulated accordingly. If it can be shown that an ingredient either is a single entity or complex, can be found in our diets, and there is no evidence of ill

effects, that ingredient should be allowed for sale. Moreover, FDA should not assume that changes in the processing or formulation always result in a change in the chemical structure that would require an NDA filing. Such an interpretation is consistent with the intent of Section 413 in that it would require exempt entities which known safety records based on food usage from the NDA pre-market submission requirement.

Our next concern in regard to Section 413 is the lack of clarification as to whether components of food, such as the lycopene found in tomatoes are subject to the pre-market notification requirement. NNFA takes the position that components would also be subject to the not chemically altered exemption in Section 413(a)(1); thus, if the extraction method used to isolate components does not results in the chemical alteration of the component, the component should be exempt from the NDA filing requirement. Moreover, the 413 exemption should extend to the components to the components that are chemically

altered during the extraction process but are in a form that is found in nature. Such components, again, have been proven safe within the food supply.

NNFA's next concern is in regard to how the NDI substance should be chemically identified, an issue FDA raised in numerous questions about it in the Federal Register notice. NNFA takes the position that chemical identifications of a substance must reflect the level of variation of the substance that is found in nature. For example, botanical ingredients vary in composition depending on where in the world they are grown. Certainly the agency would not require an NDI notification for each region unless there are significant differences that result in a safety issue. In addition, other ingredients may vary as percentage of certain confirmations. Again, however, this level of differences should not trigger the new NDI requirements as long as the variation reflects that which is found in nature.

Next I would like to comment on the type

of information about a dietary supplement product that should be included in the NDI notification. NNFA has some specific concerns about conditions of use and labeling as put forth by the FDA in its notice. NNFA would like to point out that when the agency raises such questions, it blurs the line between an NDI and a dietary supplement product as a whole. FDA should not be concerned with how an ingredient was used unless it was previously used as a drug, which raises other sections of DSHEA or how it was labeled. This information does not go to the safety of the dietary ingredient and should not alter the review process as to whether a specific dietary ingredient is safe for use.

My final comments have to do with establishing a reasonable expectation of safety. FDA raises the question of what quality and quantity of data and information are needed to establish a reasonable expectation of safety based upon the history of use. NNFA takes the position that FDA should establish clear parameters regarding what kinds of evidence would sufficiently

demonstrate reasonable evidence of safety. However, NNFA cautions that FDA's guidelines should not be so rigid so as to establish inflexible requirements. The kinds of data available for dietary ingredients vary widely, from very long documented history of use to clinical studies to observational reviews. The kinds of data available may also change over time. NNFA is concerned that the NDA process, along with the FDA's recently issued initiatives, does not become a mechanism to stifle or halt NDI submissions by presenting an almost insurmountable barrier for acceptance. To adequately reflect this reality, FDA should continuously exercise flexibility in the types of evidence required, for example, where an NDI does not have a long history of consumption by human, such as novel extractions of grandfathered botanicals. Moreover, an NDI that is an extract from an old dietary ingredient and is significantly similar to the old dietary ingredient might require less safety data than a new one. To respond otherwise would result in the stifling of research

and development for the use ingredients.

FDA also raises questions about what quality and quantity of data and information are needed and to establish a reasonable expectation of safety based upon information other than a history of use. Here, NNFA would simply like to point out that while a certain amount of scientific evidence is certainly necessary to establish safety, the burden should not be so high as to mirror a drug safety review. NNFA submits that information to establish a reasonable expectation of safety should suffice. This may include animal and in vitro studies conducted in an appropriate model or other test.

Finally, the FDA specifically questioned what types of documentations are necessary to establish that an ingredient was marketed in the U.S. before October 15, 1994, and thus grandfathered. NNFA and other industry groups in 1994 took the lead in developing lists that reflected products marketed prior to that year. Those lists have been relied on by industry, by

industry lawyers, consultants, and presumably even the FDA. NNFA submits that they have achieved authoritative status and should continue to be available to be relied upon for confirming grandfather status. I'd also like to point out that if an ingredient does not appear on one of these lists, it may also be grandfathered if there is evidence of marketability prior to October 1994. Examples of such evidence may include human studies, product advertisement, product catalogues, order forms, and invoices.

Again, in closing, I'd like to thank the FDA for the opportunity to comment on the NDI process.

DR. FRANKOS: Thank you.

Any questions? Jason?

PARTICIPANT: [inaudible, off microphone] variation in nature. Does that mean just in one species or parts or portions of the plant or [inaudible]?

DR. FRANKOS: Can you repeat the question, please? Or go to a mike, yes.

MR. SECKMAN: You want clarification of what--

PARTICIPANT: Clarification to variation in nature, extending to just the different growing conditions you might find in botanicals, or different portions of the plants being used?

MR. SECKMAN: Both.

DR. FRANKOS: Any other questions?

PARTICIPANT: How did you postulate human studies that may have been done on an ingredient prior to October of '94 would constitute reason for those ingredients to be grandfathered in? [inaudible] on ingredients never led to or related to those ingredients being sold in the marketplace?

MR. SECKMAN: Did everybody hear the question?

DR. FRANKOS: No. I think paraphrase it.

MR. SECKMAN: Studies done on humans before 1994, is what your question really was, how does it relate to the new dietary ingredients for the new dietary ingredient requirements?

PARTICIPANT: Right. I asked [inaudible].

DR. FRANKOS: Mike, please.

PARTICIPANT: Okay. I asked you how is it that you could postulate that human studies or studies--you know, clinical trials perhaps, done prior to October of '94 on certain dietary supplements or ingredients should be equivalent to those ingredients being grandfathered in if those ingredients were never sold on the marketplace?

MR. SECKMAN: I mean, there are valid studies that were done prior to. They just haven't been used in the filing of the new dietary ingredient. I think you can make a fair argument to that sense and be able to file it based on that information. I think that should be able to be used.

PARTICIPANT: Will the person who just asked the question identify himself, please?

MR. KALMAN: The person that asked the question was Douglas Kalman from Miami Research Associates.

DR. FRANKOS: Any other questions?

[No response.]

DR. FRANKOS: Okay. We're on time, actually a little early. I think we could just go right into a 15-minute break and then start again. I would like to point out that the next speakers can go to a breakout room during the break and prepare their slides. There's a room set up. I don't know what room it is, but it's next door to the auditorium.

PARTICIPANT: 1A-001.

DR. FRANKOS: 1A-001.

[Recess.]

DR. FRANKOS: We're having some audiovisual problems, so I'd like it if everybody could come back together, we'll have Alan Feldstein give an oral presentation, so he is the slides, and so we can start, and hopefully they'll get the audiovisual stuff together shortly.

And one other thing: There is overflow in Room 1A-001, if there are not enough seats or if anybody is feeling hot, there is a room that has been set up, and there is an audiovisual connection in that room as well. So there are also chairs

that are open down here at the bottom, up front.

I think we will start then with Alan Feldstein. He is counsel with Collins, McDonald & Gann. Alan, I think they're working there. Maybe you could sit here.

MR. FELDSTEIN: Sure, that would be fine.

Good morning. Can everybody hear me okay? Great. Collins, McDonald & Gann is a law firm located in the State of New York that represents manufacturers, distributors, marketers, and individuals in the sports and fitness supplement industry. Again, my name is Alan Feldstein, and I am your slides today. And with me is my colleague Richard Collins, principal of the firm; I'm of counsel of the firm.

Again, as everyone has said, we appreciate the opportunity to share our thoughts, and we welcome the opportunity to present our comments on this matter, which is of great importance not only to our clients but to the segment of the industry we represent as a whole.

We have reviewed the Federal Register

notice of this meeting, and we have also read with great interest the recent Guidance for Industry on Substantiation for Dietary Supplement Claims, as well as Dr. Crawford's recent statements before the Council for Responsible Nutrition. And while today's meeting is on the topic of new dietary ingredients and the 75-day pre-market notification process rather than substantiation of label claims, our comments address a fundamental issue that is relevant to both topics. And that issue is the perception--and I underline that, the perception--that both FDA and the sports and fitness supplement industry have of each other and how that perception impacts the actions, philosophies, and attitudes of both sides.

One of the threshold questions that remains a mystery is, Under what circumstances must a pre-market notification be filed? According to the Overview of Dietary Supplements posted on January 3, 2001, on FDA's website, DSHEA "requires that a manufacturer or distributor notify FDA if it intends to market a new dietary supplement in the

United States that contains a `new dietary ingredient.'" However, the law appears to say something a bit differently.

DSHEA actually says that a District which contains a new dietary ingredient shall be deemed adulterated unless it meets one of two criteria. One of those criteria is the submission of a proper pre-market NDI notification 75 days before marketing the product. The other, however, is that the dietary supplement "contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered."

Industry has widely interpreted this language to require pre-market notice only if the product's new dietary ingredients are not present, unaltered, in the food supply. In fact, many manufacturers have chosen to decline to submit pre-market notice based upon their belief that their products comply with this provision under DSHEA, and it appears that in ten years, FDA has never taken an action under this provision with

respect to a single product other than the recent action involving androstenedione. If FDA has an alternative interpretation of the statute, it has never explained that to industry, and that is an example of the problem--a classic failure of communication which escalates distrust on both sides.

Further, in situations where all sides agree that pre-market notice is required, what sort of safety data does FDA require? One only has to look at FDA's website on new dietary ingredients to understand the communication problem. If you look at the FDA website to obtain guidance on information that the agency requires to approve or at least not object to a pre-market NDI notification, you will find this language: "To date, we have not published guidance defining the specific information that the submission must contain. Thus, you are responsible for determining what information provides the basis for your conclusion."

And while I appreciate that the meeting

today is the start, that is another example of the communication problem that I think persists today.

The law states that new dietary ingredients which are not in the food supply can be introduced when there is a history of use or other evidence of safety establishing that the dietary ingredient, when used under conditions recommended or suggested in the labeling of the dietary supplement, will be reasonably expected to be safe. Despite pronouncements otherwise, the law does not state that there should be a risk/benefit analysis, as was done with ephedra. It does not suggest a requirement of zero risk, as an FDA working group was asked to determine. The process should not be a roundabout way of allowing the agency to say no, as is perceived by many of our clients. If the NDI process is to work within the parameters of DSHEA, then we would submit that the following steps need to be taken:

Any guidelines that are propounded by FDA, and actions undertaken by FDA, must adhere to a reasonableness standard, as was intended by

Congress.

And, equally important, the standards must be applied in a transparent and reasonable manner with specific guidelines. In other words, we believe that if you submit the proper materials, your ingredient will be either approved or not objected to.

In addition to these specific steps, it is our sincere hope that our comments today and this meeting today will also be the beginning of a dialogue to help change perceptions that exist about FDA's attitudes towards supplements. The debate here today is not whether or not there is a negative bias by FDA but, rather, again, the perception that such a bias exists and the perception that there is no one within the agency that is an advocate or supporter of the industry. We believe many of the issues raised by FDA for this meeting and in recent draft guidance documents on substantiation can be resolved with improved cooperation and communication.

In speaking with our clients and other

members of the sports and fitness supplement industry, there is a sense of mistrust or that the process is stacked against anyone who wishes to file a pre-market notification. That is not true, you might hear people within the agency say. And you may be right. But if you were to poll our clients and others in the industry, you would find that the perception exists. Why does it? For a moment I ask you to put yourself in the shoes of a company in the sports and fitness supplement industry. Here are some of the things you have seen in the last ten years:

You have witnessed the publicizing of a group of anecdotal adverse event reports in such a manner as to give the impression that they conclusively support a claim that dietary supplements containing ephedra are dangerous. You then learn that the GAO in 1999 in its report concluded that FDA failed to establish that the proposed rule would have any public health benefit and that FDA did not establish that there was, or is, the need of any regulation. Now, one may argue

that this is old news and FDA was eventually right in banning the product, but since then the same issue arose with respect to Kava, and as recently as several months ago FDA was criticized by the American Herbal Products Association on AERs involving bitter orange. AHPA was quoted as stating FDA is willing to regulate by anonymous press release and be cavalier in its approach to informing the public about the safety profile of bitter orange. And while there have been announcements recently of a change in this policy, it is these cumulative actions that contribute to industry's perception.

Number two, you are viewing FDA's newly heightened attention toward dietary supplements from a historical perspective dating back to a period before DSHEA, when legislators and federal judges were expressing concerns over FDA's activities against dietary supplements. For example, a Senate committee found FDA was "distorting the law" to prevent safe supplements from being marketed, and a federal judge, in

adjudicating a seizure action by FDA of encapsulated black currant oil, chided FDA for engaging in an "Alice in Wonderland approach" to make an end run around the statutory scheme.

You have also seen androstenedione sold openly as a dietary supplement for many years, then suddenly removed from the market not only for safety reasons but for failure to file a pre-market NDI notification. Industry is suspicious of FDA's claim of safety because of the long delay. And even more puzzling is FDA's claim that it was not aware of evidence that the compound is present in the food supply. Studies have confirmed its presence in meat. The literature is there.

And, finally, as an example that has just recently occurred with one of our clients, you are a company that obeys the laws and has ceased selling ephedra in the United States. Further, you've complied with all the procedures necessary to permit you to sell your product overseas to a country that permits the sale of ephedra. Yet despite this fact, you are visited no less than

three times over a period of two weeks by FDA field inspectors who continually are looking for a way to prohibit you from selling your product overseas.

Thus, from our client's perspective, they have seen FDA take actions that they believe were not based on science, and when they ask what are the rules that they have to play by, they are told there is no guidance for determining what information needs to be provided. Or if they play by the rules, they still encounter resistance. This fosters a climate where many people believe that no matter what is submitted, you will not get a fair hearing. Some industry representatives have told us that they believe that virtually all NDI notifications submitted in the past year have been rejected. That perception creates an atmosphere fostering noncompliance with the law in which no one benefits.

Recently, Dr. Crawford echoed these sentiments when he stated that the agency in the past had said "we are going to enforce the law, but you are going to have to guess what the standards

are." We admire Dr. Crawford's candor, and he zeros in on the exact kind of atmosphere fostering this perception. Our industry members are concerned because of the perception that the rulemakers are biased against them. The question being asked by them is: "Are these guidelines and proposed rules being drafted in the spirit of DSHEA or in the spirit of pushing the industry to a pre-market approval drug model?"

The latter would be detrimental to the American public. The economic, technological, and innovative advances which have guided this country and made it a leader happen when the framework of the rules are clearly set, while at the same time there is cooperation between industry and the government agencies that regulate them, allowing ample room for innovation. Given our growing health crisis, FDA should be encouraging, not discouraging, innovation within a framework of safety.

Therefore, in addition to our specific proposals about NDIs, we would ask that FDA give

serious considerations to three other proposals that we believe will go a long way in improving its relationship with the sports and fitness supplement industry in general:

It must, in a meaningful way, create lines of communication with all segments of the industry to better understand the different segments of the industry and their needs and desires;

It should take steps to communicate with and learn about the segment of the American population that uses sports and fitness nutritional supplement products so that it can create and implement its policies and procedures in a manner consistent with the public that is serves;

And, finally, we'd also recommend strongly that FDA have an ombudsman within CFSAN, as it does with many other industries that it regulates. This would be someone who will investigate complaints from outside FDA and facilitate the resolution of disputes between CFSAN and the industry it regulates. Having someone who can help with communication between industry and CFSAN will go a

long way toward achieving a balance between the need to keep Americans safe and the right of Americans to make their own health decisions about dietary supplements.

Until there is better cooperation and communication between FDA and industry and until there are people within the agency who support the use of supplements, we believe this will continue to be a problem. To begin to solve the problem, there needs to be an effort to change the perception that exists. And in any relationship, there's always somebody who has to take the first step, and I would ask that FDA be the one that takes that first step.

Thank you very much.

DR. FRANKOS: Any questions?

[No response.]

DR. FRANKOS: Okay. Now, our next speaker is George Burdock, President of the Burdock Group, and, George, you can sit here and then she can change your slides, or stand there and she can change your slides.

DR. BURDOCK: Good morning. Thank you for the opportunity to allow me to speak to you on this very important subject. My name is George Burdock. I am a toxicologist and consult in the food ingredients and dietary supplements business. My company has offices in Florida and Washington, D.C. My contact information is available at my website appearing at the bottom of each slide or overhead here, and if you would like a copy of these slides in living color, please come to my website and request one, and we'll be glad to send you one. Because it is not in color, any refunds for admission will have to be coordinated through Mr. Frankos.

I would like to address today the dietary supplement issue as a whole, to include review, safety, and claims; that is, the claim as to supplement or nutritional status and possible structure/function claims, which I refer to in this talk as efficacy claims.

I am concerned that in response to what may seem to be a crisis, FDA may be persuaded to

take an overly conservative path which may place safe and efficacious dietary supplements out of the reach of consumers. This raising of the bar will almost certainly result in an underground/unregulated market populated by charlatans, with spurious claims of potentially unsafe products. I believe an overly conservative path is supported by several diverse groups, many of which share our sincere belief that the public deserves a safe and efficacious product. There are others, however, whose goal is not as sincere, and among these the most zealous supporters of an overly conservative pathway are those that will gain most financially, the charlatans of the underground market.

The dietary supplement market is a strongly consumer-driven market, and the public has long demonstrated a profound willingness to obtain benefit from substances outside of mainstream drugs or food. There are many driving forces behind this demand, and they included a demand for improvements in the quality of life, a lionizing of natural remedies, and a reaction to the high cost of drugs.

A strong consumer market encourages enterprise, investment, and competition within the supplier community, as long as there is adequate return on investment.

The wants and needs of the various players have created tension. This tension begs for resolution. In this graphic, consumers, industry, and the agency are depicted as the intersections of a triangle, each with examples of driving forces between the two. In this graphic, the relationship between industry and the consumer is depicted by consumer demand on the one hand and the need by industry for a return on investment. Between industry and the agency is a demand by industry to exercise its freedom of speech, and the response by the agency that only efficacious products may be marketed. Between the consumer and the agency, I have shown a demand for greater access to fulfill the wants and needs described earlier by consumers, or of consumers, and the pushback from the agency that only safe products should be allowed in the marketplace.

The tension demonstrated in the graphic sets the stage for a possible response by the consumer; that is, if an overly conservative pathway is taken by the agency, it will affirm the beliefs of many who preach there is a conspiracy to keep inexpensive natural substances off the market by "big pharma" and by regulators. And it will also give affirmation to those who want to believe that we are all witless incompetents that ignore the lessons of our forebears about the natural remedies of "Mother Earth." Setting the bar too high will ultimately result in the loss of our credibility and the faith of the consumer.

The last time the bar was raised and threatened to cut off the source for consumer satisfaction resulted in the passage of DSHEA, which was meant as a safety valve to ease the tension between the public and what was seen as an overregulation by the agency. Locking down this safety valve with an overly conservative response will cause consumers to lose faith in the very agency responsible for their protection, and with

the aid of the Internet, give rise to an underground, uncontrolled, unsafe wild, wild West of a marketplace.

Maintenance of the faith of the consumer is essential, but in order to achieve this goal, the agency, as the key player, needs the active involvement of industry. Only FDA can elevate the role of industry from producer to participant, and in so doing, FDA becomes the engine for resolution. To do so, FDA must take three steps.

First, the promotion and use of independent expert panels for the determination of safety and efficacy; second, initiate a notification program and post the results on the Internet so consumers will know what is safe and efficacious and debunk illegitimate or copycat products; third, provide a term of exclusivity for industry. This period of exclusivity will allow industry an opportunity to return on investment without which there will be very little R&D and only the wild, wild West that I mentioned a few minutes ago.

There is precedent for the use of independent experts, such as GRAS panels, generally recognized as safe for food ingredients; GRASE, that's generally recognized as safe and effective, for drugs; and any number of FDA advisory committees on FDA issues, including OTC drugs, dietary supplements, food ingredients, and others. The FDA fact sheet describing a strategy for dietary supplements includes a statement that third-party reviews will be permitted. There are other examples of involvement by independent expert groups, and I implore the agency not to follow an overly conservative path as exemplified by significant scientific agreement where only institutions could approve claims. If the precedent of SSA is followed, then something like the Health Independence Information Act will be passed, which essentially takes all authority out of the hands of the agency.

The second of the three steps forward is a notification program. There is precedent here with the GRAS notification program and the program for a

new dietary ingredient. The results are posted on the agency website, and the public would be informed about what was safe and efficacious, and retail merchants could self-police, knowing what is legitimate and what was not. Simply put, a notification program rewards the legitimate players by letting the public know who plays by the rules and who does not.

The third of the three steps forward is to allow a legitimate manufacturer a period of exclusive marketing rights. That is the period when safety information on the product is made public, but information supporting efficacy remains embargoed by the agency. Also, any other manufacturer wishing to sell an identical product using the same claim during the period when efficacy information is embargoed must present his own efficacy information to the agency. While immediate release of safety information is essential, immediate release of the data supporting efficacy does not help the consumer. It only eliminates the incentive for investment.

There is precedent for embargoed information as seen with the food master files where safety information is released while manufacturing and other key information may not be. And we all know about drug master files where all information is held secret, and for the same reason: to allow the manufacturer a reasonable period for return on investment. Without return on investment, there is no incentive for performance of safety or efficacy studies and we are back again to the wild, wild West scenario.

Without possibly jumping the gun or belaboring the issue, but to illustrate a point, consumer demand and the promise of reward motivates manufacturers to fund R&D, safety testing, and efficacy testing to support claims.

The agency with the notification system can inform the manufacturer that it has no objection to the finding that the product is safe and the claim is adequately supported.

Following this positive feedback from the agency, the manufacturer can crank up his

marketing, manufacturing, and distribution arms to respond to consumer demand.

If, however, as illustrated above where the no-objection notice has a lot of little arrows coming off of it, if this is where the no-objection notice is publicly broadcast and the information is not embargoed, then for lack of a better term, pirates can share the claims support information, and because the pirates' only expense is marketing, manufacturing, and distribution, the pirates can sell at a cheaper price and consumer dollars go to someone other than the manufacturer that paid for the R&D, safety, and efficacy testing.

Therefore, there will be no return on investment. Funding for R&D, safety testing, and efficacy testing will dry up.

Now, if I haven't gotten too far ahead of myself on exclusivity, to get back to the three steps forward program, we need to examine the use of independent experts and the notification program, for both of which we are showing adequate precedent.

First, in this regimen for independent expert review and FDA notification, a dossier is prepared and reviewed by a group of independent experts to determine if the information supply supports safety and a specific claim.

Once approved by the experts, the dossier is then provided to the agency on a non-public basis and is reviewed by the agency within certain boundaries. The object here is not to have the agency reinvent the wheel or take full ownership of the decision by an examination of all the data as it might do for a food additive petition, but maintain the spirit of the notification program by paying closest attention to three points: first, the credentials of the experts. Are these reviewers qualified by training and experience to make this sort of decision? Secondly, is the rationale provided logical to support the claim? That is, if the evidence is narrow and specific and supports an equally narrow and specific claim, where is the claim is overly broad? Lastly, is the supporting evidence credible? Not all studies need

to be double-blind, placebo-controlled studies, but does the information provided have adequate rigor to support the claim made? The goal for the agency here is not to abdicate its authority but to provide oversight to ensure that legitimate experts are approving equally legitimate claims.

The oversight function will also allow the agency to get along with its other work at hand and not become bogged down in the details, the very problem that plagued the GRAS affirmation process.

Upon completion of its review, if the agency determines the notification is inadequate, the agency offers a description of the deficiencies and an opportunity for withdrawal of the notification. If withdrawn, the information in the notification is not made public and the submitter has an opportunity to remedy the deficiencies without loss of the proprietary information therein.

If the agency determines the opinion of the experts is sound, the agency responds to the submitter with a no-objection, followed by a public

notice on the FDA website.

The public notice would consist of the name of the manufacturer, the product identity, the truthful statement or claim, and the safety data. Not made public nor shared outside federal agencies for at least five years would be the efficacy data, the time and investment by the manufacturer to prove the claim, and should not be dissipated to the pirates.

Again, the FDA should make public the safety information, the claim, the product name and the manufacturer. The evidence for a claim should not be released for at least five years. This is the same as with the food master file or a drug master file, and the option of releasing the data would be at the election of the submitter.

Now, what benefit would be derived from independent expert review and FDA notification? First, the agency would be relieved of a possible logjam of petitions. Second, the agency and public would benefit from the addition insight provided by experts outside the agency. Third, consumers would

know that the agency and industry were taking reasonable steps to respond to their demands for empowerment and access.

How would ensuring return on investment to industry benefit anyone else in the triad of players I talked about earlier? First, consumer demands for a variety of safe and effective products would be met. Second, the agency and consumers would know that products were properly examined for safety and efficacy, that consumers would get not only value for their dollar but safe products as well. Lastly, return on investment would ensure competition and new products in the marketplace.

If FDA acts to take the three steps, all the players will benefit. Consumers will be empowered with more and better products. Industry will be assured of its right of free speech and a legitimate need for return on investment. FDA will know that consumers are protected from unsafe or fraudulent products. This is a win-win resolution.

Thank you for your attention and allowing

me to address you today. I'd be delighted to answer any questions and, again, if you would like copies of any of these slides, in color as well, please contact me at my e-mail or website.

Thank you.

DR. FRANKOS: Any questions? Please come to the mike.

PARTICIPANT: George, you ushered in a topic that is outside the scope of this focus, but I'll address you on it, and that is efficacy. What would you qualify as a sufficient amount of evidence to support an efficacy claim that would be overseen and reviewed or allowed by the FDA on a dietary supplement?

DR. BURDOCK: Something that meets the criteria of a structure/function claim. I'm not trying to avoid your question, but I don't see what are the grounds on which I could answer.

PARTICIPANT: Structure/function claims do not have to be supported by a clinical trial for an actual finished good.

DR. BURDOCK: They don't have to be

supported by a clinical trial, that's for sure. But there are other methods that support a structure/function claim.

PARTICIPANT: So I'm still asking for an exemplification of what you think would be sufficient for efficacy claims to be allowed or approved.

DR. BURDOCK: Adequate animal studies, proof of absorption, proof of mechanism. There are a lot of ways to get to it. It doesn't always have to be--in fact, I think for a structure/function claim, adequate human data may not be necessary at all.

DR. FRANKOS: Anyone else?

[No response.]

DR. FRANKOS: Thank you.

Good, we've got color. Our next speaker is Wes Siegner, and he is with Hyman, Phelps & McNamara, and hopefully things are working now.

MR. SIEGNER: It must be my lucky day here. I was actually looking forward to using the overhead because I used to be a teacher, and my

first year one of my important lessons I learned was never turn your back on the audience, being the class. So overheads were my favorite tools. We didn't have computers back in those days.

Well, thank you for this opportunity to speak, and welcome to this meeting. Before I start here, I just want to note that there seems to be a lot of agreement in what we're seeing in this notice, and that makes me very happy. I think industry recognizes what the stakes are here.

I have a presentation which I typed out, which is a little different than my overheads. I noticed that there's no copies left out on the table. I have a few copies here for people who are desperate to read it before they go home tonight. But if you want to give me your card or give me a call, I can give you another copy if you're interested.

Just starting out, the issues that are presented in this notice are very, very significant for the industry. And as I said, I'm glad to see that trade associations and others recognize that

because one of the things, I think, that we need to fix immediately is that not enough time has been given to allow people to consider what the issues are. There won't be enough time to prepare comments by the 3rd of December, certainly, and I think actually my feeling is it ought to go well beyond February 3rd. But whether that's on the FDA table at the moment or not is an issue, but we can fix that.

The other thing I want people to understand is that it's not that FDA is doing anything wrong in what is going on here with NDIs. I have a very strong feeling that it's becoming a food additive approval process. That will be the natural tendency of FDA if we leave them to their own devices, not because they're not doing their job but because they are doing their job.

If you put safety in FDA's hands and say, look, we want you to go out there and enforce the law and protect consumers and make sure that the products are safe, you can't imagine that they're going to say, well, we're just going to kind of

gloss over these safety reviews. They're going to do a hard-nosed food additive type approval of those safety reviews. And you as industry and I as a lawyer for industry need to find ways to give FDA an option to get out of that box. I think we've seen some good ones today in terms of suggestions.

My other point--oh, sorry. I'm already on the next slide. What do we do here? There we go. Sorry. No? There were are.

I'm the ten-year issue. Basically what has been happening here with the development of NDI policy is that over a ten-year period, people have been submitting NDIs without the rules being known. FDA has been writing back, and the process has been evolving over this ten-year period, and there's a lot of important information in those NDI reviews and objections and filings. I commend Michael McGuffin and Tony Young for trying to parse through all that--there's a huge volume of material--and pulling out some important lessons. But I'm going to go through a few important things that I've seen in these notifications and correspondence. I think

industry deserves a fair break here in terms of being able to respond to all this. We can't do it in 45 days. My feeling is we need at least six months to really put this all together and get good comments in.

I'm also encouraged by Bill Frankos' comment that this is maybe the beginning of a process, that there may be other meetings. My concerns would be less strong on the comment period if the plan is going forward to say, okay, this is the initial review, we're going to consider these, give you some more chance to comment and to have public meetings.

The other argument for more time here is, of course, all the other things that are coming down the pike. We have the substantiation document, which has a 60-day comment period. We have GMPs coming out. We have new FDA directives in terms of their strategies for regulating supplements. And I don't know how many people have read all that, let alone absorbed it. I have read it; I'm not sure I've absorbed it.

I've tried to boil this notice down into five issues. They're not all the issues, of course, that are in this NDI notice, but to me these are really the most important issues for the industry looking forward and wanting to market as many safe dietary ingredients as the industry can market and that consumers deserve.

The first issue here is that FDA is going to have a tendency to restrict the market by very narrowly defining "dietary ingredient," and I'm not going to go into all the shades of that, but I'll bring up one issue relating to that definitional issue.

Annette Dickinson broached on this second point, which I think is critical. There's this new standard creeping into the old dietary ingredient category where they're saying that the ingredient has to be lawfully marketed before 1994. And if we go that route, there's some big problems for industry.

Third, this issue with "present in the food supply," FDA wants to narrowly define that to

mean just foods, not components of foods. David Seckman picked up on this to some extent in his discussion. That would be a very narrow interpretation of that. I've got to be honest, the statutory language, as is typical of statutory language, is not entirely clear on this point. But the goal here should be to assure safety but permit the broadest definition we can.

The fourth issue is what does "reasonably expected to be safe" mean. You know, I think industry would all agree that it means something less than a food additive safety standard. But it's not defined, and, you know, there's no actual precedent in the act for this standard, and we can talk a little bit about that. But the bottom line is people need to come to an agreement in the industry and at FDA what it all means.

Then the last thing I'll touch on briefly is this issue of risk/benefit, which has come into play through the ephedra final rule and how it might apply to NDIs.

The issue of narrowing the definition,

we've already been through the dietary ingredient definition several times. This is just a paraphrasing of it without all of the statutory sections. I want to focus on the underlying language, which is "a dietary substance for use by man to supplement the diet by increasing the total dietary intake."

Now, if you know exactly what that means, raise your hand. It's a lot of words. I'm not sure what it means myself. The problem here is that FDA wants to define it in a way that's very narrow. My view of this is that that was put in there as a phrase to kind of say, okay, we have amino acids, botanicals, herbs, vitamins, minerals; here's a phrase that's going to capture everything else that might be suitable for people to eat. And "suitable" is kind of a nebulous word, but, you know, you don't want people eating unsafe things. That's captured in the safety review.

Now, of course, the statutory definition also excludes ingredients that are being investigated as new drugs or were on the market as

drugs before they were on the market as supplements. But barring that, we should have a big, broad array of substances that we can market as dietary ingredients. There will be new things discovered down the road, and we want to keep that door open.

What FDA is saying in these letters back in the NDI process is that in order to qualify to be a dietary substance, it has to be part of man's usual food or drink. Now, I'm not sure what that means either, but it doesn't signal to me that they're headed in the right direction. I think that's a very narrow reading of the word "dietary substance." We need to make sure FDA doesn't go down this path, that we keep that door open.

And in the end, I can't estimate it. You know, it could be several hundred ingredients. It could be thousands of ingredients that the industry could lose if we don't get the right interpretation here.

This is something that Annette hit on. I won't go into it in great detail. But, again, we

have all assumed that there are a lot of ingredients out there that FDA and industry would view as old. If we allow this lawfully marketed interpretation to creep into what FDA's thinking, what's going to happen is a lot of these old ingredients will suddenly become not legally marketed pre-'94 ingredients, and that means--not that they're necessarily going to come off the market, but they have to go through the NDI process. And a lot of the old ingredients I don't think would make it, would have a tough time, and we'd end up losing a lot of ingredients.

I have a list in the last point here of some of the ingredients that FDA, I believe, would view as illegal food additives, pre-'94, and if that's the case and the lawfully marketed standard is the one FDA is going to apply, all of these would need to come off or go through the NDI process. And I think a lot of the herbs would suffer the same problem.

Moving on to the next point, this narrowing of the "present in the food supply"

definition, this is really a simple matter. How are you going to interpret the statutory language? The statute says "dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered." Well, we've had a lot of long discussions in our firm about what this means, and, again, it's not exactly clear. You can subject it to several interpretations. FDA wants to focus on the words "article used for food" meaning that if you have a potato, it's only the potato that is subject to this exemption from NDI notification. It's not any of the ingredients in the potato, the components, not the carbohydrates in there, not the proteins in there, not the vitamins or minerals in the potato. It's just the potato.

Again, the problem with this is that if we go down this route, we're going to lose a lot of dietary ingredients probably, but the real importance is that it forces a huge number of ingredients into the NDI review process. And, you know, there ought to be some logical conclusion we

could come to or interpretation with FDA that everybody could agree to. And if it's a de minimis ingredient in a food that's been marketed forever, that doesn't give you any assurance that the ingredient might be safe. But if it's a very substantial substance within a food that's been widely consumed, that really gives you an assurance of safety. And why would we as industry need to spend the time to put together a panel of experts to review those? And why should FDA have to review those types of substances? My view is they shouldn't.

This is the whole thing here: What does "reasonably expected to be safe" mean? Yes, it was great, we pointed out through DSHEA that FDA was not supposed to treat dietary supplements as food additives. We have a different standard for NDIs. But Congress didn't really define it. As a matter of fact, in this case, Congress decided that the legislative history wasn't going to be legislative history, so they in passing the law said, well, none of this that we've said about this law that

you might use to interpret it really should count. You know, we still read it and put meaning into it, but, you know, this is a problem. And I think that several people--Annette and others--have kind of hit the nail on the head that industry needs to do good self-reviews, either in the context of the GRAS self-affirmations, with panels of experts, or setting up their own panels of experts, like the cosmetics and flavors industries have done. Somehow industry has got to take this thing by the horns and do their own safety reviews, because if you don't, what's going to happen is, again--and it's not that FDA is doing anything wrong. But if they have to protect the public and declare things safe or not safe, they're not going to say half-safe, they're going to do a full-blown safety review. There's no other way around that.

Then the last thing here is risk/benefit. This is something that I think a lot of people haven't thought about, but there's a problem that comes into play as a result of the risk/benefit standard that FDA created through the ephedra rule.

The problem is that if you look at 402(f) or 342(f), as it's in 21 U.S.C., (A), the section of the law that applies to adulteration has a section in it that applies to the adulteration of NDIs. And that section applies the same unreasonable risk standard to NDIs as it does to any other dietary supplement. And I'm not saying this is going to happen, but I can very well see down the road, again, if we leave FDA to kind of run this safety review, they're going to say, well, it doesn't make sense to put an NDI on the market under just a safety review. When it's on the market, we have to judge it by safety and benefits. So what we're going to do is require NDI notifications to prove benefits. They're not doing this now. I hope it never happens. But this is just something that--another problem we need to keep an eye on.

I just want to bring some notice to something here. My first point, my conclusion, is that industry is at a crossroads. Peter Hutt's conclusion is FDA is at a crossroads. Well, so industry and FDA are meeting at the crossroads, and

we need to through this notice get together and decide what the best path is. And I'm confident that if we have enough time to parse through these issues and work them out with FDA, we can come to conclusions that are going to be benefiting industry and that are going to be benefiting FDA and not wasting a lot of your time, because I think that if you really get into this as a food additive review process, it's going to be very hard for you in terms of having to review things, and it's going to be terrible for industry, because in the end we'll be back where we were in the '80s and early '90s where the whole system kind of bogs down and we can't get anything on the market.

Thank you.

DR. FRANKOS: Any questions? Yes, can you come to the mike down here, please? And please identify yourself.

DR. BECHTEL: I'm Dave Bechtel, senior toxicologist with Cantox. Wes, interestingly, I totally agree with the issue of FDA's review of data for a new dietary ingredient. I would ask you

the following question: Under DSHEA, it is my clear understanding that there are two options for new dietary ingredients: one is a notification, the other is a new dietary ingredient submission. And that's in the regulations.

Do you see any advantage or any opportunities in the existing regulations in the format to be able to deal with defining how FDA operates with the notification versus a submission?

MR. SIEGNER: Answering from where we stand right now and in terms of how I would advise a client to go forward, our view toward this is that we do treat them very much like GRAS self-affirmations and prepare the NDIs in a very thorough manner with a panel of experts or however many experts you need to address the safety issues that the ingredient raises. And I don't really see the difference, unless FDA tells us otherwise, as to whether you do the notification or submission process. It's all really the same thing. You know, we can't really say what "reasonable expectation of safety" is, but if the industry or

the company submitting the ingredient really takes it on its shoulders to get the experts lined up that FDA is going to say, okay, these are really qualified experts in the industry, they know their stuff, that's immediately going to set FDA at ease, more so than if they get a submission that's, you know, got some studies attached to it and says we're safe.

So I think answering your question, I don't really see a difference between the two processes. I think it's really more focused on right now how do we make FDA happy.

DR. FRANKOS: Wes, I'm a little confused. Once you determine you have a new dietary ingredient, I'm only aware of one process that you have to notify. So you were talking about another process?

MR. SIEGNER: Well, actually I'm familiar with the notification process, and--

[Inaudible comment.]

DR. WALKER: This is Susan Walker. There is only one notification process. Basically the

75-day notification process is a process where you send in a submission. So unless someone has clarification on something else, there's really just one process.

MR. SIEGNER: I think we're all talking about the same thing.

DR. FRANKOS: Okay. I do have one question. You brought up the issue of a de minimis level of a constituent of a food, let's say. Could you define "de minimis"? Is there a way to define that for us? We would be very happy--

[Laughter.]

MR. SIEGNER: Bill, I thought we were friends.

[Laughter.]

MR. SIEGNER: I think my main point is that we ought not to be saying component or, you know, non-component. And that, I recognize, does lead FDA into another, you know, part of the woods. I think we can get out of it. But my point is I don't--let me be truthful. I can't answer your question.

[Laughter.]

DR. FRANKOS: Very good.

MR. SIEGNER: Very unlawyerly, but I'll be honest. But the point is let's not review ingredients that we know people have been exposed to at significant levels for, you know, forever. I think that's something that should not be in the NDI review process. Things that, you know, don't warrant that kind of safety presumption, then we ought to figure out what they are.

DR. FRANKOS: Okay. Any other questions? Yes?

MR. SIEGNER: Now I'm really in trouble.

[Laughter.]

DR. DICKINSON: Annette Dickinson with CRN. As a regulatory wonk, I can't resist looking up the answer to this question that you were just asked. In DSHEA, under the new dietary ingredient section, after it talks about the notification part, there's a separate section on petitions, which says, which appears to say that apart from the requirement to submit a notification from an

NDI, any person may file with the Secretary a petition proposing the issuance of an order prescribing the conditions under which a new dietary ingredient under its intended conditions of use will reasonably be expected to be safe.

So I assume that's the separate thing that he was talking about.

PARTICIPANT: That would be like getting a regulation--

DR. DICKINSON: It would be like requesting a regulation right.

DR. FRANKOS: Okay. That's what you're talking about.

MR. SIEGNER: Has anybody ever gone that route?

DR. DICKINSON: We've ignored that.

DR. FRANKOS: We're not aware of any.

MR. SIEGNER: Well, I guess I didn't answer that question very well either.

[Laughter.]

DR. FRANKOS: Any other questions?

[No response.]

MR. SIEGNER: Thanks.

DR. FRANKOS: Well, thank you.

We're actually moving along pretty well, and we're on time. So let's take a 15-minute break and come back and finish up. Let's meet at 20 of.

[Recess.]

DR. FRANKOS: Okay, we're into the home stretch here. Our next speaker is John Zenk, and he is chief medical officer of Humanetics Corporation.

DR. ZENK: Thanks. Five minutes left of the morning, so good morning.

I'd like to begin by thanking the agency for allowing me to be here and have some input into this very important subject. My name is John Zenk. I am a board-certified, licensed physician in Minnesota. My specialty is internal medicine. I also have a degree in pharmacy and actually was a practicing pharmacist before I started medical school. I'm currently the chief medical and scientific officer for Humanetics Corporation in Eden Prairie, Minnesota.

Humanetics is a privately held company that discovers, researches, develops, and commercializes new ingredients for the dietary supplement and drug industries. We have made a substantial investment in the research of our new dietary ingredients, and our company has more than 20 patents. Our current ingredients include 7-Keto DHEA, which is a metabolite of DHEA; D-Pinitol, which is a naturally occurring methyl inositol which comes from legumes and the heartwood of pine trees. We also have MicroLactin, which is a specially processed dairy protein, and I'd like to point out that the MicroLactin ingredient does not meet the definition of a new dietary ingredient.

Our direct investment in research associated with our ingredients is in excess of $10 million. Much of the investment has gone toward well-designed human clinical trials to establish safety and efficacy of our products. To date, more than 16 clinical trials have been performed on our ingredients.

When Humanetics made a decision to enter

the dietary supplement market, the company looked at the Dietary Supplement Health and Education Act and saw that our 7-Keto ingredient met the definition of a new dietary ingredient. With our first customer, General Nutrition Corporation, we notified the agency, as required by law, in May of 1997 prior to commercial sales of this ingredient. We appear to have been the 14th company to actually file a pre-market notification for a new dietary ingredient at that time. Our company has now filed or supported the filing of six new dietary ingredient notifications. Two of these were for our patented ingredient 7-Keto DHEA. Another was for our D-Pinitol ingredient for which we presently have three U.S. patents. Another was for D-ribose, and two were for a polyphenolic extract of the evening primrose plant. Four of these NDIs were filed by the agency without objection, and the new dietary ingredients were introduced to the market by our company.

As I mentioned, the company completed two NDI filings for the polyphenolic extract, and the

agency concluded that the ingredient was not shown by the data submitted to be reasonably expected to be safe for use in dietary supplements. Although we didn't agree with the assessment, out of respect for the agency and the provisions of DSHEA, neither Humanetics nor the New Zealand company that developed that ingredient introduced it for sale as a dietary ingredient in the United States.

DSHEA established the shape and the contour of the playing field for new dietary ingredients. The agency promulgated implementing regulations in September of 1997, and we have structured our business model for dietary ingredients around these regulations. As competitors in the marketplace, however, we are at a disadvantage because others ignore this important part of the law, and the agency has only once (in the case of androstenedione) invoked this part of the law in its ten-year history. Although we have followed the NDI provisions of DSHEA, we compete with many who do not. I am sure many of us in the room today are aware of ingredients that would be

considered new dietary ingredients for which no pre-market notification was filed. We are also aware of ingredients for which pre-market notifications were filed, subsequently objected to by the FDA, and the ingredients are sole on the market in the United States.

This public meeting appears to approach the new dietary ingredient provisions of the law as if they were just discovered and need to be explained. These provisions have been in the law since 1994. They became effective upon enactment. We are here today to express our opinion that the agency should focus its efforts on the enforcement of this most important aspect of DSHEA. We believe that it is a good provision, we support it, and we feel that it is critical for many reasons, including the most important reason of, to protect the safety of consumers.

Thank you again for allowing me to be here and provide this input. I'd be happy to entertain any questions.

DR. FRANKOS: Thank you.

DR. ZENK: Thank you.

DR. FRANKOS: Our next speaker is Paul Bolar, Vice President of Regulatory and Legal Affairs with Pharmavite.

MR. BOLAR: Good morning, with about one minute to spare. Someone mentioned to me earlier today that all these flashings of red and blue colors up on the screen are symptoms, after-symptoms of the election. Being in the Washington area, we're still undergoing some of the convulsions, I guess, the aftermath.

Pharmavite is a 33-year-old company based in Los Angeles, and we manufacture a broad line of vitamins, minerals, botanicals, and a wide range of other dietary ingredients. Our products are sold in food, drug, mass merchandise, and chain stores throughout the United States. I should mention that we have also submitted three NDI notices to the agency, so we're somewhat familiar with the process that we're discussing today.

We're pleased that FDA is taking steps to clarify the regulatory requirements related to new

dietary ingredients, and we support FDA's efforts to develop a more structured framework for the submission of NDI notifications. As a result of these efforts, we believe consumers will benefit from a higher assurance of product safety and responsible companies will benefit from operating on a more level playing field resulting from a clearer understanding of the requirements.

We will submit more detailed written comments to the docket on a variety of issues raised in the Federal Register notice, but for today I would like to specifically address three important issues related to this topic. I'll first address the types of changes that should influence whether an old ingredient should be considered as a new ingredient; secondly, the type of information that should be required in NDI notifications; and, finally, some points about enforcement.

With respect to the statute of new dietary ingredients, determining all of the variables that may impact whether a dietary ingredient is considered new is a difficult undertaken, and no

single answer will satisfy all situations. Furthermore, DSHEA does not clearly define the types of changes to a so-called old dietary ingredient that would result in a new dietary ingredient. Given the broad diversity of substances that potentially qualify as dietary ingredients and the wide range of possible effects that ingested substances may have on the human system, we believe it is better to err on the side of caution when determining whether an ingredient is a new ingredient and subject to the FDA notification requirements.

Therefore, we believe that in many situations changes to the chemical composition or structure of an old ingredient should cause the altered substance to become a new dietary ingredient. This would include modifications to existing ingredients that result in new salt forms, new esters, chelates, complexes, and other chemically modified or stabilized forms of old ingredients.

For example, and ignoring for the moment

whether or not an ingredient is old or new, zinc sulfate is markedly different from zinc chromate. Chromium chloride is significantly different from chromium picolinate. We think there are any number of other examples that could be cited where different salts and complexes and so forth may have different safety profiles associated with them.

This reasoning would also extend to old ingredients produced through new or unique manufacturing processes if the new processes result in significant alterations to the composition or chemical structure of the old ingredients. Additionally, botanical ingredients obtained from plants used in dietary supplements before 1994, but obtained from parts of the plant not previously used should be considered new dietary ingredients. In contrast, old ingredients that undergo changes in their manufacturing process that do not alter the chemical structure of the ingredients should not be considered new ingredients. Such changes may include the use of different synthetic pathways to achieve the same ingredient or the use of

different filtration or purification techniques, but may not necessarily alter the basic chemical structure of the dietary ingredient.

While we support a broad interpretation of what constitutes a new dietary ingredient, we feel it is equally important that requirements for NDI notifications should be sufficiently comprehensive but not overbearing. We believe that notifications should contain sufficient information to clearly characterize the substance in question. As a general rule, more information is always preferred. There was a whole series of possible types of information suggested and asked to have comments submitted on. We think as much information that can be provided certainly provides more certainty of what is being discussed. But at a minimum, notices should include a clear description of the chemical structure of an ingredient containing a single compound and provide a reasonably complete characterization or profile of major constituents for more complex substances, such as fatty acid complexes and botanical extracts.

Recommendations for conditions of use by the consumer and the amount of the new dietary ingredient contained in a proposed dietary supplement should be clearly stated in the notice. However, the formulation of the finished dietary supplement and copies of the actual labeling of the product should not be required because in many cases the formulations of labeling just simply have not been created at that point in time. We also feel that there needs to be flexibility in the manner in which new dietary ingredients may be combined with other ingredients, and it should not be a process wherein the use of a new dietary ingredient is locked into just one particular combination of ingredients.

The level of evidence needed to establish a reasonable expectation of safety should remain reasonable and flexible. For instance, the nature and amount of evidence sufficient to satisfy a reasonable expectation of safety may vary according to the degree of knowledge about the composition of the substance or whether the NDI is closely related

to other known substances with known characteristics. In cases where a modification to an old ingredient results in a new ingredient, required safety evidence should generally focus on the impact of the change in the new ingredient. We believe that appropriate data comparing the new form of ingredient to the existing ingredient generally should be sufficient for acceptance by FDA rather than the kind of data package needed for a completely new substance.

In order to reduce unnecessary burden on dietary supplement and dietary ingredient companies, we believe that FDA guidance should affirm that redundant NDI notices do not have to be submitted for ingredients for which another company has already submitted a satisfactory notice. This assumes that the ingredient is essentially identical to and used for the same conditions of use specified in previous filings. For example, while data submitted by the ingredient manufacturer covers those who use and distribute the substance in various dietary supplements, it should also be

made clear that a submission by one distributor of a dietary supplement also covers the same use by other distributors of the same substance whether or not in the same chain of distribution. However, this is not to say that one size fits all. Previous notice submissions should only be relied on if the levels of consumption and other conditions of use are consistent with the limitations specified in previous submissions. Where significant changes occur, new NDI notifications should be required for the new ingredient.

Now I'd like to turn lastly to the issue of enforcement, and I'll probably echo some of the sentiments already presented by Dr. Zenk.

We also believe that enforcement of the NDI notice provisions is an important issue for FDA to begin to address at this time. Consistent and evenly applied enforcement of the NDI requirements will be a key factor in creating meaningful guidelines and a level playing field for manufacturers of dietary ingredients and dietary

supplements. A number of products exist on the market today that contain new dietary ingredients for which NDI notices have not been filed. In some cases, the companies may either be ignorant of the notice requirements or they may have simply proceeded on the basis of liberal interpretations of the law. Unfortunately, there are others who are blatantly cutting corners and exploiting the lenient enforcement environment that we have today. These situations have resulted in an unfair playing field for companies that attempt to uphold their end of the bargain. As an example, Pharmavite recently considered an opportunity to market a supplement that included what we believe to be clearly a new dietary ingredient. Upon diligent review, we declined to market this product because we did not feel that there was sufficient data at this time to submit a satisfactory NDI notification. We are, therefore, pursuing additional studies to verify the safety of this ingredient. However, others in this industry, including major competitors, have chosen to market

this same product without filing an NDI notification. This obviously is putting us at a significant competitive disadvantage.

We urge FDA to establish reasonable guidelines for NDI notices and to institute enforcement measures as soon sa possible. Recognized that FDA has limited resources to police this situation, we suggest that FDA consider using an enforcement approach similar to the issuance of "Courtesy Letters" that are used for structure/function claims. Such letters have been used effectively to advise companies about FDA's interpretation of appropriate dietary supplement claims, and we believe that a similar approach could be effectively implemented to notify companies who have failed to meet their obligation to file NDI notices, without a large investment in time and resource by the agency.

Now, I recognize that there is a process by which FDA issues warning letters, but what I'm suggesting here is something a step back less--I guess less...

PARTICIPANT: Formal.

MR. BOLAR: Less formal, yes, than a warning letter.

In conclusion, I'd like to say that we believe it is in the long-term best interest of consumers and of responsible businesses to carefully review the safety of all dietary ingredients. We believe that a conservative approach is preferred when determining the status of new dietary ingredients. However, this should be balanced with reasonable and focused NDI notification requirement. Finally, efforts to enforce the NDI notice provisions will help assure broader compliance within the industry, promote a fairer markets environment, and ultimately assure the availability of safer products for consumers.

Thank you.

DR. FRANKOS: Any questions?

[No response.]

DR. FRANKOS: Thank you.

Let me just reiterate that it's very important that any comments or ideas you have get

submitted to the docket. The docket is the only place we can officially look at information, so please get your submissions in. Everything that is being discussed today will be documented, so part of the discussion here is also important to the deliberation.

Our next speaker is Willi Hunziker, and he is CEO for Morpho (ph).

DR. HUNZIKER: Okay. I guess I'm the first one in the afternoon, so good afternoon, everybody. I put my talk under the name "the Swiss perspective," and that has actually two reasons: first of all, I am Swiss, so my perspective is the Swiss perspective; but not only that, I also used to work for a long time for one of the big Swiss pharmaceutical and nutraceutical producers, and now I also run my own consulting business consulting for people in that area.

What I would like to present is a little bit an outside view and my personal view. If you just look at nutrition and health, a large body of evidence, as I'm sure you're aware, substantiates a

relation between nutrition and health. And the health benefits are the result of a continued ingestion of specific substances or combination of substances contained in the food chain or in related areas. And I'm mainly concentrating today on the food chain, and I'm mainly concentrating on pure substances derived from the food chain. So it's a subset of the whole thing.

The health benefits are mostly disease reduction, although there are others, but to a large extent, for example, cardiovascular risk, cancer risk, Alzheimer risk and so forth. And the nutraceuticals, how we call them, are the active ingredients that kind of provide those health benefits.

Now, looking from a public health point of view, the disease risk reduction at low cost is an attractive way to slow the continuous rise in health care costs of the aging population in the Western world, provided that these substances are safe and efficacious, I would say. The safety, first, the food chain is a positive selection of

substances having a low toxicity profile, either it's by selection or it's by co-evolution between the food chain and the human species. There is, thus, the history of safe human use of these substances at the exposure levels obtained by the respective food, and I stress the exposure levels because I think that's an important kind of criteria. And I think that's a good basis, this history of safe use is a good basis for assessing safety, but it might not be enough in all cases.

The efficacy should be substantiated by a mechanism of rationale, and all clinical studies and mechanisms of rationale can be, of course, rather broad, can go from in vitro studies looking at mechanism, can be in animal studies, and so forth. At the end, I think it would make sense to have authorized health claims that guide the consumer if we want to fulfill what I said about the public health of these products.

Now, what package would one want to have? From a scientist's point of view, I would say substance source and available data, the presence

in the human food chain, as I said, is a subset that I'm mainly dealing with, the documented evidence of safe human use, its documented evidence for efficacy, mechanistic plausibility and/or clinical data, and the safety profile of the substance.

The conditions of use, those should be guided by the level of chronic exposure and, again, plasma concentration via the respective diet, so we want to be in a similar range as with the respective food.

The target issue concentration reached by the respective diets, the safety profile of the substance, and the target organ concentration needed for efficacy, because if we want to have efficacy, of course, we need to have the concentrations required for efficacy at the target organs.

Now, from the industry point of view, it looks a little bit different. Establishing safety and efficacy data you might argue is fine, but how do we get investment back? And that point has

already been raised once before, because in the present situation, competitors can piggyback on established safety and efficacy data, and the tight patent protection is rarely possible for these kinds of products. So that also kind of invites competitors to come in. And that's why to a certain extent the industry shies away from making the necessary investment in safety and efficacy data.

So a proposal would be, as already mentioned before by coincidence, a time-limited marketing exclusivity for the first mover in the field, similar to, for example, in the drug area. The orphan drug, somebody who develops a drug for an orphan indication has market exclusivity for a certain period of time. Other possibilities would be prohibition of (?) piggybacking, altering brand-specific claims, and maybe other ideas, with the goal to kind of allow the first mover to get his investment back in the solid data that he has created.

Now, nutraceutical, as I said before, we

use for substances having a health benefit coming from the food chain. Regarding the DSHEA regulation, they can fall in two categories, the dietary ingredients or the new dietary ingredients, as was discussed before.

A question that came up is when does a dietary ingredient become a new dietary ingredient, and I would say by a significant change in the conditions of use leading to an increase in exposure. So if the human body is exposed to a much higher degree by the new conditions of use than the old one, I think then that warrants--because of safety consideration warrants a new dietary ingredient status. And, of course, also the safety profile, if it's a critical substance, then smaller increases in exposure might already trigger that. Or by a significant chemical modification of the dietary ingredient, and there I see a little bit more from the liberal side that modifications, chemical modifications, for example, esters and so forth, which are readily cleaved on ingestion, they should not necessarily be

considered as a new dietary ingredient; whereas other chemical modifications which are not readily cleaved or even lead to different metabolites in the body, of course, those should be looked at more carefully.

What information on the chemical nature of the NDI should be provided? Of course, origin, extract, raw, enriched, purified, fermented, chemically synthesized, chemical name of the efficacious molecule, as I said before. My interest is mainly in the purified chemicals, so the impurity profile will only be a few percent in the normal case, at max.

In the case of non-single compound NDI, one would have to look at the standardization question, the dose content of the efficacious molecule, provide evidence on the role of the other molecules in the mixture, what they contribute to the effect in the body, and the stability of the compound in the (?)-enic form and the bioavailability in humans.

Now, another question is: What is an

acceptable ratio of the intended dose to the dietary intake? If we assume that the safe human use of an NDI is documented by food-based exposure data on, again, plasma levels, because depending on the formulation with the same milligram amount of compound, you get highly different exposure levels, and additional pre-clinical tox and clinical safety data is available, like single ascending dose in humans or multiple ascending dose, then the dietary intake of the population with the highest safe beneficial intake should be used as a basis to define the intended dose so that kind of sets the bar. And depending on the data situation, the bar can be raised, also the situation if you need higher levels for efficacy, the bars can be raised to even higher than three-fold if supported by additional safety data. But the recommended dose at the end must be at least a small multiple below the safe upper limit of the dietary ingredient.

So quite a few times it was discussed what is an adequate safety evidence, and I think that safety is a must for nutraceuticals, provided that

for food chain compounds there is evidence for a beneficial effect and it has a wide safety window. I think, on the other hand, it should be approvable a NDI.

So what specific type of safety data would I suggest? I think to know the fate of the molecule in the mammalian species, I would like to have an ADME started. That means an absorption, distribution, metabolism, excretion study in rats, normally done with C14-labeled nutraceutical, a 13-week oral tox in rats, then developmental tox, teratogenicity studies in rats, and tension of toxicity tests like the Ames test or a mouse lymphoma test. That would be a first package to look at the safety to get some indication if there is a problem somewhere and at what dose.

And then depending on the outcome of the first set of studies would be additional studies if required, and here it would help to have guidance from the agency kind of like a decision tree to say, okay, if you have a problem in that assay, then you might have to do this additional kind of

study. For example, a 52-week toxicity study in rats, two-generation study in rats. Standard carcinogenicity study, we kind of consider overkill. We would rather see a SHE assay done. That's the Syrian hamster embryonic cell assay, which shows actually a good correlation in the data to the standard carcinogenicity assay. And as I said before, we would like to have some guidance on what to do if one of the tests shows positive effects.

Now, another thing is safety factors. In the food additive, it's clearly stated that the safety factor of 100 is applied for estimation of an upper safe level in humans from the no observed adverse effect level found in rodent studies. We think that this factor cannot be transformed into the nutraceutical area because the food additives are new to the human body, the human body was never exposed to them; whereas, the nutraceuticals you have a history of safe human use over centuries and centuries. So I don't think that they should be treated the same way.

So the proposal is to have no standard safety factor. I'm not saying no safety factor, but no standard safety factor. The upper safe dose is derived from pharmacokinetic data in both humans and rodents, plus data from rodent tox studies, also considered the exposure needed to have the desired efficacy. And from that data compiled should allow to determine an upper safe dose, which in humans leads to plasma levels not exceeding the no adverse effect level observed in the rodent tox studies. The intended dose should then be a multiple below that level, for example, three times below the upper safe level, and it should also, of course, allow for the desired effect.

I maybe will just skip that one in regard to the time. So, in summary, nutraceuticals can provide the risk reduction for disease. Thus, they may sense from a public health point of view. They must be safe in the recommended dose as evidenced by appropriate safety data. Efficacy should be evidenced by a mechanistic plausibility and/or clinical data serving as a basis for honest claims,

and I would kind of stress the term "honest claims."

Legislation together with the industry has to find ways that allow the first mover to protect his investment in safety and efficacy.

Thank you.

DR. FRANKOS: Thank you.

Any questions?

[No response.]

DR. FRANKOS: Well, thank you. That brings us to the end of our meeting, and I just have a few comments. I'm absolutely thrilled at the kind of dialogue we've started here, and I hope that we can continue more of this dialogue. As a lot of you alluded to, there are quite a few questions that are in the Federal Register notice. Those questions were put together because there is a lot that's still to be done as far as coming up with more consistency in the NDI process.

I encourage you each to address those questions individually. Today we had a lot of general discussion, but I think it's important that

we get direct answers to the questions we've presented.

As far as timeline goes, we'll wait to hear about extending the comment period, but we've heard quite a few suggestions here as to why we might want to extend it. And I don't know about this last suggestion about going to six months, but we will--I don't think that's been officially submitted yet.

The other thing that I'm very hopeful about is this whole idea of continued dialogue. I've heard quite a few commenters indicate that more dialogue is needed, and I would have to agree with that, and I'm looking forward to more meetings. We may have to look at more specific questions based on the comments that we get.

So I'd like to thank everyone. It was really a very good meeting for me and for our panel. I'm sure each of us has learned something today.

So we're finished. Have a great lunch.

[Applause.]

[Whereupon, at 12:31 p.m., the meeting was adjourned.]

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