ORIGINAL

FOOD ADVISORY COMMITTEE MEETING

PUBLIC AGENDA

300 Army Navy Drive

Arlington, Virginia

February 12, 1998

P A R T I C I P A N T S

DR. EDWARD N. BRANDT, Chairman
DR. RHONA APPLEBAUM
DR. E. WAYNE ASKEW
DR. STEPHEN H. BENEDICT
DR. BRUCE M. CHASSY
DR. KATHERINE L. CLANCY
DR. FERGUS M. CLYDESDALE
DR. OWEN R. FENNEMA
DR. NAOMI K. FUKAGAWA
DR. SUSAN K. HARLANDER
DR. ROBERT W. KATZ
DR. LYNN A. LARSEN
MR. JOSEPH A. LEVITT
DR. DONNA R. RICHARDSON
DR. PATRICIA RODIER
DR. MARY Y. WANG

C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

DR. BRANDT: Time to begin. If everybody would be seated, please.

Welcome this morning. I hope everybody got rest last night. I have the distinct honor of giving the administrative announcements today instead of Dr. Larsen. He delegated to me.

We should finish this committee meeting at the latest by noon. As a matter of fact, I'm leaving at a quarter till twelve, so.

The Keystone working groups will meet this afternoon. There are rooms, and later on, Dr. Larsen will tell you where. If you wish to stay overnight before you go back, that's fine. The rooms are reserved. If you're not going to stay overnight, but are going to attend this afternoon's working group, then please notify Sylvia Washington, who's manning the desk (or personing the

desk) out there at the front so that she can help you with flights and so forth and so on. So, that's pretty much it at the moment, although Dr. Larsen has a whole bunch of stuff, but that's coming up at 11:00.

So, any questions or comments from anybody on the committee? Okay, seeing and hearing none, why, we will proceed.

Our first presentation is from Mr. Duane Fimreite, from the University of Illinois Functional Foods for Health Program. Welcome, and thank you for coming.

MR. FIMREITE: Thank you for the invitation to come.

DR. BRANDT: Oooh.

MR. FIMREITE: I don't think we need the lights down that low. I can't read my notes that way.

DR. BRANDT: He can't read his notes. We'll try to give you some light. Let there be light. Here it comes, looks like. They've just got to figure out how

many people it takes to turn on the lights. There we go. Okay.

MR. FIMREITE: Okay, good morning. I was asked to come here because the Functional Foods for Health Program sponsored a workshop called Developing Incentives for New Functional Foods. My presentation today is going to cover four aspects. First I'm going to tell you a little bit about what the Functional Foods for Health Program is and what we're about, then go into a little bit of background why we held this workshop, and finally, the third point is to give you the highlights of the workshop. And I'll finish up with telling you what direction we're going to take and our next steps.

The Functional Foods for Health Program is a joint program between the Medical Complex at the University of Illinois at Chicago and the Land Grant University of Illinois at Urbana-Champaign. We have participating faculty from over 30 academic

units ranging from pharmacognosy, to surgery, to the dental school at UIC and ranging from crop science, to food science and human nutrition, to marketing at Urbana-Champaign.

We are the nation's first and only full-scale scientific program devoted to the study of phytochemicals and other functional components. Our mission is to improve human health through research and education by identifying food components and developing food products that have health-promoting benefits.

The next six slides will be a list of our industrial affiliates, and I'm going to read them relatively quickly. ADM Bear; Burns, Philips. We have two commodity boards: The California Almond Board and the California Prune Board. Cargil, Con Agra, General Mills, Hershey's, Kellog's, Kraft Foods, Mead, Johnson, McCormick, McNeil Specialty and Consumer Products, Monsanto, Nestle, Protein Technologies International,

Reliv and Roche, Sunstar, Warner Lambert and Welch Foods. And we have one academic affiliate, and that is the National College of Chiropractics.

The Surgeon General's report on nutrition and health states that diet has been implicated in six of the ten leading causes of death in the United States. Our program wants to gain a better understanding of this relationship of diet and health, and we believe that industry is our partner in this relationship, and it is with good science that we will grow this emerging field of functional foods.

This is just the cover page from our workshop brochure. The Functional Foods for Health Program held a forum for our industrial affiliates to discuss incentives. The title again was Developing Incentives for New Functional Foods.

We had two objectives for this workshop. Day 1 we wanted to define and

refine the issues around the topic of incentives for the development of functional foods and incentives for research into functional foods. Day 2 of our objective was to develop an implementation strategy or a consensus statement. Unfortunately, on Day 2 we ended up with more questions than answers, and we ended up putting together a outline for further discussion and an action list of homework assignments, and I will get into those a little bit later in my presentation.

I want to emphasize that the participants in this workshop represented industries, the package-goods' industries, the supplements' industries, ingredient suppliers ranging from grains to spices. And the field of expertise that was represented at this workshop ranged from regulatory affairs, product development, marketing business development and policy making.

The reason for this workshop is that we wanted to continue a regulatory

workshop that we held in 1995. At that time, market exclusivity had come up, so we wanted to further those discussions. Also, the Keystone dialogue had an impact of why we put this workshop on. We wanted to continue the discussions from Chapter 6 of the Keystone dialogue. And then the final reason for the industrial affiliates wanting this workshop was that they wanted more information and a better understanding of the process that Quaker Oats went through in their first food-specific health claim brought to the FDA by a food company.

So, to further expand on the purpose, we wanted to further explore the whole concept and idea of exclusivity, but I think furthermore, we really wanted to gain a better understanding of what is an incentive and what could incentives possibly do for us. And that's where the focus of the workshop really went.

And I think everyone at this

workshop wanted to end up in a win-win-win-win situation in which the consumers are provided with better information to make better food choices.

Government is given the opportunity to reduce their health care costs. Industry has new product news to talk about. And the university systems have more research dollars.

Now I'm going to go to the highlights aspect of this workshop, and the people that presented on the first day. We started out with Melanie Fairchild who started us out by summarizing Chapter 6 of the Keystone dialogue, and she wanted to encourage us to think beyond just the Keystone dialogue and think outside the box in trying to create other ideas for incentives.

Constance Geiger next spoke on economic impact with the use of health claims, and what Constance talked about was

the Quaker Oats' health claim. She took us through the petition process, talked a little bit about the consumer research they did on the wording of the health plan, and, finally, gave us a little bit of a perspective of how they're doing in the market place with their health claim and how their sales are doing.

Martin Star took the opposite approach and gave us the economic impacts without the use of health claims, and he gave us a grass roots approach to how Ocean Spray took the message out about cranberries and urinary tract health and emphasized that what they were doing was they were gaining case sales, but not necessarily market share with that strategy.

Next in our presentation, we had Steve McNamara talk about the current regulatory environment. He talked a little bit about health claims and structure function claims and what other possibilities were currently out there within the current

regulatory environment.

Nancy Childs gave us a marketing and business perspective of the incentives that were in Chapter 6 of the Keystone dialogue, and Peter Barton Hutt took us through how to get action from FDA, FTC, and Congress. He basically took us through a process of how to create change within these agencies.

We had Norman Farnsworth give us an overview of how the dietary supplement policy was evolving. Dr. Farnsworth, with USC and the Functional Foods for Health Program, was on the Presidential Commission for that policy.

And then finally, Ellen Sullivan, on very short notice, from the Institute of Food Technologists, was good enough to come over and give us an overview of how the working group was doing and how they were coming along in the process that they were making.

As I stated earlier, we did construct an outline, and this outline is of possible incentives for either further discussion, or areas that needed further investigation, or that we felt needed further investigation. These items were not necessarily agreed upon as being on this list; they were just agreed upon that they needed further investigation.

The first category we listed under Requires Legislative Action or FDA Policy Change. The three keys are incentives to increase functional foods research, the reduction in current requirements, and, finally, education. I'm going to expand a little bit further on each of these.

The incentives to increase functional foods research, we felt, belonged in four different categories. The first is Market Protection, and under Market Protection we felt Market Exclusivity, Data Compensation, and Royalties fit under this.

There was, obviously, slight discussion that went on about each of these, but because we're not agreed upon, I'm just going to list our whole action list out here, or our outline out.

So next was Tax Reductions, which could either be deductions or credits; Patent Term Restoration, and that was about the current law and what it states; and then Government Funding is the last under incentives.

The next key under the Requires Legislative Action or FDA Policy Change is Reduction in Current Requirements. Under this we felt that the substitution of Pre-Market Notification for Pre-Market Approval could be an incentive. The Elimination of Model Claims, to create some flexibility; change the Significant Scientific Agreement standard; modify the definition of food and nutritive value; and change the definition of health claims.

The final key is Education, and I think the concept around Education was to try to increase consumer demand. So within Education, we listed trying to find government agencies or grants to help in this process.

The next bullet point does not require legislative action; so these are the things that would not require legislative action, but FDA could still have an influence in. The first one is Current Incentives, and I'm going to expand a little bit further on that and then go back to the rest of the list. Within Current Incentives, we felt that Tax Reduction, Grants, Research Pools, Patents -- and under Patents, Use Patent and Formulation Patents fit best.

Now going back to the list, and we have worked with you guys, the FDA Advisory Committee on Policy Changes would be one process of non-legislative action. Broaden the definition of food using the new

legislation, and that is using authoritative bodies. Narrow the definition of health plans by the use of a court case, and I believe they identified a court case that was going on in New York that might be an example of this going on currently. And, finally, build a mechanism for significant consensus outside the FDA.

So that is the outline that we put together. Now the question is, where do we go from here? The first depends on what I learn today at these meetings, what I learn this afternoon at the Incentives Working Group. We are very interested in working with other industry groups as well as the Incentives Working Group on furthering this effort of trying to find an incentive for further research into functional foods.

Second, we did compile an action list, and this action list is our homework assignments. And, of course, the action list you're going to see follows closely to the

outline that I put up. People were assigned to either write a paragraph or find an expert on each of these topics. They are Market Exclusivity, Data Compensation, Royalties, Patent Term Restoration, and that's the current law, Tax Deduction/Tax Credit, redefine the definition of food, redefine the definition of a health claim.

To continue on that, define what significant consensus is, gather a list of government agencies that could help provide funding, someone who's going to take on patents, and what could be done with the current law to create incentives that we hadn't really looked into yet. And then everyone's assignment was to find other groups that were working on this issue.

This action list is the homework, and at our next meeting, we will share the results with each other and broaden this discussion, because we will have more of our affiliates actually in attendance.

Hopefully, all of our affiliates will be in attendance at our annual retreat. Unfortunately, our next meeting, which is the annual retreat May 13th, is a closed meeting. It's only open to our industrial affiliates and our faculty members.

Where we want to get to is we want a collective opinion of the industrial affiliates of the Functional Foods for Health Program that can either be presented back to the Food Advisory Committee of the FDA or that can published as an opinion for public record. We believe that our work is not done. We believe that the FDA can create policy to increase incentives for further research and the relationship of diet and health.

So in summary, our program believes that human health can be improved, that good science will provide the consumers with credible information to make sound food choices.

Currently, industry is not heavily pursuing the type of scientific research that could lead to health claims. One of our affiliates actually stated that this research will not be done unless we have incentives. As a group (I'm sorry, here), we're not sure what this incentive is. We do believe that there should be incentives, and that we agree upon that, we do want to emphasize the relationship of diet, and health and human health. Thank you.

DR. BRANDT: Thank you very much. Are there questions from the committee? Yes, Dr. Benedict.

DR. BENEDICT: A couple of things. In your presentation toward the end, you mentioned in the single, one-line thing.

DR. BRANDT: Yeah, I got that, yeah.

DR. BENEDICT: You want to change the significant scientific agreement standard, and you've mentioned several times

you're enthusiastically in favor of good science, and I'm wondering how you reconcile these two statements?

MR. FIMREITE: Again, we don't necessarily have agreement with everything that went up on this list. What we wanted was further discussion, and I know that there are groups working on individual aspects, and I think there is a group working on that significant scientific consensus or agreement statement, but it is something that we felt as a group we needed better understanding of before we could really truly pick out or say this is the incentive we want to follow.

DR. BENEDICT: So you would argue that there would be something less than significant agreement that would be possible and not allow anarchy?

MR. FIMREITE: I can't answer that question.

DR. BENEDICT: Well, what about the mechanism for consensus outside the FDA, that

one-liner that you had on that other slide? What does that mean?

MR. FIMREITE: There was very little discussion around that, other than that at least one person in our group wanted to consider that a little bit further. What we could do with trying to gather a consensus of industry and consumers is take that consensus outside and gain some momentum that FDA would take notice of.

DR. BRANDT: Dr. Askew.

DR. ASKEW: Along those same lines over here, which was to investigate changing the definition of a health claim, what did you have in mind there? It's something we've been dealing with, and we'd be interested in knowing what you are talking about.

MR. FIMREITE: Again, the discussion wasn't very in-depth on that. I think where that conversation came up and went to was that Constance Geiger presented to us on what Quaker Oats had done with their

health claim and the wording of their health claim, and I think from an industry standpoint, they just wanted a little more flexibility in wording of the health claims. So, I think it was just looking for more flexibility.

DR. ASKEW: Just one further question, if I may, please. With regard to incentives under Market Protection, you mentioned data compensation. What do you mean by data compensation?

It brings to mind paying someone to do research and give their data to the company; is that right?

MR. FIMREITE: Yes, I think the concept there was that because if you petition the FDA for a health claim, your research becomes public knowledge, that one way of creating an incentive would be that public research is not for free use, that there is some sort of fee for use if you're going to use that data in your health claim.

And, again, this is just discussion that we had as well.

DR. ASKEW: Interesting concept.

DR. BRANDT: Ms. Richardson.

MS. RICHARDSON: I noticed at the end you mentioned that one of the participants had said that without incentives, the research would not be done. Is that just one person speaking, or was there a consensus?

MR. FIMREITE: That is one person, and I put that in there because it's just one person's opinion. It was not a collective opinion. At this workshop, there were other people -- it wasn't just one -- there were other people that believe that, and the affiliates that have aligned themselves with our program and have membership in our program have an interest in this area of functional foods and this area of diet and health, and they are interested in doing product development in that area and believe

that within it, there must be good science. But what they're afraid of is that if they do all the work, someone else is going to be able to take all that work, and they're not going to get any return on their investment.

Constance Geiger gave us one example of that in her presentation where Quaker Oats went and petitioned FDA for the Oats' claim, General Mills has it on all six sides of the packaging of the Cheerios' box. So industry is just trying to say, we just want to see a return on our investment of these research dollars.

DR. BRANDT: Yes, ma am.

DR. BENEDICT: When talking about the tax reductions, did anyone bring forth any examples of what they would see as changes in the tax law?

MR. FIMREITE: That is one where the concept got brought up, and immediately it was, like, we do not have any tax lawyers here.

DR. BENEDICT: We've heard that before.

MR. FIMREITE: We don't know the rules, so therefore that's why it went on our action list. We're going to try to bring our tax lawyer to expand on that issue.

DR. BRANDT: Okay, thank you very much for being with us, and let's now turn to our good friend Dr. Lewis, who wants to do something, I'm not sure what.

DR. LEWIS: I'm always doing something. I just wanted to take a few minutes to tie things together. We've had to spread these presentations out over two days, and I think sometimes things get a little discordant, and I wanted to talk a bit more about the focus. We will continue in a few minutes with the GMP issues for dietary supplements. But, on behalf of the Center, and particularly on behalf of the Office of Special Nutritionals, which has worked with Dr. Larsen to pull together the presentations

that you're seeing today and did see yesterday, I wanted to take just a few seconds to respond to some concerns and questions that were raised late yesterday.

I think, first, we need to be very clear about what we're asking the committee to consider, and we are focusing specifically on strategies for consumer research for dietary supplements, on improving and collaborating, relative to post-marketing surveillance, and then in particular on two naughty issues relative to GMPs who are not, for example, asking that the committee consider alternatives for post-marketing surveillance. We're asking, rather, what is there can be improved? So we want to focus very specific.

I think it's also important to note that we believe that valuable time not be used to reexamine DSHEA. The agency wants to be responsive to the White Commission Report, and we want to take the opportunity to

establish GMPs as provided by DSHEA, and that really is the focus we're asking that you folks take a look at.

Secondly to that, there's been some interest in the expertise needed by these working groups that we will establish to take a look at these three issues. And in particular, because of the emphasis on collaboration with the industry, there's been some discussion about a need for a type of expertise, perhaps by ---- that would perhaps not necessarily be from industry, but that would have ways of making a liaison. Some of the trade associations have indicated that they could identify for us this kind of expertise, but I want to open it up and re-ensure the committee that the expertise that you need probably is fairly wide and broad, and that we do want to be very, very responsive to that need.

So, the those were a couple of concerns I heard yesterday that I thought

before we proceed we might just put on the table. I think it's important to come back and revisit all of this, but I would like to move on the GMPs, and particularly a very interesting presentation that we have next.

DR. BRANDT: I talked to both Dr. Tetley and Dr. Larson to tell them to begin to identify some of the special expertise that we will need. We are going to be forming new working groups as soon as we get this Keystone stuff out of the way. That will deal specifically with the three issues on dietary supplements. Those will be augmented by others, or we will at least have them participate in the deliberations of the working group.

Okay, we move on. Dr. William Obermeyer. Yesterday you received a copy of his slides.

DR. OBERMEYER: Good morning. Thank you for the nice preface here and coming back to GMPs. Today the topic for

this discussion really is chemistry. I know everybody loves chemistry, but we're back to it and how we can use identity, especially in the botanicals, since it is a major part of the dietary supplements to help the GMPs.

This slide could have been named, or titled, The Past of Dietary Supplements or Botanicals, because we really see it as a cyclic event that botanicals come into, if you want to call them, fads, time and time again. I'm a trained pharmacognisist, and we have another one at the agency; we were actually trained in this. This is a very classic science, and so I'm just really excited that we can do what we were really trained to do in a real profession. And it's very interesting.

One of the many concerns, though, in the identity is to ensure the public that they're going to receive a safe product, that they will get a commodity off the shelf and they can expect to receive a safe product.

So the main emphasis for good manufacturing practices is to assure the consumers that they're provided with a safe dietary supplement, products that are not adulterated or misbranded, which have the identity and provide the quality of dietary ingredients declared in the labeling and meet the quality specifications that the supplement is representing. That was something that I thought was a very good statement in a nutshell of what GMPs and identity were all about.

The practical approach to meet the GMP objectives is basically what the topic is today. As we were trained as pharmacognosists, we basically used applied science to provide a systematic check along the way for basically raw materials to finished products and the botanicals. And these are similar to standards and approaches that are already established out there by the World Health Organization, German Monographs,

Canada, and things like that. They had GMPs already set up, and these are very similar to that. But unfortunately, we do not have them as of yet in the United States as a real rule.

So, the topics today will be identification, basically, raw materials all the way to a finished product; what a certificate of analysis is; adulteration, and how a monograph could help standardize things, which would even enhance post-market surveillance.

Somewhat fundamental is we need to collect the raw material, and first off, we need to make sure that we have properly identified the botanical that we are collecting. It seems pretty basic but we've seen difficulties in this area because they sometimes used untrained collectors. We have to remember that we are dealing with imports and domestic botanicals. So a lot of these people are just going out collecting, and

they're not trained. They use the common names that aren't Latin binomials that would really distinguish a plant, and sometimes a common name here is different than in another country, and so there could be problems there.

Also, many times voucher specimens are not collected, which, to a systematic botanist, is the key to identifying a whole plant and what was collected. And these types of specimens actually should be collected for every lot that is out there. Sometimes there's mixing of batches and lots together to form one larger bulk commodity.

And the other thing that I didn't put on here, which I thought of later, was the reserve sample for every one of these lots that are collected should be kept to basically identify these products later if there is a problem.

Testing. Testing is a large group here. We have everything from the

organoleptic, which is a sensory evaluation, generally taste, smell, sight. This is used quite often, and I think it's of limited value because you have to be specifically trained in this area, and you would really only see a representative small amount of basically the 550 to approximately 3000 plants -- that's a conservative estimate -- that are being used out there.

Later Stanley Cichowicz will speak about the microscopy, how to use microscopy as a tool for identifying these botanicals. I'll be discussing different aspects of chemical analysis and, generally, that all these more or less can be performed on the raw commodity extracts of those, or the finished product, or anywhere along the way.

The botanical constituents. We categorized these in three broad ranges. The active ingredients are a known principal, and these are very few, like I said, of the 550 to 3000 plants or parts that are out there.

Very few have known active principals in there.

The second, with actually a lot more, are unknown active components in there, but there are some known marker chemical constituents in there that can be used to help quantitate or qualitatively measure these constituents. And most of the plants have unknown constituents in activity, and based on a pattern recognition, which you would see on thin-layer chromatography or things like that, that you would have a general idea of quality.

So here we have some chemical tests that can be used in conjunction with organoleptic microscopy, whatever.

The first test is a color test, and this is pretty much a qualitative, and it tells you whether the chemical is there or not, and it just is a color reaction and may form just pink or whatever.

Gravimetric is a weight, if you

would, maybe you extract alkaloids and then want to weigh it.

Titration, again, could be for any acid or basic moiety to use a color indicator and get a total look at the active constituents, UVs, spectrophotometric, maybe with the cavalactones as there's a whole extract, or St. John's Wart for hiperisin, pseudo-hiperisin, things like that.

And then we get down to sometimes quantitative or even qualitative, the thin-layer chromatography where we actually separate some of the chemical components. Gas chromatography, again, can separate the components. We can also use these for pattern recognition and liquid chromatography. And generally the last two would be combined with maybe maspec to do a confirmation of the identity's constituents.

Certificates of analysis. These are things that are coming up right now, and these generally identify the plant with

physical characteristics, ash content, dry weight, moisture content. They also have chemical constituents in their tests, and hopefully, they're using a validated method. Many times these are not validated and ---- i.e., they would be consistent from one laboratory to the next. Again, trying to get some sort of standardization. And whether these laboratories that are doing the testing are actually credited or not, these are all very important again. So, all the correction factors and analytical chemistry could be applied, and all the constituents then would be more uniform.

Botanical monographs. These are another very important tool in the herbs, and again, this is really a condensed literature search of the collection. When is the proper time to collect the plant? How you would process it, because the processing can reduce or diminish the active component? And basically, how you would identify the plant.

Again, these monographs then would have standard ---- methods included with them, so everybody would be testing the same type plant the same way so all the values are the same.

And how to do a proper extract. We have different ways to do extracts, and these are ways to do it. For example, this would standardize ginger so that if we had ginger in California as a commodity, it would fit within the chemical requirements and specifications listed in the monograph, and it would be the same as another commodity on the east coast, et cetera. And again, this would help in the post-market surveillance so that we start to increase standardization of these products.

The identity of active constituents from various plants. Again, monographs are very helpful to indicate what type of extraction process would give you the active components. Sometimes they're not given, and

in GMPs we'd like to be able to see what types of solvents they'd be using, because this identifies what constituents would be in the plant. Extraction process also depends on efficiency, and that would be similar to extracting coffee or something like that that you'd be familiar with, but a finely ground plant would be more efficient in some instances than, let's say, a whole coffee bean. You would get more of your caffeine out of it or taste quality.

Other issues associated with identity are basically adulteration. Addition or accidental substitution of other commodities in here, deliberate addition of that. Poisonous or deleterious substances, I'll be giving an example of this at the end. ---- Pesticide residue and economic adulteration. Types of economic adulteration, putting a cheaper component in for a more expensive one. Another is substandard substitution of material and also

removing a constituent of value. I think Stanley will speak of this, but this is removing the ginsenocides out of ginseng, basically, leaving what would be the sawdust.

And that is it, really, a very quick overview of this. There is much more to this; anymore would be boring, probably.

DR. BRANDT: Are you ready for Mr. Cichowicz?

DR. OBERMEYER: Yes, thank you, sir.

DR. BRANDT: Hang around, because we'll ask questions after.

DR. OBERMEYER: Right. I have another presentation right after this.

DR. BRANDT: Huh?

DR. OBERMEYER: There's one more presentation after this.

DR. BRANDT: Oh, okay, fine. So you are going to hang around.

MR. CICHOWICZ: Can we have the lights, please? I'm Stanley Cichowicz. I

work for the Food and Drug Administration. I've been a light microscopist for about 26 years now, and I want to talk a little bit about light microscopy. And this is a detailed drawing from an old book, turn of the century. Almost a hundred years ago now, people devoted their lives to doing these drawings, and they were using light microscopes to do the work. Most of us here know what a microscope is. We've all, one time or another, tried to look into a microscope. And these people spent their lives doing these drawings, and the only problem with it is that they stopped in 1930s, and I don't know why. I guess it fell into disfavor, and a lot of people today like to think that the microscope is an old fashion tool and doesn't have a lot of use. I'm here to sell light microscopy and what it can do.

These books are not available any more. You can't go out and find these

leather-bound volumes. If you could pay for them, you can't find them. They're not available. And they're limited to a few hundred European/North American herbs. So this is not there. The literature isn't there. And you need this literature when you get into the laboratory and you want to look at something that's ground up. It's nice to have a book, a picture there done by someone who's looked at it before, and then you look at your reference specimen, and then you look at your unknown.

My background is partly from forensic microscopy. The microscope never left the forensic laboratory. We've all seen Quincy or some medical examiner solve a case in half an hour or an hour on television using a microscope looking at fibers. We've seen a lot of court cases recently where they're talking about trace evidence. And there's a body of microscopic methods in the trace evidence in the forensic community.

They've been using the microscope for years. And McCrone Institute in Chicago almost by themselves have been carrying the torch for microscopy when it was really going down in the 70s. You know, everybody's coming out of school, and they wanted to do chemistry. And when I graduated from Ohio State as a botanist, I was a chemist more than a botanist. I didn't know an oak tree from a maple tree, and that's maybe not the university's fault; maybe it's mine. We didn't use microscopes very much. We were using chemistry all the time. And this is one of the fewest places in the country where they're still doing some microscopic teachings, at McCrone Institute in Chicago, and they specialize in polarized light microscopy. And that's what they use in the forensic community.

I got an old slide here that I wanted to look old. I distressed it a little bit to make it look even older. But I just

want you to see that there are some trace evidence categories that compare with ground botanical products. We trace evidence people are looking at botanical materials, papers, fiber, wood. That's what you see when you grind up any kind of a plant. You see fibers. You see cell material. There's a lot of similarity here.

Some people carry pictures of their kids in their wallet. This is my laboratory. It took me 25 years to put this together the way I wanted it.

This is what I call the latest technology in polarizing microscopes, which are much more affordable now than they were in the 60s, and the latest computer digital imaging, high resolution digital imaging.

This project started a few years ago. I came back from the forensic laboratory, Bureau of Engraving and Printing, and started setting up this laboratory. And the bosses are saying, well, you got all

these pretty toys now; what are you going to do with them? Show us what you can do with them. And so this is an evolution of show and tell. We're using television cameras for training microscopists. And we're using digital imaging to capture images.

This is a garlic, a mass of garlic cells with some crystals in them with bright field illumination. This is what most of us are looking at through the microscope. We see a bright light. Sometimes it's too bright; sometimes it's not bright enough. We see some pretty much non-colored material. You run it through a polarizing microscope, all of a sudden you have color differences. If you take a pair of polarized sunglasses and cross the lenses together, you'll see the light goes dark. And you put any kind of crystalline material or any kind of complex organic material between those polarizing filters, and it'll rotate the light, and it'll rotate it different amounts, and it

gives you different colors.

And that's what polarized light microscopy is. You're getting different colors, and you're using the colors to help see things in a microscope. You don't have to use stains. All my preparations virtually are wet, quick and dirty. You mix up something, put it on a microscope slide with a drop of alcohol, a drop of water, and then put it between the cross polars on the microscope.

We started a manual two years ago. And this manual was full of images and with instructions for people. One of the important things here is diagnostic features of ground-up material.

We look at a couple of house flies on the railing on the back porch, and they look pretty much alike. I don't know how houseflies can tell each other apart, but they obviously can. They're used to looking at each other closely.

If we look at plant material closely with a microscope and start studying it, we start seeing differences that were not particularly obvious when we started. If you throw a bunch of ground plant material in front of somebody in a microscope, man, they're just going to scratch their head and say, yeah, it's a bunch of ground-up stuff that all looks alike. Well, ---- spend some time looking at it.

I'm going to go through just some diagnostic features of brown plant material to give you an idea of some of the images we're generating in the laboratory in this manual. It's going to be used as a training manual.

You have resins in cells, and sometimes the color differences suddenly look different. This happens to be a bright field of some ---- cells. Remember garlic cells under cross polars. The colors are beautiful here, by the way. I hope most of you can see

them. Eh, a little dark here in image. We have bast ring, and these bast rings -- you don't see them very often, but this is *Glycyrrhiza* from licorice. When you see these bast rings, they're supposed to ring little bells in your mind.

I'm going to go through these. Here's some resin that's broken up. These look like glass fragments. This resin must be hard. This is from [INAUDIBLE] berries, fruit ---- coating of the berry, of the seed. The resin breaks up and looks colloidal fracture-like, and this would be characteristic of a resin. It's hard. It doesn't dissolve easily. And when it breaks up, it breaks up like a piece of glass.

Here's some crystals laying on a vein from a leaf. But the crystals are deposited on the outside of the vein. You can zero in on these crystals and look at size, shapes, all kinds of measurements on them.

Okay, stomata, stomates from a leaf. They have patterns. The stomate cells, when you look at them, each particular species of plant or group of plants can have different characteristic stomata, different crystals, or maybe no crystals at all. There's differences here.

Vascular tissue. The vessels in the plants. They've got pores in them. And you're seeing some of the pores in an echinacea vascular bundle. Starch grains. There are lots of starch grains. You can spend the whole day in here just talking about starch grains and how they look. These look like, God, I don't know whether they look soccer balls or ---- balls or something. These starch grains looked a lot different in cava cava. I've never seen starch grains quite like this before.

And valerian with sand in it. Sand jumps out at you. This is supposed to be a contaminant. This was supposed to be, well,

it's a root, and we ground it in the laboratory, and sometimes the roots don't get washed off too often. I didn't wash the root off. Didn't think too much about it. So all of a sudden we had a lot of sand in this group when we ground it. And this is a typical sand ---- and they jump out under polarizing microscopy, another cross polars.

I'm going to pass something around the table here. Two little Petri dishes of powder. One of them's a real regulatory sample, and the other is an authentic sample. And they're just a nondescript powder. I'll leave them here. Don't open then up; it'll be everywhere. It's a very fine powder. First thing I looked at the powder from the regular sample. I started seeing cell structures, and if you'll look over on the left side of this image, you'll see some little donuts in there. They look like donuts on the vascular tissue. The sample was labeled as ginseng, powdered ginseng in

55-gallon drums. Our FDA lab in Buffalo said, is it really ginseng or not? And I started looking at this, and I said, something doesn't look right here. We stained it with floric lussinol, which is a stain for ---- which is a chemical in the cell walls of plants. Floric lussinol makes a nice red color, and 95 percent of the particles in my microscopic field were nice and red like this, and a lot of them had these nice little donuts on them. And I said, wait a minute. Ginseng root shouldn't have that much ---- in it, and the donuts, they don't belong there either.

Douglas fir has nice little donuts in its vascular tissue, and when you taste the stuff going around -- which I don't recommend -- it tastes like sawdust. It burns and smells like sawdust, and it's virtually 100 percent soft pine or fir sawdust. And it had a label on it as ground ginseng.

Take some ginseng root, grind it up and look at it, and you just have large dark mass of starch. We've all taken iodine and put it on some bread and see how dark it gets. And ginseng roots have a lot of starch in them. Most of your roots are storage organs, and there's a lot of starch in there. You see huge masses of starch in the ginseng root and a few little particles of lignent flying around in there. Not 100 percent red, not 90 percent red, maybe 1 or 2 percent are red particles.

Why are we doing this manual? For teaching. We hope to market it through the University of Maryland and put it on the Web for people to look at. Some of you people out there have see some of these images. These were the old images for the manual. These are digital images. For you computer types, these are 4.5 megabyte images. We got a new digital camera a couple of months ago. We're playing with 25 megabyte images now

that are incredibly photographic quality. These are the old images, and they look pretty good. I was pleased with them until we got the new camera. Now we're going to redo the whole manual, do it with the new high resolution, new digital camera.

This is light microscopy. Take the manual into the lab, set it next to you while you're working with it. And the manual's going to be on a CD. You can't sell and produce expensive color manuals anymore, but you can put them on a CD, and you can sell them for a few books.

So it is the latest technology combined with some of the oldest microscopy skills out there. Thank you.

DR. BRANDT: Thank you very much.

MR. CICHOWICZ: Oh, which powder is which?

DR. BRANDT: I have no idea.

MR. CHICHOWICZ: A is the sawdust and B is the ginseng. You can smell it,

though, and it definitely tastes like it. This is some of your finest, pure American panex, ginseng. Otherwise, they look pretty much alike.

DR. OBERMEYER: I just wanted to complete this session with a case we had in last May, just after the GMP rule was out for comment. This happened in May, and you may have read about it in the paper, about a plantain that contained some digitalis. This is actually an industry presentation that we gave after for recommendations. Again, just to keep it with the regulator aspects here -- just one slide -- this was an adulterated botanical product because it contained a poisonous or deleterious substance, and ordinarily rendered injurious, so it was an adulterated product.

We basically had to work backwards in a sense. Stanley just showed how you'd look at a commodity and identify it. Here we had toxic episodes with a herbal dietary

supplement, and we needed to go back and actually analyze and figure out what was causing the problem. We did basically these points here, and this will be the topic for the presentation.

The initial reactant was a 23 year old woman, and she was using a cleansing program. She complained of nausea, vomiting, dizziness, irregular heartbeat with heart block, abnormal EKG. Tested with ELISA and had toxic levels of digoxin and digibind, which is supposed to reduce digoxin specifically, was really ineffective.

The ---- program itself was five products made by Rise and Shine Company, and they had this little note in their pamphlet that went with it, that if you're having a cleansing reaction, discomfort, diarrhea, vomiting, headaches, fatigue, dizziness, don't move to ---- This is a common reaction. These are symptoms of mild poisoning from digitalis, so a lot of these

reports never came to the agency.

With the EKG and the digoxin assay, we had an idea that we would be looking for a cardioactive substance, probably glycoside, and so we did more or less basic classic chemistry to look for this and the extraction.

A keddie reaction, which is a color reaction, a quick test for it.

Some thin-layer chromatography, again just what I explained before, and some screen tests on the five products.

The glycosides are ---- rings on the bottom, basically like digoxin. And toxicology just changes with a few OH groups and things like that, so half lives, or they can be extremely toxic.

We have at least ten plants that we have more or less known standards for. For example, there are two digitalis. There's one *digitalis lanata*. A major group over there in *digitalis purpurea*. *Digitalis*

lanata has about 60 active components, where *digitalis purpurea* has about 30, and the list goes on. So all these ten plants that I'm mentioning in general have a lot of active components in this general type of structure.

The color reaction. We just went with positive and negative controls just to show you that regular plantain, which is a perennial weed, does not get this cardiac glycoside reaction, this color test. And we actually had a reference sample from the Smithsonian with *digitalis lanata* and one of the reference sample extracts. What you can see with the voucher plant specimen that we got the positive color reaction, nothing with the actual plantain, and a positive with the sample extract.

that was really our screening tool. It was one of the kedde reactions and also with thin-layer chromatography.

Out of the five products, we've narrowed it down to one product, the Chomper

product, and it contained 14 botanicals. So each one of these raw materials had to be screened for these cardiac glycosides. This is just a list of the botanicals that were in there. The plantain raw material, the first on the list, actually had the positive kedde reaction, and when we looked at with thin-layer chromatography, we had a match pretty much with lanatoside C, but we also had a fairly close match to *digitalis purpurea*.

At this point, I really had no idea that we were dealing with plants of origins outside the U.S., so *purpurea* is generally something that is in the United States; *digitalis lanata* is not. So we were comparing also then, microscopically, the plantago, which is plantain, with all the species that we could find.

This is plantain. I'm sure all of you, unless you have the golf type lawn, have this as a weed growing in your lawn. It's

very common besides dandelion. And it's generally used as a diuretic. A lot of people use this in the Caribbean as a diuretic to make a tea out of it.

Here is a microscopy. This is one of the tools we use to identify the material in here. We can see in this one when the characteristics are these glistening hairs. This is without the polarized run, yet this is more or less a large chopped piece of leaf of the other reference sample of plantain, of plantago major.

Under the polarized scope, we can see that this is one of the tricomes, the covering hair that would be on the leaf. We can see that it has actually a corkscrew-like configuration tool. You can see colors and some bends in there; that it actually is a corkscrew appearance on them.

When we powdered it, again, this is with the polarizing scope, you can see quite a few hairs, and you would have to look at a

few fields to really get a feel for this.

When we looked at the official sample, we have lots of plant material in there and literally none of the hairs, and they should be all over the place because they're not obliterated by the fine powdering that the raw materials actually were put under. So this gave us the good idea that we weren't dealing only with plantain.

Here we have just the drawings for *digitalis purpurea*. This is just to distinguish between *digitalis lanata* and *purpurea*. These are covering hairs also, nonglandular hairs. And they're huge; they're big.

The lancelot of the European variety, we did not see any of the hairs in this drawing. These glandular tricomes were actually one of the key characteristics in this plant.

When we looked at the reference sample that we obtained from the National

Herbarium, lo and behold, that's what the glandular hair looks like. It's actually broken away, but you can still see it.

Here's our official sample, and right there we can see still attached to the plant material is the same glandular hair.

We backed this up by LCMS confirmation. The constituents on the bottom, Lanatoside C is one of the major components in there, one of the 60, and we have it here. But we could also see B and A with some standards. In our samples extract we could actually physically see A, B, C. We didn't have the reference standard for D, but that actually matches D.

The trace-back of the adulterated plantain. This is very interesting. It actually came in through Germany. We had two companies that brought it in as an import. It came in and was redistributed by a primary importer to nine companies. Some of the difficulties we had were basically because of

the poor records. It was really hard to locate where all these shipments went, so we were just really trying to get a recall on these. From this distributor, they also sent it to a secondary distributor, that then sent it out again. Interestingly enough, the second distributor sent it out to 18 companies.

Also they sent it out to one company here, but they rejected the material. Based on their analysis, they returned it to the company.

This company then re-blended the material with some other material, so they increased the volume of adulterated material, and then that was sent out.

Rise and Shine purchased it. Over in here they had a person that would actually test it. There was a certificate of analysis that was done, only based on organoleptic analysis. There was no chemical testing. A certificate of analysis was drawn up that it

was plantain. It went through the milling process, and then was made into the Chompers.

During this investigation, we found that in 1995 there was a recall because of similar adverse reactions, but since they don't really have to notify the FDA on this, we never knew about it. But when we looked through this, this is it.

At this stage, we had actually stopped shipment of one of the productions. I think there were like 7 million tablets or so of the Chompers on line being ready to be bottled up and moved on.

During the trace-back, we found out that generally there was about six thousand pounds of adulterated material that had been shipped through the United States, about two and a half years. Fifteen different companies received all the recalls. Hundreds of establishments got this, but, luckily, there were no known deaths.

So what happened? Obviously, the

first one seemed to be mis-identification. The digitalis, it sometimes seems like plantain when you don't have the flowers. The second year of the plant, the digitalis had actually flowered. So immature plants could have been improperly picked, collected and put in there.

It could have been a warehouse error, labeling. Shipments going through every process. In fact, one of the German folks retested their material and found that, in fact, they had digitalis in their material.

Poor testing. I don't believe any of the material was really tested along the way.

Poor record keeping. That was very difficult to find all the lots of the material going back and forth. They weren't well labeled.

And again, the blending of adulterated material to increase the problem.

So some of the recommendations that were made at this time was really just what we had spoken about before.

Proper identification of the materials through different check points. The manufacturing process also.

Voucher specimens being collected and contained.

Testing. Again, organoleptic just wasn't really sufficient to do this, but with the aid of microscopic chemical, you should be able to test.

A lot of checkpoints everywhere, from raw materials to finished product, to make sure that it wouldn't be contaminated.

And record keeping. To do a better job of keeping records, putting lot numbers on there, and actually being able to follow things up.

Certificates of analysis using validated methods to actually run chemical tests on them, or even microscopy. And using

recognized credited laboratories. Again, this is pretty much a nutshell/GMP case.

It was very interesting after this. The American Herbal Association came up with a list soon after, and they are now testing for these materials. The herbs of commerce are on the left; so the Siberian ginseng with Aristolochia, which caused the hairy baby syndrome. Plantain ---- now that they are testing generally for adulterated *digitalis lanata*. Skull cap, there were tests with germander herb being put in in Europe. Stefire root with *Aristolochia*. These are all now being tested by at least one trade association to make sure that these contaminants are not involved in at least these herbs in commerce.

DR. BRANDT: Well, thank you very much, and we can have the lights again, please. The presentations are now open for questions or comments from anybody. Dr. Applebaum.

DR. APPLEBAUM: I have might have a couple of questions. Right now I only have one. Are most of the ingredients sourced from overseas for these types of foods?

DR. OBERMEYER: It's varied. A lot of them do come from Asia, Europe. They're all over, worldwide.

DR. APPLEBAUM: I'm just wondering. When FDA found out about this particular product, was the ingredient from that source -- I'm assuming it was Germany -- was it blocklisted? Did FDA do anything?

DR. OBERMEYER: That's through the imports. It's really difficult, because most of these come in as dried vegetable matter, and so there's a category, and this has to do with all the import stuff and takes it well beyond my scope. So it comes in as dried vegetable matter, and it's very difficult to police.

DR. BRANDT: Dr. Benedict.

DR. BENEDICT: First of all, my

degree is in microbiology, so I'm very cheered to see all this microscopy, and I enjoyed the presentation greatly.

DR. BRANDT: There weren't any microbes in there.

DR. BENEDICT: That's okay. The question I have is, with microscopy and with chemical testing, what is your limit of resolution -- and I know this is not a fair question -- with respect to adulteration of plants, not looking at chemicals like digitalis, but just a ballpark figure?

The reason that I'm asking is, of course, two things that weren't mentioned, biological testing with antibody-based methods or ---- chain reaction, and I realize that developing these things is extremely expensive. But I'd just like to get a ballpark figure for whether we're moving in that direction, whether we need to move in that direction. What are your comments?

DR. CICHOWICZ: I'm not sure what

you mean by resolution. We're down to the micron level.

DR. BENEDICT: Oh no, I understand that.

DR. CHICHOWICZ: Do you mean percent?

DR. BENEDICT: What percent contamination of ginger with pepalopia would you be able to detect?

DR. CHICHOWICZ: With my mold contamination methods, we're down in parts per trillion, so microscopic methods can be in parts per million, billion and trillion.

DR. BENEDICT: So if I give you a gram, you can absolutely tell me that it's been contaminated in a part per trillion?

DR. CICHOWICZ: It depends on the product. It depends on how finely it's ground. There are a lot of variables here. You can grind something so finely that you can obliterate all the microscopic characters.

DR. BENEDICT: Exactly.

DR. CICHOWICZ: And then there's nothing left to see.

DR. BENEDICT: Which is my point. The question then devolves to, eventually, contamination speciation is done best by preliminaries chain reaction, which is an extremely expensive thing to develop for each species.

DR. OBERMEYER: Right, but this is also, again, why you'd want to keep a voucher specimen back further. Every place it could be adulterated. That's why you'd really need to check, going along to make sure that it was an adulterated ---- Correct.

DR. BRANDT: Dr. Wang.

DR. WANG: Thank you for a very nice presentation. I realize that you show that we can test for raw material, but I have a couple of questions regarding testing where you can differentiate a finished product, where you have powder product verses extract.

If you can give us some enlightenment on that.

There was a question raised yesterday regarding testing for potency. I was reading US Pharmacopeia that the definition there stated identify, strain, quality, and purity. However in the GMP, it's stated in quality, and purity and composition, and then you have to go back to the definition to look at what composition is.

And the third one is also in the USP. Identify the finished product testing for desolution, and time and all that. And, again, it's for the finished product for formulated tablets. Will you be able to share that, too, on the finished product testing?

DR. OBERMEYER: I'll try. I'll try. You can bring me back up to speed or get me on track. The finished product. I guess it really depends on what type of

finished products we're looking at. Obviously, microscopy is difficult on abstracts of materials or composite materials, in the sense that they're in tablets. It might be able to work with mixtures if they're in capsules. Might be able to do something. Maybe not fourteen botanicals, that might be pretty difficult, but a lot of it combined with the chemical testing, if you really knew more or less what you're looking for.

Here in our last example, we had a very good hint at what type of chemical we were looking for in an adulterant, and so we could, I guess, hone our chemistry to look for those types of things. The mass fact right now is a very, very good tool; we're down well into the pico gram. As long as you have a standard, pretty much we're okay.

Again, that's one of the things that you need standards for. Outside people also do the validated methods. So that's one

of the things that they would need to have to do a finished product analysis, would be more a validated method or a way to validate their method.

DR. WANG: How about potency?

DR. OBERMEYER: Well, I don't know if we really are addressing that issue.

In the monographs, I think the raw material and the range of active constituents were something that, I think, we wanted to have standardized more or less in the monographs.

The active ingredients or the market compounds or whatever would be established more or less and by the monographs. There'd be a range because the plant itself, annual geographic variation, things like that, there might be a range, hopefully a limited range of active components.

Potency was also dependent on stability, and I don't believe that it deals

with stability of these products, so that would also be part of the potency.

DR. BRANDT: Dr. Rodier.

DR. RODIER: As you said, you had a good clue here after a consumer did a nice bio assay for you. Someone who's producing these products hopefully wouldn't have such a bio assay. In a sense, their job is much more difficult to characterize what they've got.

How long did it take you to get from being aware of the heart block to figuring out what was in this product?

DR. OBERMEYER: Relatively short time, really, several weeks, less than a month. We were very directed, we were able to get standards, we were right next to the repository for the voucher specimens. I mean, everything was very, very clean on this one.

For other plants that you wouldn't know what to look for in the adulteration,

they're, historically, a lot of these plants have been used for hundreds of years, so adulterants, we found out later, *digitalis lanata* was actually listed in a reference as being a common adulterant, but with the use of microscopy no one would ever dare to do it.

Microscopy has fallen on the wayside so it was something that nobody really looked for then.

DR. LEWIS: I think the point of GMPs and the point of Bill's presentation is that in the case of the manufacturer they wouldn't want a bio assay. You don't need that.

With good GMPs they would have caught it ahead of time, and I think the point Bill was trying to make was that the visual test was not enough, and so for certain products you might need something more than that.

DR. RODIER: No, nobody wants a bio

assay. I think that's an issue.

DR. WANG: GMPs are to avoid that.

DR. RODIER: Right, but think that in characterizing what you've got, it's quite different to take a mixture that you don't know what's in it and try to figure out what's in it versus having a clue.

DR. LEWIS: Again, going back to the manufacturer's role before they made that mixture, if they checked the plantain, if they checked the kelp and whatnot, you wouldn't have had the problem.

DR. OBERMEYER: Right. It was a key that the plantain, if it would have been really looked at, is not plantain. I guess it wouldn't really matter that is was something else, but it wasn't plantain. You wouldn't want it. It wouldn't meet your standards.

DR. BRANDT: Last question is Dr. Fukagawa.

DR. FUKAGAWA: Along those lines,

then there are two levels that we're looking at things. First of all, for GMP, for just the identification of the product, not necessarily at the level of what is active in that product, correct?

I mean, we're looking that somebody is mixing X with Y, and that they have a 100 percent pure X and a 100 percent Y, rather than saying that this is pure because many of these compounds, presumably, don't have identified active ingredients.

DR. OBERMEYER: That's exactly right. Very few have active ingredients, and one possible labeling, I actually shouldn't get into labeling, but you could actually state so much of an active constituent, and that would be very few plants have that. More so, they may use a marker compound.

We use so much of this marker compound, but we don't really know the active constituent, but we can see that this plant

or this capsule contains this much of the marker compound.

Like I say, most of them really fall in the unknown category of activity and known compounds. It's a little bit problematic in that sense.

DR. BRANDT: One more question, then we got to quit. Dr. Applebaum.

DR. APPLEBAUM: Very quickly. Dr. Wang, you mentioned USP talking about --

DR. BRANDT: You're going to have to talk closer, you're going to have to get closer to the microphone.

DR. APPLEBAUM: That USP talks about identity, strength, quality, and purity. I guess, my question is, in reading the GMPs, they list purity, quality, and composition.

Now, maybe because I'm also a microbiologist and not a chemist, when I think of composition, I also think of

strength and identity.

Is that how FDA would interpret composition to give you guys a better feel for comfort or raise your comfort level?

DR. LEWIS: It's a very good question. I'm not sure we've got through to that level, and I think it's something the working group could help us address.

DR. BRANDT: We're now going to take a break and reassemble at 10:15 for the public comments.

(Recess)

DR. BRANDT: Let's reassemble, please. If everybody would be seated we can get started. We can all come to order, please, so we can get started.

Our first presenter is Mr. Lauren Israelson, who represents the Utah Natural Products Alliance.

For all of you that are presenting, you have five minutes. When you've got two minutes left, you'll see this. When you got

one minute left, you'll see this. When there's zero time left, you'll see your mike goes off.

MR. ISRAELSON: Good morning. I am Lauren Israelson, Executive Director of the Utah Natural Products Alliance.

In 1992, it was our trade organization that worked with Senator Hatch in developing the core language and concepts which are embodied in DSHEA, so I'm intimately familiar with the law, and also, like you, recognize the tremendous opportunities it creates, as well as the challenges for industry and for consumers to make sure that it's implemented correctly.

I would like to do a couple of things this morning. First is to help you understand that we are here to assist this committee and any working group that is formed. We'd very much like to be a part of this process.

I believe we can bring a great deal

of expertise and knowledge to the questions that have been raised by the agency that they've been asking this committee for advice on.

There's been a great deal of consumer research done recently by trade associations and companies to understand who the consumers of these products are, what their expectations and intentions are.

I'm sure that we're in a position to share a good deal of that information with you and with the agency, so that we can all have a better sense of why people take dietary supplements.

What seems to be quite clear is that people do have clear expectations of these products. They're looking for health benefits. It's, therefore, in the interest of industry and every company in this industry to sell products that are safe and meet the quality standards.

To the extent that there are

problems and issues where that is not the case, we very much want to work with the agency and with this committee to resolve those issues. We believe that can be done within the framework of DSHEA. Particularly, with GMPs, the statute's quite clear, it was written deliberately to say that GMPs are to be modeled on food GMPs because dietary supplements are a subset of foods.

The four major trade associations have worked long and hard to try and create a model set of GMPs that will largely resolve and respond to the concerns that Dr. Obermeyer raised about potential adulteration of products.

Botanicals are a particularly troublesome area, because there's a lot of expert knowledge that's required to identify and to properly manufacture that particular class of dietary supplements. We share a common concern and interest.

My own background, I was with a

major manufacturer of herbal products for over ten years. I really appreciate and understand the problems and challenges that manufacturing these products present. I'm also confident that the industry is fully committed to creating systems and procedures that will protect consumers and also provide for a high level of expertise within the industry.

You will hear in a few moments from my colleagues at the American Herbal Products Association and a number of the projects that are going on currently to deal with identification and analytical methods, which is a very daunting task.

That one of the things that we need are harmonized analytical methods, so that when we test something, that we're all using the same methods, so that we achieve the same results. It's crucial. It's also a very expensive process. As you well know, it's difficult to develop methods that are

discrete and yet usable by many, many companies.

One last comment is that in developing GMPs, as an industry we're concerned about the effect it will have on small companies, and our's is still an industry which is largely made up of smaller companies, and the implementation of GMPs will affect them very directly.

If it serves the purpose of many of these companies out of business because they're not able to achieve those levels of GMPs, that's a great concern to us. We're also equally committed to everyone complying with appropriate GMPs.

I don't have a solution for you today but simply to say that this is something that we have to bear in mind as we go forward. The Small Business Administration has recently made some comments with respect to the Federal Regulations, and many of us sat together on

that working panel, and we can appreciate how difficult that issue was, and the challenges we face as we go forward with GMPs generally.

Finally, again, I'd like to say that we're very committed to working with this committee and any working group of this committee, so that we can jointly go forward and work on many of these issues.

Consumers are very, very interested in dietary supplements. Every trend and indicator suggests that people will use more and more dietary supplements in the future; therefore, it's incumbent on us as industry representatives to step forward and work with the agency who we have a good working relationship with and will continue to do so, as well as this committee.

We're pleased to be here for the last few days and look forward to continuing to work with you. Thank you.

DR. BRANDT: Thank you very much, sir. Appreciate your comments. Next is Jeff

Morrison from the American Herbal Products Association.

MR. MORRISON: Good morning. I'm Jeff Morrison. I'm the president of the American Herbal Products Association. I'd like to thank this committee for the few minutes to address you.

Yesterday, while we were watching and sitting during the proceedings, it became evident that many of the members are just not aware of the industry's effort to take on the responsibilities that DSHEA has presented us, and I'd like to share with you what the industry and AHPA has done to date.

Many years ago, AHPA recognized that some botanicals needed to have appropriate cautionary labeling language for a variety of reasons. We have ethics that are implemented in our association that, specifically, address certain botanicals cautionary labeling language that we recommend to go on the labels.

In addition, in 1992 we recognized that there's a great deal of confusion on the common names that were being used in the process of manufacturing and labeling. We published the herbs of commerce, which consist of approximately 500 herbs, their Latin name, and a standardized common name, and the effort is to have the same name on the label and reduce confusion to the consumer and, of course, the system manufacturer in this process.

The Food and Drug Administration recognized that effort, and in their recent publication of Dietary Supplement Labeling Recommendations, they referenced this as a source for labeling purposes.

At this moment, the association is about 75 percent through of a second edition of that, which will compose, or comprise of about 2000 herbs. It's quite a daunting task. We just need to finish the editing phase and get it peer-reviewed. In the near

future, this is going to be available. It will be a big benefit to the consumers and to our manufacturers.

Recently, and, I mean, within the past few months, we have published a botanical safety handbook. It's published by CRC Press, who I'm sure many of you are familiar with.

I will pass the this handbook around. It consists of about 500 herbs with four safety classifications, contraindications, serving size recommendations, and, when appropriate, cautionary labeling language.

This was done for primarily two reasons: One, to assist our manufacturers and provide them with a source material of accurate information for labeling and, two, for health care practitioners.

I do want to emphasize that industry did take the initiative on GMPs, and that's been repeated. We also are currently

working on extract guidelines.

Dr. Ertl, who you will hear from shortly, is the chairman of our Standards Committee and works as liaison with the Council of Responsible Nutrition, the National Nutritional Foods Association sister committees on standards.

This industry is full of expertise, and we, at the American Herbal Products Association, wish to convey our sincere desire to provide that expertise to this committee and would certainly urge you to form a working group for dietary supplements and herbal products, and let us help you.

Thank you very much.

DR. BRANDT: Thank you, sir. Appreciate your being here.

Next is Dr. Ertl from the American Herbal Products Association.

DR. ERTL: My name is Fran Ertl. I work for Botanicals International. We are a bulk manufacturer of botanicals, and I want

to talk about, first, to present AHAPA and the Activities in the Trade Association ---- .

Just later on indicate briefly about the QC perspective that we follow as a box offer botanical.

DR. BRANDT: Would you get just a little closer to the microphone?

DR. ERTL: Sorry about that. First of all I heard some of the concerns and the comments that were raised in this committee yesterday, and I want to say I share some of those concerns with you. Because of that, I try always to play an active role to set up the quality standards for Botanical Industries.

Some of the activities within the Standards Committee of AHPA has been already mentioned by Jeff Morrison, and that's Herbs of Commerce and Botanical Safety Handbook. We are working currently on extract guidelines because there's a lot of questions

in industry regarding botanical extracts, nomenclature, terminology, labeling guidelines, and everything related to botanical abstracts. Different ratio ---- , so we're going to clear these questions in this guideline.

We are also developing a quality control manual that talks about quality control basic principles and procedures that is applied to botanicals, and it can be used by all of our member companies that might not have access to all the documentation.

Since Lauren has already mentioned that we represent a lot of the smaller companies that they might not be financially capable of buying AOSC, USP, BAM, and all the those methodology books, so we are providing them with this booklet.

One of the other activities taking place today, within the Standards Committee of AHPA, is DAL Data Collection System, and that ANPR regarding GMP FDA pointed out to

the defect action level.

We do not have any defect action that is established for botanicals, and what we are doing today is we are trying to take samples from our member companies -- and these are whole, unprocessed, dehydrated botanicals -- and sending it to a third party laboratory for DAL determination.

Our goal is to establish at least a 100 data points on each botanical, so we can have a guideline on defect action level even though we realize that defect action level has to be established by FDA, but that is a starting point for us.

We are also working on a HACCP guideline, even though we are not in agreement with the mandates at HACCP, but we recognize that there are larger companies in our industry, that they want to be in compliance with HACCP, and we want to provide a guideline for those companies to follow HACCP.

On the analytical side, I know there was a lot of concern regarding methodology. There's a huge activity taking place in our industry today, and what they are doing is they are trying to establish analytical procedures for measuring market compounds in botanicals, and they are trying to take those methods from all the European companies, basically, and some of the U.S. companies, that they already developed these methods, and they have some preliminary validation on it and then go through the whole evaluation process on ---- .

Also, you have Monograph here working very closely with USB and AHB in the laboratories within the companies to establish monographs and methods for monographs. In our company we have quite an extensive approach to measuring cleanliness of botanicals.

We measure ash and area, moisture and ---- at the minimum level. We also

measure defect action level even though there is no standard established, but we are trying to set a guideline in our company.

We look at identification. We have quite an extensive database ---- transfers, infrared espectroscopy, TLC, and also microscopic image on ---- , so we are trying our best to set up a guideline and accomplish, some of the question that is raised here.

Their industry is very proactive when it comes to that, but there are some limitations when it comes to botanicals just because of the nature of the product.

Thank you.

DR. BRANDT: Thank you very much. Pleased to have you here.

Dr. Ed Kroon from the University of Mississippi, the National Center for Development of Natural Products.

DR. KROON: Thanks.

I decided this morning that I

should at least talk a little bit about what we've been doing to help the committee. I will also say that sometimes coming from Mississippi to Washington, I feel like a stranger in a strange land, and so when I heard all this about adulteration, I started thinking in my room upstairs. I have decaf coffee and caffeinated coffee, and it's all ground, and how do I know what's really in there?

My point is, that's an herbal powder that we all have in our room and somehow -- and I do want to bring us back to foods in a way -- because it's a beverage. I drink it as a stimulate. It's just a legal beverage drug if you want to look at why I drink it. Somehow I don't have to worry about it.

The challenge in the future is to make it that easy, that we could all go to our room, or wherever we go, and have that confidence of what we do. I say that to try

to put it in perspective.

My personal background is I first lived with Native Americans and other rural people in the south. I found that swamps of Carolina's as wild as I wanted to live.

To, again, put us in perspective here, people have had a process for a long time, and commerce has too, and let's face it; the potential risk of people using herbs, we think in America of the high media drama.

There is a risk. I think we need to figure every way we can to minimize it, and GMPs are going to be part of that. We survive pretty well. Most plants are not toxic, and I think we have to be assured what we're buying.

I do think that, in a way foods -- and I, too, have been through this dilemma -- is not a bad model to start out.

Now, I want to point out to you, though, that sometimes I feel like I've heard simple answers. At least, in my life, it's

never that simple. There are many variables and many things we have to set up. What are some of the expertise you can call on us.

Let me mention to you, we do identity, too. We have botanists. We have agronomists for growing herbs, for identifying herbs. We look at the variation, depending on all the plant parts, when they're harvested, how they're dried.

I've done ethnobotany. We have true pharmacognosist, natural products chemist. At this point, matter of fact, one of our chemists is validating some of the even proposed USP methods versus other published methods to see do these things really work throughout all products and major ---- for our leading products.

We also have pharmacologists who are doing assays to see, can we help standardize products *in-vitro,* even if you think it's anti-inflammatory. We do have environmental toxicologists who haven't

published yet but have actually looked at things like pesticide residues on herbs.

I want to point out we have both those, to answer some of your questions. I'm going to leave it with Lynn. I've shown it to him.

As a master student, I was not a major professor who looked at pharmacist knowledge and attitudes on herbal medicines. This is a summary of her Master's.

She is formulating her questions for a PhD, which ironically is going to be "What Does the Consumer Know and What does the Consumer Need to Know for Using Herbal Products." It's going to be her PhD thesis as a survey.

We have even done random household surveys in Rowe, Mississippi, to see what people are using, from over 200 homes. For many of the things you're doing, we, I think, have the expertise, and that's where I'm going leave you.

It's not just me but others. We welcome to help this because our mission at the National Center, which is part of the School of Pharmacy, is to work with industry and government and academia to say how can we help bring better health to people. That's our goal.

I do want to comment that for years I have had interactions with the trade organizations. I will give you a reflection. The dynamic I see when we're first all strangers to each other, it takes a while to get to know each other. These people, when you get to know them, are very open, will share very much their real problems, and thanks for telling me I'm number one, so it is a good way to start a relationship because it is more complex than you've sometimes heard.

I worked on things like digitalis and plantain; it's a very difficult problem. I also believe we have to start at the living

plant is my mantra, that we start there and end up with a final product. What are our tools to assure that.

Thank you.

DR. BRANDT: Thank you Dr. Kroon.

Now, Dr. Alvin Segelman from Nature's Sunshine Products.

DR. SEGELMAN: My name is Alvin Segelman. I'm the vice president of the Health's Sciences Nature's Sunshine.

To the best of my knowledge, we're the largest, now, international encapsulator of what used to be called medicinal herbs -- now we call them dietary supplements. Our sales are about $300 million a year. We're a multi-level marketing company.

I am a pharmacognosist who's been with the company for the past seven years. Prior to that, I was a professor of pharmacognosy and head of the department for several years at Rutgers University. That's

my background.

I've been listening to everyone here for the past two days, and Dr. Christine Lewis is the only one, so far, who hit it right on the head.

What this industry needs, and what you as a committee need to listen to a pharmacognosist. It's very simple. I'm talking about pharmacy-trained pharmacognosist. Now, the several guest speakers who preceded me here are doing the best they can, the industry particularly APPA, ANPA, and the vendors.

As I see it, the situation we have right here is what the pharmaceutical industry had about 25 years ago when generics first hit the market. Everyone started to come out with generic pharmaceuticals. Of course, the problems of pharmacokinetics and quality control were the big issue.

Pharmacists don't want that situation. I know, because I'm a pharmacist,

and I also sat on the Formulary Committee in New Jersey for several years. Pharmacists dealt with that situation very easily with the vendors. They said, show me the data. Show me the area under the curve. Show me the air you seize with regard to bioequivalence. If you don't show it to us, we won't buy your product. Simple as that. I think the onus of assuring quality should be on the shoulders of the manufacturers, of the vendors, of the people who supply the plants.

No offense, Fran, Dr. Ertl, but you're the people who have to assure us that we're getting what we want.

Now, I can go on and on; I have tendency to ramble and ramble. I'm going to address a couple of points.

Someone asked here this morning, well, what's the minimum detectable level, one of the gentlemen here, with regard to adulteration using microscopy. The answer

was by someone, well, it depends on the plant. That's right. We've been able to go as low easily 0.1 percent contamination using light microscopy easily. See?

May we have the first slide please? The purpose of this little presentation is to sensitive the Committee.

Our company, by the way, is in complete accordance with the GMPs, with operating under GMPs, *et cetera., et cetera.* We operate at a pharmaceutical level in our particular company; we don't see why everyone else can't.

Someone asked a question, what impact will this have on small business? It's a very good question, and we believe that methodology should be simple, and cheap and easily carried out by someone in Kenya as well as someone here in Washington, D.C. See?

Now, this is to show the committee here, how, even from the same vendor,

biological variation occurs, meaning the amounts of that constituent's implants varies even from season to season, even from month to month.

This is a plant called *Uncaria Tomentosa*, commonly known as *uña de gato*, a cat's claw. I don't want to get of on another subject, but this cat's claw --

DR. BRANDT: You have one minute left.

DR. SEGELMAN: It really represents at least 20 different plants in South America. Someone brought up the problem with synonymy. I think someone who spoke this morning anyway.

These are the active ingredients. They're oxyindal alkaloids, and these are the ones we're interested in. These are the good alkaloids; these are the bad guys down here. They're toxic. We're interested in herbal material, the bark, that contains this and not this.

Now in July here in 1990, These toxic alkaloids are at a minimum. Look at what happened in July of 1992. Complete reversal. Here the good guys are very minimal in terms of concentration, but look at the toxic alkaloids. They're way up there.

This is a problem in the Europe industry. It's easily dealt with by good qualitative and quantitative methods.

DR. BRANDT: Your time has expired, sir.

DR. SEGELMAN: I just want to take two minutes to show you an experiment we did a couple of years ago.

That is, one can take horse manure, cow manure, and make it look like an authentic herb. Here's the cows -- we have lots of them in Utah, and that's what cows make -- a lot of manure.

We took some authentic belladonna, and we took some cow dung, and we added

hyoscine, hyoscyamine, and scopolamine to the -- this is GC maspec.

To make a long story short, you couldn't tell the difference between the cow dung spiked with the three belladonna alkaloids and authentic belladonna by conventional means.

We went to microscopy, and thank goodness for the Bill Obermeyers and the Joe Betzs at the FDA. I'm sincere when I say that.

We went through microscopy, and I won't go through the whole thing. We were easily within about 30 seconds to determine what was the spiked cow dung and what was authentic belladonna.

DR. BRANDT: I'm sorry, sir, but we're going to have to quit.

DR. SEGELMAN: I think I've made the point here in terms of the importance of quality control in the herb industry.

Thank you very much.

DR. BRANDT: Thank you for being here.

Is there anyone else in the audience that wishes to address the committee?

Dr. Larsen.

DR. LARSEN: I had originally prepared some notes from the FDA Modernization Act on the impact of that act on advisory committee activities in the agency.

Rather than take your time today, I'm just going to put my notes in a hard copy and get them out to you in the mail or by fax.

It's now time for discussion about the task that we are asking you to perform following this meeting.

Do you and Bob want to come up to the table and, so if the committee goes into questions here, you'll have a chance to talk with them.

Chris and Bob, of course, are the folks that we'll be dealing with from the side of what the task is. I will deal with the task from the standpoint of the mechanics of the advisory committee.

DR. LEWIS: Maybe it would be helpful if you backed up first to talk about the working groups, and how they might be convened. I think there's been some confusion that we might convene them today, but they need to understand that.

DR. BRANDT: The Keystone working groups will convene today. The Dietary Supplement working groups we're trying to structure, right now.

You've got, received, a potential list with your year of graduation on it, as a matter of fact, and you need to review that and see if you are happy with the one that you are on. If not, indicate which one you would prefer to be on, and let Lynn know as soon as possible about that. That structure

is there.

We will go into those as soon as we possibly can so that we can get moving. We'd like to complete a lot of this by June or the end of June. That's the marching orders that Dr. Lewis has given me, and so, obviously, salute and move on. Right?

Everybody find that list? Everybody knows what your tentative assignment is?

DR. LARSEN: Is everybody reasonably satisfied with that tentative assignment? If you want time to think about it, that's fine. Get back to us fairly quickly on that.

One of the reasons the list is divided is because some of you will be going off the committee at the end of June, and that brings up the issue of why are we putting you on the list.

Well, first of all, we hope that we can have most of this work done by that time,

but if we don't, I would like for you to go off and think about the possibility of us continuing your appointment, but as a consultant to the committee for the purposes of completing this task.

You obviously are familiar with that process, because we just had Ed Kroon at the table. Ed Kroon was a consultant to the Center and a temporary appointment to the Committee when we were dealing with the ---- issue. So, it's not an unfamiliar role for you. If you are comfortable with doing that, we would appreciate your agreement to do that, and let us know as quickly as possible so that paperwork can be moved forward.

That also has an impact on the Keystone working groups. We've been very slow about getting those Keystone working groups pushed forward, and should those particular activities not be completed by June, we would like to have you still

available to finish off that task.

Time frames, well, at Keystone we wish we were done. I had hoped that we would have.

DR. BRANDT: We have one.

DR. LARSEN: We have one done; that's right. Dr. Askew and his crew pushed theirs through.

We have one that I think is probably pretty close to being done, Ms. Richardson's group on the incentives.

We, now, have at least a draft report that they will be discussing this afternoon, and looking through and debating about whether everything is in there that needs to be there; whether there's stuff that needs to come back out; whether that accurately reflects what the conversations have been, and so forth.

By the end of today, perhaps, we will have another draft that we can then distribute to the committee and have the

committee address it at another meeting. I say another meeting; that doesn't necessarily mean a face-to-face meeting. We possibly could constitute that meeting as a conference call, and that would probably be the fastest way.

We tried to do that once before, and we did have some members who wanted a face-to-face discussion, so it's really up to the committee to decide whether or not once you see the document and so forth, if you feel you need a face-to-face meeting, or whether we can complete that task as a public conference call.

We would have to do it as a public conference call. We would have a space in our building or wherever available for interested members of the public to attend and listen in from that side, and then you folks would be on the telephone from wherever across the country.

The Dietary Supplement working

groups. Chris, do you want to say something? I'll let you say something about what we're thinking about or what you're thinking about in terms of the facilitators of those groups. We obviously ran out of time to do it in time for this meeting, but go ahead.

MS. LEWIS: Well, there are three working groups, and when we looked at them, we felt very strongly that a lot of outside help was needed, and I say that guardedly because we're not sure yet ourselves what type of help, specifically. But consistent with what I said a little earlier this morning, because of the notion of collaboration with industry and others, the idea is to bring to the working group those that would be most helpful.

Secondarily to that, our experience with Keystone was that you are all extremely busy people, and it would be difficult for any one person to take on the burden to get this done as quickly as we need to get it

done.

We want to be responsive to the White House report, and we do not want to let the GMPs languish much longer. We are looking to identify what we're calling facilitators, someone who can work with the people who've been assigned to these working groups and can do what we would call the yeoman's work of writing, investigating, pulling together, and organizing. That was what we hung up on as far as getting these groups up and running, finding the appropriate facilitator for each group. We will continue that search.

We do want to talk to the working groups about how they would like to structure this, perhaps get some ideas from you folks. That's our working plan at the moment. Did I forget anything, Lynn?

DR. LARSEN: ---- working groups because we want to get moving. We'll probably try to have a conference call

amongst those that are assigned to the different groups, even, to get some of your input and thinking as we try to pull this facilitator in, as well.

That can be part of your thought too, to provide us with your ideas of who might be useful to help with that task.

DR. LEWIS: The members of the working group should contact us as far as what types of expertise, but as I mentioned before, we are interested in hearing from others, too, who feel they have something to contribute.

DR. BRANDT: To keep this process moving as rapidly as possible, it would be a good idea if you could let Lynn know by Monday whether or not the working group assignment is okay with you. If you have thoughts about other types of people that ought to be on it, you can let him know that as well, so that we can move along.

We've got our work cut out for us.

Are there questions or discussion of where we're going now, where we think we're going now?

We anticipate the next meeting of this committee to be in the month of June at least, topic not yet settled. Isn't that right, June?

DR. LARSEN: That's right, Tom. We won't be ready for any meeting, and the date I had you hold on your calendars for April. We are working on two potential topics.

DR. BRANDT: The April thing is gone?

DR. LARSEN: The April is gone as far as I'm concerned, unless someone else has something they want to bring up real quick.

DR. BRANDT: No, that'd be fine with me that April be gone.

DR. LARSEN: We do have a couple of topics we're working on, and the next two meetings that are on your calendars, the one for June and the one for August, are the

targets we're shooting for those.

DR. LARSEN: I have it on my notes here if I can find. I'm having you hold the week June 14th through 19th and the week of August 17 through 21. I don't expect that in either case we will use the entire week, but we're not sure how many days we're going to need. I've asked you to try to block off the whole week.

DR. BRANDT: Anybody have anything to say? Anything to discuss, any questions to ask, *et cetera*? Do you feel like you understand what we're about to try to do?

DR. LARSEN: We do have Brenda Derby back here, too, if you have some more on the questions on the consumer research.

DR. BRANDT: Then I guess we'll just as well start the Keystone working groups a little early. We are hereby adjourned.

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