FOOD ADVISORY COMMITTEE MEETING

PUBLIC AGENDA

300 Army Navy Drive

Arlington, Virginia

February 11, 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

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P R O C E E D I N G S

(8:30 a.m.)

CONVENE, INTRODUCTIONS, ADMINISTRATIVE

DR. BRANDT: We are going to go ahead and start so we can stay on schedule. We have quite a bit of material to cover. We will go around the table and let everybody introduce themselves, starting down here with?

DR. FUKAGAWA: Naomi Fukagawa from the University of Vermont.

DR. BRANDT: Raise your hands when you are getting ready to talk.

DR. RODIER: Patty Rodier from the University of Rochester.

DR. HARLANDER: Susan Harlander from The Pillsbury Company.

DR. BRANDT: Ed Brandt from the University of Oklahoma.

DR. LARSEN: Lynn Larsen, FDA.

DR. WANG: Mary Wang, California Department of Health Services.

DR. ASKEW: Wayne Askew, University of Utah.

DR. RICHARDSON: Donna Richardson, Howard University, Women's Health Initiative.

DR. BENEDICT: Steve Benedict, University of Kansas.

DR. CLYDESDALE: Fergus Clydesdale, University of Massachusetts at Amherst.

DR. APPLEBAUM: Rhona Applebaum, National Food Processors Association.

DR. CHASSY: Bruce Chassy, University of Illinois.

DR. BRANDT: Welcome. We haven't met in a while. It's good to see all of you again. We have a lot of stuff to cover today.

First, we turn to Dr. Larsen for administrative announcements and other stuff.

DR. LARSEN: The first thing I need to go through is the conflict of interest clearance. We asked all the committee members to advise us of any potential

conflicts of interest with respect to the entire dietary supplement industry. We have two members. Dr. Askew has a $10,750 contract with a dietary supplement firm, and those funds are used to support research for one graduate student. Dr. Clydesdale has served as a consultant to a dietary supplement firm, for which he was paid $6,400, including travel reimbursements.

Both of these gentlemen have been granted waivers to participate in the meeting. I have already had Dr. Clydesdale sign his waiver. Sometime this morning, Dr. Askew, if you would see me so we can have you sign your waiver as well.

We have at least three invited speakers from outside of the committee, who will also need to sign guest speaker forms. I don't think any of them are here right now, but I'll contact them during the day.

The next announcement is about the open public hearing session. The Federal

Register announced that open public hearings would be from 4:00 to 5:00, both today and tomorrow. We always put that in there, but we always end up having to change it. The times have been changed. This afternoon, the open public hearing session will begin approximately at 3:00 or 3:30, depending on how fast we move through the day.

We have three speakers signed up to participate in that session, but one of them just asked me this morning if he could speak tomorrow instead, and that second session, then, tomorrow will begin about 9:30 or 10:00, again depending upon how fast we get through the early part of the morning.

Currently, there are no other folks registered to speak at the open public hearing.

At the table for the committee members, you have another stack of materials. I'll quickly go through everything you should have there.

You should have an updated agenda, but as I'll tell you in a moment, that's already been changed again.

You should have hard copies of slides for presentations by Drs. Miles and Obermeyer. This is not necessarily in the same order as you have it on the table, but it should be somewhere in that packet.

You should have information on the MedWatch program and on our Food Safety Initiative. In fact, there probably are two packets of material on food safety.

You should find the minutes of last September's meeting, and that includes the report of the claims wording working group that completed its work as of that meeting, except for editorial changes.

There should be a set of materials that has the charges for the committee related to this meeting's issues.

There is a piece of paper that says the suggested assignments for the new working

groups that will be related to this meeting. We will get into a discussion of that tomorrow. You will have an opportunity to make switches if you want. Those are my judgments as to where I think you would best fit, but we can talk about that in the discussion period tomorrow.

You will find a bio for our new Center Director, Mr. Joe Levitt.

There is a paper by Mike Taylor that he wrote for presentation at the Food, Drug and Law Institute's meeting in December, but he did not actually deliver it because he became ill at that point. I think that paper -- I've used that paper as part of the materials and input to the incentives working group's final report. That is the intent of the use of that material.

There is a red report and some inserts that have a press release and so forth. The report is from the National Health Council. It's a survey that they

commissioned on how and where Americans get science and medical information. I thought this might be useful to the merging science working group and, perhaps, to one of this meeting's working groups as well.

Those of you who are going to be helping Dr. Harlander tomorrow and discussing the merging science, the Keystone report in the merging science working group, take a look at that. The entire committee has it because you will eventually have to deal with that working group's report.

The incentives working group members at the table also will have some materials specific to your task tomorrow. You got a draft report that was put together, and I've gotten some comments back, and what you have are the edited versions, so that you have a place to start your discussions tomorrow.

Dr. Harlander faxed to her working group on merging science some materials for

their discussion tomorrow. I have taken the liberty of starting a draft outline for your report using that. I've handed a copy to her, but before I give it out to the rest of you, I wanted to see if she likes it, and then you can use that for your discussion tomorrow as well.

I want to try to quickly go through what the agenda will be. The reason I'm looking around is because one of our first speakers this morning is supposed to be on, and he asked to be moved up to be very first because he has to go back and meet with the Guatemalans on raspberries. I don't see him yet. We will put him on when he gets here.

What you see on your agenda as the first two items for this morning are update briefings on the Food Safety Initiative and on the food section of the FDA Modernization Act of 1997. The background materials for those are in Tab 3, which in your notebook had a blank page, but as I mentioned, it's in

the pile in front of you, and Tab 4 for the FDA Modernization Act.

Tomorrow during the committee's discussion period, I want to make some comments at that time about the FDA Modernization Act and what impact it might have on advisory committees *per se*.

This morning what we will hear is simply the impact or the provisions that deal with foods.

I'll come back to Mr. Reynolds' presentation in a moment.

At about 10:00, we anticipate our new Center Director will be here, and he will be given an opportunity to provide a few comments to you from his perspectives as he comes on board with the Center. He's been with FDA for some time. Also on the table should be a copy of his bio. I think I mentioned that.

The main focus of this meeting of the full committee is to begin the process in

obtaining your assistance on some issues stemming from the White House Commission on Dietary Supplement Labels. From our FDA advance notice of proposed rule making published about a year ago on good manufacturing practices for dietary supplements, you will see that some of the items on the agenda may touch a sensitive nerve among some of you, and I'm sure among some of the folks who are guests out in the audience.

I wanted to assure all of you that FDA has no preconceived notions about what eventual direction the Agency will take on these issues. We are trying to set the stage for your task, however, and we felt it was necessary to provide a context for those issues with examples, taken largely from outside the dietary supplement arena.

With that in mind, I was going to say that our first speaker is Mr. Carl Reynolds, but since he's not here yet, we

will continue on.

DR. BRANDT: That sets the stage for what we are going to be doing today and tomorrow. You will also note on the proposed working group roster that it is divided into members of the Class of `98 and the Class of '99. Our alumni association is growing at a rapid rate, and one of the issues we are going to have to resolve one of these days is what the annual dues are going to be for the alumni association. I just thought I would get you to start thinking about that.

I guess we are ready to go on. Any questions or comments by anybody on the committee?

Dr. Larsen?

DR. LARSEN: The Office of Special Nutritionals asked me to quickly go through this so we could set the stage for you, as I said.

When Mr. Reynolds gets here, what we have in mind is that he will talk to you a

bit about FDA's statutory authority for records maintenance. FDA's GMP ANPR incorporated a submission from the dietary supplement industry, and records retention was a topic addressed both by the industry submission and by the ANPR. We felt that you needed to lay the ground work by what our current authority in the foods area is for records.

Following the break, as I said, we are taking that GMP one out of order because of Mr. Reynolds' need to get back for a meeting with the Guatemalans. Following the break then, we will hear from Dr. Bob Moore, who will provide an overview of the White House Commission report, which is at Tab 5, but clipped in the back of your briefing book.

You may recall that Ken Fisher talked to us back in September about the draft Commission report. Bob will go into a bit more detail. He will cover the final

report and then go into a bit more detail about the two issues that we are going to ask you to help us with.

Dr. Castro, a Senior Research Fellow in the Department and working on the White House Commission staff, will provide some detailed perspectives from her end on those two issues.

The agenda calls for a "to be arranged" speaker to talk about consumer research. We were unable to do that in time for the meeting, to get somebody to speak. We will use that agenda time instead for a brief discussion amongst you and with Dr. Levy and Dr. Brenda Derby from our consumer study staff from FDA.

Some of you will recall that we had discussed consumer research results with you for the Keystone reports, and both of those folks had talked to you about that. During that discussion, we are going to want to hear what your thoughts are at this point in time

on what additional expertise we need to pull in to pursue and facilitate your assignment on that issue.

After lunch, Drs. Goldman, Lewis and Litovitz, whose affiliations are listed in the agenda, will tackle the issue of post-market surveillance. We also had Dr. Ellenberg from our Center for Biologics scheduled. She called me late yesterday afternoon, had a family emergency, but she did talk her Branch Chief, Dr. Marcel Salive, into substituting for her, and he is fully cognizant of all the materials that she would have presented and will do a fine job on that.

Again, remember that all of these presentations only address what exists now, largely for other purposes, and this is an area of post-market surveillance. Some of those existing systems do capture data on dietary supplements, however.

I have already noted the open

public hearing time change. We have scheduled at the end of the day, Dr. Miles and Dr. Kvenberg of FDA to provide the overview of GMPs. We are going out of order, as I said, but we will get the overview at the end of the day, even though we get the statutory authority for records at the beginning of the day.

Dr. Miles will cover the overview and provide some perspective on the focus issues on why FDA is seeking your assistance, and Dr. Kvenberg will provide a view of records from a HACCP perspective.

GMPs is what the issue is, and that was the focus of the ANPR, but GMPs do also form a foundation when HACCP is used in other areas. Consequently, we felt it might be useful for us to hear about this, even though your focus is to be GMPs.

Tomorrow morning, we will begin with a presentation on the Functional Foods for Health program at the University of

Illinois, and that group's meeting last fall on Research Incentives for Health Claims. This ties into the afternoon discussions of the incentives working group and their task to present a report to FDA on what incentives exist or where we should go with incentives for health claims.

That presentation is being provided to the full committee so that it will serve as a topic of discussion both at the afternoon session and when you get around to discussing the report of the working group.

Dr. Obermeyer and Mr. Cichowicz from FDA will close out the formal presentations tomorrow with discussions about chemical and microscopic testing for identity of materials, but of course, the issue is how do you identify materials under the GMPs for dietary supplements.

There will be a second opportunity for public comment. As I noted a minute ago, one of our registered speakers has asked to

switch from this afternoon to tomorrow morning.

That is the time scheduled for the main committee meeting. There will be discussion time after those presentations tomorrow morning. We expect the committee itself can adjourn by noon. After lunch, we will begin the work of at least two working groups, and I think Dr. Lewis wants the significant scientific agreement working group to come together for a bit as well. The two working groups that we had originally scheduled would be the incentives and merging science working groups.

Does anybody have any questions about where that's going to go? Some of the questions maybe you want to hold off, especially on the working groups for this particular task that we are meeting for today. That will be part of tomorrow morning's discussion.

Is Carl Reynolds here?

If Carl Reynolds isn't, we will go on with the schedule as it lists, and we will put him in when he gets here.

DR. BRANDT: Our first speaker is going to be Mr. Louis Carson, who is going to talk about the Food Safety Initiative, Produce & Import Food Safety Initiative, and there you are.

FOOD SAFETY INITIATIVE

MR. CARSON: Good morning. My name is Lou Carson. I'm with the Food Safety Initiative staff at the Center for Food Safety and Applied Nutrition. Today, I'd like to also introduce my colleague, Dr. Wes Long, who will speak to you a little bit about a risk assessment in a moment. We were awaiting Dr. Robert Buchanan also to speak about research, but perhaps I'll do that myself.

At your last meeting, I realized that the Food Safety Initiative was also presented to you, and I wanted to just give

you an update and not go over old ground.

In January, the President announced the first Food Safety Initiative. Again, the goal of that Food Safety Initiative is to reduce food-borne illness to the greatest extent possible.

In October, the President announced a second Food Safety Initiative targeted to produce. That second announcement was based on an increased reporting in incidence of food-borne illness associated with produce. We in FY'98 are working on both initiatives within the Food Safety Initiative staff. We have just announced our budget for FY'99 and are also building on that in the next years.

For the FY'98 budget, the President submitted, and we received, $24 million within FDA, $20 million for CFSAN, $4 million for the Center for Veterinary Medicine.

Within the Food Safety Initiative, we have six major activities.

There is surveillance and

coordination, which are predominately carried out by the Centers for Disease Control, in coordination with Food Safety and Inspection Service and the Food and Drug Administration. These are seven sentinel sites around the country, which gather and interview physicians and health care providers on epidemiological information, provide that to the state/federal agencies so that we can coordinate and know about food-borne outbreaks earlier and then better to respond to that.

In the FY'99 budget, we are asking for an increase over and above the $24 million that we received in FY'98 of $101 million. That is for USDA and the Department of Health and Human Services. Within Health and Human Services, we would receive $55 million: $5 million for CDC to carry out the surveillance network, and the balance, $50 million, for the Center for Food Safety and Center for Veterinary Medicine.

In addition to surveillance and coordination, we have an expanded inspection and compliance area. We are hiring additional inspectors, and we are pursuing within the produce initiative to establish good agricultural practices for fresh or minimally processed produce.

Some of you may have heard or been in attendance at our grassroots meetings that we carried out over a four week period in November and December. We started with a public meeting on November 17 and announced our intention to put out this guidance, and in six meetings around the country plus an international meeting, we have shared our working draft document, which is on the Web Page, and we have received approximately 54 comments written to the dockets, as well as numerous comments within the transcripts at those grassroots meetings.

By and large, we are trying to establish, based on the best science

available today, through the pathways that we have described in that guidance, through water, manure, food handling, transport and trace backs, how we can advise farmers and producers to reduce food-borne illness in the production of fresh produce or minimally processed foods.

This endeavor has been quite challenging for us. We have worked closely with USDA in reaching out to their constituents the farmers, and we are still striving to make this document as practical and useful to that end user as possible.

Our time frame for producing the guidance is that we will produce the next draft in March. There will be a 60 or 90 day comment period. We are looking for a final proposal sometime in September/October.

We have engaged states' departments of agriculture and of health to come into the Food and Drug Administration, along with our colleagues at the Department of Agriculture,

OSHA and EPA, to assist us in working on this draft guidance.

It is a large undertaking. It really does take the best expertise of all the state, local and federal agencies for us to come up with a practical guide in reducing microbial risks.

We have also expended an awful lot of attention to education. You will be hearing from Dr. Levy and others later, but we have a major campaign to try to educate food handlers and consumers in the proper handling techniques for food. Whatever we do at the producer side, we must continue through the farm to table distribution of food delivery to the consumer, so that at each and every stage, we have appropriate measures and means to preserve the quality and safety of food.

We have a number of education activities at the retail and consumer level. In October, we kicked off the fight back

campaign along with our colleagues at USDA, both Secretary Glickman and Secretary Shalala, along with Acting Commissioner Freeman, kicked off this campaign, which is targeted to consumers in how to properly store and treat food in the home.

We recognize that many of the food-borne illness outbreaks have occurred at the retail and consumer level and we need to address those.

In addition in education, we are conducting a number of research activities to find out how best to reach consumers and how best to get this message across. We will be increasing those efforts in FY'99.

Lastly, we are devoting a major effort in the $50 million towards research and risk assessment, and I saw Bob Buchanan did join us here, so he will be able to talk to you directly about that.

Yesterday we met at the White House with our constituent groups, the constituents

that impact EPA, USDA, FDA and CDC. We kicked off the budget for FY'99. We are seeking each one of their contributions, and advice and support for our increased dollars to move forward on the food safety initiative.

What we have started here in FY'98, we need additional dollars to carry out in FY'99. For example, the produce initiative which the President announced in October, we had no funding in FY'98 to carry out. All of the dollars, approximately $25 million, are contained in the FY'99 budget to carry this out. Predominately, the budget will take care of the research initiatives to better understand pathogens and their role in the environment, especially with fresh produce, as well as in risk assessment, and what role sampling/targeting of our resources will play.

I've tried to give you just a broad overview because this is a very big project.

We in the Food and Drug Administration are not only working internally, but we have tried to improve the overall food safety network between USDA, CDC, EPA, state and local governments.

The statement was made yesterday at the White House, and I think it is very accurate, we have tried to be a virtual food Agency in FY'97 and `98, by collectively and collaboratively working between all federal agencies. We are trying to plan together so that we do not duplicate efforts, but that the sum of the parts is greater than what we could do individually.

There is a great deal for us to do. Most of the progress that we have made really deals with science that is well established. We have a lot to learn in new science, and I'd like Bob Buchanan and Wes Long to talk to you about the new science that we see, that we need to have to give better guidance to farmers, retailers, processors and consumers.

Let me turn it over to Bob first to talk about research.

DR. BUCHANAN: You will forgive me for not getting to the podium. I went one on one with my car and a bus and lost. I'm finding it difficult to stand for any period of time.

I would like to express my enjoyment at getting to see this committee for the first time. For those of you who don't know, I've been a long time employee of the Department of Agriculture and just joined the Food and Drug Administration about three weeks ago. I'm the brand new kid on the block.

I have been appointed as the lead scientist for the Food Safety Initiative, and what I would like to do is review the research component of the food safety initiative, to talk about what the areas are, and then talk a little bit about where we are going and hopefully do this all within five

minutes.

I do want to indicate that in the Food Safety Initiative document, there were really two research areas that were put forth. One was a general bio research area, and the second was risk assessment. Because it was such a high priority, it was pulled out and put there separately, and Wes will be talking about that in a minute.

We have had a changing world in terms of food safety, microbial food safety, and we found that we were facing a lot of problems that we hadn't dealt with before, things like new pathogens emerging. We had organisms that we had always thought were pretty innocuous, all of a sudden acquiring disease capabilities. We had a lot of non-traditional uses of food showing up. We had an expanded menu or availability of commodities. We have made seasonality disappear, so now we have a global market bringing in fresh products all throughout the

year.

We also have a new paradigm in terms of how we are dealing with food safety issues, and that in turn has produced a lot of need for additional information in how we grow foods, how we process foods, how we distribute them, et cetera.

What I would like to do is just quickly go through the five areas that were identified in the food safety initiative.

One was improve detection methods, our ability not only to detect the organism, but detect it in the very low levels that we occasionally find in food. One of the things that has happened over the last decade is that we have had a series of pathogens where one, two, maybe five viable cells have been capable of producing disease. Things like E. coli 0157 or cyclospora, which are extremely infectious. We now have to deal with looking for very low numbers of organisms that may only occur sporadically in a product or

commodity.

These are examples of some of them up here. We have had low level outbreaks of cyclospora, hepatitis, salmonella. I think the estimate in the Schwans' outbreak, that there was maybe one viable cell per every ten mills of ice cream, so it's a new world.

We also have to get a handle on understanding resistance. We had two areas identified in the Food Safety Initiative. One is understand how resistance is developed. Two, our preservation systems. We have organisms that are now extremely acid tolerant. We have organisms that seem to have acquired additional heat capability. Even if it's a couple of degrees, we need to know this, because if our current recommendations or guidance is wrong, we are going to be under processing or over processing, et cetera.

We also have the continuing need to understand the development of drug

resistance. Antibiotic therapy and its use throughout the medical community and also in the agricultural community is an area that we continue to look at, and we still need additional research on this one, because the questions get more and more complex.

We have an area where we have surprisingly little research in order for us to do risk assessments or to provide guidance. This is in the handling, distribution and storage of foods, after it leaves the processing plant, or between the farm and the processing plant or between the processing plant and the home. There is an incredibly complex distribution system, for which there is very little scientific data looking into what we should be controlling. Again, thinking in terms of a HACCP type of an approach.

Finally, preservation techniques. This includes both preventing the organism from getting on in the first place and also

for ways of removing it if it does. We have now had a series of microbiological problems associated with products that really can't be treated by conventional types of food preservation.

For example, you wouldn't want to take a fresh, soft berry and run it through a retort and still expect to have the fresh, soft berry come out the other end.

We need to have different types of technologies that can be used for these foods. When we think about it, they are ready to eat, but traditionally we have thought of them as raw agricultural commodities.

That was just a couple of examples. As part of the Food Safety Initiative, one of the things that was an underlying theme was cooperation and coordination. In conjunction with this, we have had extensive interactions with our counterparts in a variety of agencies, at USDA, with FDA, also CDC, EPA,

DOD, DOE. It's a whole alphabet soup of agencies. What we have done for the first time is really brought each other together, said what is your inventory of research that you are doing, how can we coordinate this research. We are going to have an opportunity to have a small increase in resources. How can we best use this? What we don't need is everybody chase the same thing, and we wind up with ten projects all on one area, and the other areas go wanting.

We have developed, and it's in draft form right now, going through the administrative process, a coordinated interagency research plan. We expect this will be finished for release in March 1998.

In the longer term, we are participating in a coordination process in terms of our research planning. This is being handled out of the Office of Science and Technology Policy. This again was something that was recommended within the

original Food Safety Initiative. This process started, and we are expecting -- the deadline we have been given is the end of April, early May, to get a finished document outlining where we are going to be going, starting in the year 2000 and on.

I think that's it. We have in our own shop where we are in the process of reviewing all of our microbiological research to see where we are focused and if we are meeting the needs, particularly not only the Food Safety Initiative, but we have also through the Produce and Import Food Initiative, we are going back and fast tracking or accelerating our research in specific areas. We need to provide guidance in the area of good agricultural practices and what we need to provide in terms of good manufacturing processes to the produce industry in order to increase the level of safety assurance we have in all those commodities.

I'd be happy to answer any questions, although I would like to turn it over to Wes first to complete the other part.

DR. BRANDT: Please do.

DR. LONG: Good morning. My name is Wes Long. I'm the designated lead for the Food Safety Initiative for Risk Assessment.

The risk assessment under the Food Safety Initiative is in two primary areas. One is the establishment and development of an interagency risk assessment consortium and the second is FDA's research to develop and validate both exposure assessment models and dose response models.

The risk assessment consortium is an alphabet soup, just as the group Bob has described for research, that has been pulled together to perform a similar function to the research group, as well as to do some other things.

The consortium has three primary functions, to develop a scheme for setting

methodological research priorities, to serve as a clearinghouse for information on data and modeling methods, and to foster and augment particularly critical research needs of the member agencies.

The consortium has held two meetings thus far. We are focusing primarily on the clearinghouse aspect at this time. The President's initiative describes two goals under the clearinghouse. One is to collect and catalog data, methodology and models, and the other, which is very similar, is to do a comprehensive review of methodology and data.

I just want to explain some aspects of the complexity of developing such a clearinghouse. This slide shows what we are calling phase one, risk of food being contaminated. It goes from harvest or catch of a commodity through all of the steps that the commodity might go through in the process of ending up on your table or in the process

of being consumed.

Each of these steps could be considered a module for which you have data inputs that are necessary for developing predictive microbiological models and dose response models, which I'll get to later.

To give you a little more specific idea, this is taken from USDA's shell/egg risk assessment. Here we are at the harvest module, which is the beginning step. For them, it was the egg layer module. There are inputs such as host factors, what factors about the flock make the flock more susceptible to, in this case, I believe it's SE, the virulent of the SE, whether it's high or low, and then there's a number of environmental factors that will contribute to whether the pathogen enters into the stream at this harvest step.

This information has to be modeled in order to move onto a probable dose, that then goes into the next step, which is

transportation, and goes into the next step, which is processing.

It's the work of this group to figure out what information is useful in a clearinghouse and who would use that information if we made it available, how should we make it available. Also, with respect to cataloging the data, do we use a system similar to this and try to develop generic models of the inputs that would be necessary to set up a cataloging and clearinghouse.

Because I only have five minutes and I'm going to use a little bit more than that, I'm going to move into FDA's risk assessment research priorities. I think the first thing I need to do is explain what we are defining, in just our own definition, of what risk assessment related research is as opposed to research.

Of course, risk assessment research is research, but risk assessment research, we

are saying, must contribute data to build or utilize models, or it must improve modeling tools. In considering what research we will be doing with food safety initiative funds, it's important that we do not duplicate the research programs of other agencies, and the consortium has gone through a process where each member of the consortium has described their risk assessment research.

Ideally, the research that's done will be value added. A couple of examples of that would be enhancing CDC's food net to collect information that's useful for risk assessors.

The research priorities must include the priorities from the Food Safety Initiative book. The Food Safety Initiative book has several pages of research projects that need to be developed. We must be ready to use both intra and extramural resources to accomplish these goals.

I'm going to start out talking

about dose response. The previous slide that was a flow diagram was risk of the food becoming contaminated, and actually several steps on this slide are also a part of what I will call exposure.

I want to focus right now on dose response, two primary inputs into dose response, epidemiological data and information and what we called in this slide microbiological toxicokinetics. It's not necessarily the best term. This would include animal models, human data, et cetera, in vitro models.

Under dose response, the initiative says that we are to develop data to describe low dose infectivity. The concept here is to develop models that will serve as surrogates to human exposure. In order to get the most bang for our buck, we are studying research that will compliment ongoing clinical trials that are being done by NIH and DOD for the purpose of developing vaccines.

In those cases, they are feeding extremely high doses of pathogenic microorganisms, because their intention is to make people sick. We might consider complimenting those studies by adding a lower dose group. We might consider delivering the pathogen in a different food matrix to help us plot more data points from that human study that we can use to help extrapolate that.

In addition, we want to look at animal models that fit well with the human data, and that will allow us to extrapolate down to those low doses that we are concerned with.

With respect to bio markers, with the human work, it's possible to collect additional samples that we can look for bio markers of susceptibility as well as infectivity.

Virulence factors. Virulence factors are useful in many ways. One is in

developing methodology for detection of microorganisms. Virulence factors are often studied to determine the mechanism of action of a microorganism. We believe that these virulence factors can also play a role in model development and can be used as a predictive tool or data input into determining the likelihood of illness from exposure to a microorganism.

Enhancing epidemiological investigations, and I'm talking about outbreak epidemiological investigations. The current epidemiological outbreak investigations are not tailored to provide data for risk assessors. Risk assessors need at least four things from epidemiological outbreak investigations.

One is more information on the amount of food consumed by the individual who became sick. The second is more follow-up to determine whether a chronic sequela has occurred, to try to get a handle on what the

rates are of those chronic sequela. The third is collection of suspect food for purposes of enumeration. If we can collect the food samples and back calculate to the level of microorganism that occurred at the time the person consumed the food, we can get a better handle on dose. What is the fourth thing? I can't think of it right now.

In order to go along with this enumeration, however, we really need to develop sampling and statistical methods that consider the occurrence and dispersion of these pathogens in the food to make sure that the data that we do collect is meaningful with respect to determining infectious dose.

DR. BRANDT: We need to move along pretty quick.

DR. LONG: Exposure. This is the risk of food being contaminated slide that I showed earlier. There are three primary areas that are described in the initiative. One is focused food consumption surveys that

target susceptible populations. The second is quantifying effects of key processing and preparation steps on pathogen levels. What is the pathogen level before a process? What is the pathogen level after that process? This information is needed to fit into models. This work is being done in a number of places. Our focus should be minimally processed or alternatively processed products.

Finally, addressing the dynamics of food-borne pathogens in agricultural environments. This is of particular interest to CDC, and they are pursuing research in this area.

Last slide. Finally, modeling methodology. There are two areas of interest, developing criteria for selecting or weighing of alternative models to take empirical data and extrapolate to quantitative assessments of risk, and development of more user-friendly tools for

microbial risk assessors. A good example of that is the ARS pathogen reduction software that allows you to take pathogens and perform a number of processes on them and see how the pathogen load is affected.

That's it.

DR. BRANDT: Thank you very much. You three gentlemen hang around a little bit, because Mr. Reynolds has to leave, and we need to hear from him. Will you be here for a little while so we can ask questions?

Mr. Carl Reynolds, we are prepared to hear about the FDA legal authority on records.

FDA LEGAL AUTHORITY ON RECORDS

MR. REYNOLDS: Good morning, ladies and gentlemen. Thank you for the opportunity to share with you information regarding the basic statute which FDA operates under to address food issues.

The Food, Drug and Cosmetic Act is a very simple, but yet complex document.

It's one that can cause a lot of frustration as you understand and compare it with the regulations that are promulgated there under. The basic principle under which FDA operates is the establishment inspection.

The statute allows an FDA employee to enter any factory, warehouse or establishment in which food is manufactured, processed or held for introduction into interstate commerce, or after introduction into interstate commerce or any vehicle used to transport food in interstate commerce.

Interstate commerce is mentioned prominently in that particular section of the Act. FDA modernization has tempered or modified the rules that we will operate under regarding interstate commerce, but not significantly to modify those things that I just mentioned.

That basic statutory authority also allows us to inspect any factory, warehouse, establishment, or vehicle and all pertinent

equipment, finished and unfinished materials, containers and labeling therein.

Administrative procedures. Any FDA employee for the purpose of making an inspection must issue to the owner, operator or agent in charge, a written notice of intent to conduct such inspection. They must display appropriate credentials that identify them as an employee of the Food and Drug Administration. Inspections must be completed with promptness.

There are two additional provisions relating to the inspection. One is if the employee observes any conditions which may lead to that product becoming adulterated before leaving the establishment, he must present to the owner, operator or agent in charge a listing of such conditions. Also, if any samples are collected during the course of that inspection, the owner, operator or agent in charge must receive a written receipt from the FDA employee

outlining those samples that were collected.

That is the basic statutory authority that we use to enter a plant. Administratively, it is our position that a firm is subject to inspection any time they are open for business.

We are going to devote our interest for the next few minutes regarding records that we have access to under the statutes. Section 412 of the Food, Drug and Cosmetics Act pertains to infant formula. The statutes allow an officer or employee making an inspection for purposes of enforcing the Infant Formula Act, he shall be permitted to have access to and copy and verify any record that is required to be maintained under Section 412 of the Act.

Under Section 4(12) of the Act, Infant Formula, again, these records include all records required to demonstrate compliance with good manufacturing practices and quality control procedures. A firm must

retain results of all testing. Other types of records that are required are certificates or guarantees of analysis provided by raw material suppliers, microbiological quality and purity records of raw materials, records showing that packaging materials adhere to the food additive requirements, records for all end process testing, all complaints and related files pertaining to possible health hazards, finished product testing to assure that product contains required nutrient levels, results of regularly scheduled audits, regularly scheduled shelf life testing, distribution records required to conduct and monitor re-call activities, and records maintained for audit testing to ensure that the requirements are met.

Under Section 703 of the Act, it talks about records available to FDA from shipments in interstate commerce. The Act requires that carriers engaged in interstate commerce and persons receiving food in

interstate commerce or holding such articles shall, upon the request of an officer or employee, give access to those records and copying of all records showing the movement in interstate commerce of any food.

This applies to the shipper or consignee of food products only. However, while we are authorized access to interstate records, there are no requirements that such records be maintained.

There is a caveat in that particular statute. It says that any record provided under that section cannot be refused if there is a written request provided for such record. However, any record provided under that provision, if there is a written request for the record, shall not be used in any prosecution of that individual.

There are rather comprehensive record requirements relating to low acid canned foods. Under the statute, any firm that is producing a low acid canned food or

an acidified canned food must register with the Food and Drug Administration and file their scheduled processes with the Agency. This must be done before they can start shipping their product in interstate commerce. This particular provision also extends to foreign firms that are shipping their product to the U.S.

FDA must be notified whenever there is any change to that particular process. If they change the can size, if they change the retorting times and temperatures, if they modify the retorting system and so on.

Records must be made available upon a written request of the Agency, and we may require, and they must be provided, if we ask for data regarding the establishment of their process.

They must maintain all records for processing or deviations in processing, container closing inspections and pH or other records specified in the particular sections

for three years.

They must report to the Food and Drug Administration incidents of spoilage or process deviations which may indicate a potential health hazard.

They must report instances where production lots may be injurious to health due to contamination with microorganisms.

Those are some of the more prominent features of the particular Act. However, FDA has two additional tools that we may use to obtain information that we need.

One of those is an inspection warrant, which we are willing to use if information is refused to the Agency. There are three primary questions that we ask before we seek an inspection warrant.

The first one, is FDA entitled by the statutes to that particular information? Is there an official need for the Agency to have that information? And the third, what steps have we taken to obtain the information

that we need?

The second is the search warrant. Search warrants are effective for us to obtain evidence of a criminal conduct, contraband or the fruits of a crime, property that has been intended to be used in the Commission of a crime and so on.

Whereas an inspection warrant is used to obtain information that is refused and to which we are entitled to under the statutes, a search warrant need not be executed only for that information that we are entitled to under the statutes. Again, the search warrant is used in criminal types of activities.

You can see in this short discussion the magnitude of record requirements that is in the Food, Drug and Cosmetics Act. It is again simple but complex.

I would be happy later, I guess, this morning to answer any questions that you

might have.

DR. BRANDT: We can go ahead and take questions, because I understand you have to go to a meeting on raspberries or something.

MR. REYNOLDS: Yes, sir. Thank you.

DR. BRANDT: Are there questions?

Thank you very much, sir. We appreciate it, and good luck with your other meeting.

Let's go ahead and see if there are any questions about the Food Safety Initiative presentations.

Yes, sir. Dr. Clydesdale?

DR. CLYDESDALE: Are resources available to carry out the initiatives that were proposed, adequate resources? And how are they allocated between the two groups?

DR. BRANDT: That word "adequate" is always a difficult one to respond to.

DR. CLYDESDALE: I thought I would

try it, though.

MR. CARSON: I tried to answer that earlier, but perhaps I didn't. I believe we have shared with you a backgrounder that describes the dollars associated and how it's distributed between agencies.

Your first question about adequacy of the dollars and the scope of what we have before us, I believe we feel that the funds are adequate to get us to the next level, but they are not sufficient to solve the entire problem.

I think what Dr. Buchanan and Dr. Long presented to you in the research and risk assessment arenas are really multi-year long range research projects, certainly three to five years before we see real pay off in better understanding of the processes as they apply to foods.

Most of the methodology that we have today are based on outbreaks and on single point sources of problems, and what we

are trying to do now is a more comprehensive approach to pathogens in the food supply.

As far as education and inspections are concerned and as far as the adequacy of dollars, certainly we would like more funds, but I believe we can make a credible and very straightforward positive impact in providing a better public health to consumers with the dollars that have been assigned to us here, if we are successful in getting them in FY'99.

We got $24 million in the Food and Drug Administration, $20 for CFSAN and the field organization and $4 million for the Center for Veterinary Medicine. We believe we need additional dollars in 1999 to take on those activities that we are simply just initiating in FY'98. If we do not get the funds in FY'99, then we will be severely strapped for making that positive next step forward.

DR. BRANDT: And OMB probably

thinks it's more than adequate.

Dr. Benedict?

DR. BENEDICT: First, it doesn't sound adequate at all; it sounds decidedly underfunding. I wonder if you could comment on how you feel distribution, if there is any, is between intramural and extramural research on some of these issues.

MR. CARSON: I am going to probably defer to Dr. Buchanan and Dr. Long. There is a distribution, and we are working on that now for FY'98.

MR. BUCHANAN: The distribution in FY'98 for the research funds is approximately 70 percent internal and about 30 percent going external. This is to get us up to speed in terms of some of the short term investments we need to make in order to be able to handle the day by day activities and build our infrastructure.

As we then project out over the course of three years, that's our planning

cycle, that percentage increases in the second and increases again in the third year, assuming the projected increases that we will be requesting are being supplied. Again, it's going to be dependent on the infrastructure. We need to do our day-by-day business in terms of providing the research that's needed within the Agency to make these policy decisions, but we are also very much interested in getting that type of research that we can get out on the outside, get those new ideas in, both in the form of probable research grants and then collaborative efforts.

Eventually the idea is to get about a 50/50 split by the year 2000, that kind of distribution.

DR. BRANDT: Dr. Clydesdale?

DR. CLYDESDALE: I'm sorry. I'm a little slow. I'm going to have to come back at this again. The material that was presented this morning on the risk assessment

and research by Dr. Buchanan and by Dr. Long, that material, what kind of time frame do you hope to have that done in? I guess that's what I don't understand. What was presented this morning, what sort of time frame are we looking at? Is that over the next ten years or the next three years, the material that was presented to us?

DR. BUCHANAN: This is based on a three year planning cycle. We assume that some of the broader research questions are going to take three to five years to really have an impact. However, there are a series of short term advances that we are going to be able to realize within a year. Some of them have to do with improvements in methodologies, which, now that we have gotten additional funds, we have been able to accelerate our activities in those. Likewise, as we have moved into the produce initiative, a lot of the advances there are short term, in that we have to go through the

research to modify our current techniques and availability in order to make them applicable to produce, and some of that is going fairly quickly.

DR. BRANDT: Dr. Applebaum?

DR. APPLEBAUM: Dr. Long, you referred to a book, an FSI book. Was that an euphemism, or is there truly a book available that gives detailed information?

DR. LONG: I was referring to the Food Safety Initiative, the President's report.

DR. APPLEBAUM: Will there be a book in terms of a true strategic plan that identifies what's going to be planned and what's going to be proposed in terms of programs?

MR. CARSON: Let me try and answer that. The answer is yes. We have that as one of the major activities, strategic planning. We are still in the process of that, with all the collateral agencies to

come up with one strategic plan for food safety. That is a long range strategic plan, five to ten years. It will be completed sometime this fiscal year, is our target, but we do not have it yet.

I think to go back to Dr. Clydesdale's question earlier and one of the points Dr. Buchanan had on this slide, the OSTP at the White House is convening all the agencies to come up with a long range, starting in FY 2000, research plan that will coincide with our budget cycle. The whole purpose behind that is to ensure that we will get increased dollars for research both in risk assessment and in microbial pathogen research in the out years, so that this initiative will not dwindle; it will increase.

As you have pointed out, this is a huge endeavor, and we do need additional funds if we are going to be successful. I think everyone recognizes that money needs to

be funneled into this endeavor, and we need to make a very plausible and credible case as to what we have done in FY'98 and FY'99 with the dollars they have given us and what we can do more if we were to get increased funding.

DR. BRANDT: Other questions? Dr. Rodier?

DR. RODIER: Can you tell me how many investigators you have internally who can be put on these problems? How many in risk assessment and how many in pathogen studies, and whether that's going to change with the new research funding?

DR. LONG: I think we are both in the process of bringing on some new senior staff. I think we are all devoted towards redirecting resources to this work. I think we will be able to adequately do the things that we can do in-house; I think we will be able to accomplish them.

MR. CARSON: We are taking stock of

our current resources now, trying to find out what is currently onboard at all the agencies, what needs to be redirected and what FTEs and dollars will be from current operations versus the new dollars. The research plan that Dr. Buchanan talked to you about that should be out in March will give us a better idea at that time as to what our total resources are.

We can tell you what the new increases will give you in FTEs and dollars, but it doesn't tell you what our current operating staff that we are going to be re-focusing to these endeavors are, and that's a process that we are still involved in right now and trying to get there by March.

DR. RODIER: I really am just looking for a rough estimate, because I have no idea how many experts on pathogens you have working now.

DR. BUCHANAN: Currently, we have

approximately 30 senior microbiologists on staff. That is at CFSAN itself. In addition, we have access to microbiologists in the field laboratories and also down at our toxicology center in Arkansas. In addition, we do have several formal collaborations, our collaboration with the research group out in Summit, Illinois, an additional eight senior investigators, I believe. Likewise, we have the CFSAN activities that we are having collaborators with.

I would say right now, a ball park figure would be about 30 percent, and approximately half of those are currently working on some aspect of the Food Safety Initiative, and that's likely to increase as we weigh the priorities of other programs that are taking place that we need to maintain.

DR. BRANDT: Dr. Askew?

DR. ASKEW: For my own

understanding, let's say you are concerned about the food-borne pathogens with strawberries. At what point does microbiological testing occur? At the producer level, prior to going to market or after a pooling of producers in the market, at the plant, or what is envisioned there?

MR. CARSON: The whole thrust of the Food Safety Initiative is to get away from end-product testing and to try and devote our attention to intervention and prevention technologies.

The guidance that we are putting out on produce is devoted again to water, manure, food handling, transportation and trace backs. We don't believe that we can be effective in doing end-product testing because of the volume and fast turn around in commerce of fresh produce. We feel that the most appropriate place, and that's where the risk assessment and research dollars are going to be focused, both within FDA, USDA

and EPA, is to focus in on production at the farm and to make sure they have practices, treatments, preventative techniques that they can employ so that we can reduce microbial contamination.

Today, traditionally, FDA would test end products either at the border or in commerce, because as Mr. Reynolds just mentioned, our authority extends only to those products in interstate commerce.

DR. BRANDT: Dr. Askew?

DR. ASKEW: Just a short follow-up. Education and inspection surveillance are. Of course, important, but we will probably always fail in certain instances. To what degree is food irradiation being considered with the program?

MR. CARSON: As you know, FDA in coordination with USDA has put out a rule on irradiation and that may have been of a previous Food Advisory Committee meeting, I'm not sure, but we are looking at all sorts of

intervention technologies, ones that are submitted by petition or ones that come up with through in-house research.

There are a number of food additive petitions that we are looking at now that seem to lend themselves to some reduction of pathogen load on a food product. Certainly irradiation is one that we would have to look at, but again, even if we were to find how irradiation might be employed, it's the market place that has to put it into place.

I think this question came up yesterday to USDA about irradiation of meat and poultry products. There is an irradiation regulation out on poultry. It has not found wide acceptance. Obviously, we would have to work with industry to see how best this could be done.

Any and all suitable intervention strategies will be pursued. I think Dr. Buchanan mentioned that earlier in his slide on research that we are undertaking.

He may want to follow-up on that.

DR. BUCHANAN: Currently, there are several approvals for irradiation. Our primary thrust now in looking at irradiation will be to see how adequate the current one kilogray limit is in terms of getting rid of the pathogens that would be susceptible to that.

For example, Hepatitis A in strawberries would not be a particularly good application for irradiation due to the nature of viruses. On the other hand, irradiation, low dose irradiation and possibly as best we can get from the experts at the Agricultural Research Service, the one kilogray should be more than sufficient to kill protozoan parasites, such as cyclospora. This is an application that is already approved.

One of the tasks that I'm giving one of the people coming on board to serve a detail with us is to go out and look at the whole radiation database that we have and see

if there are additional modifications that we should recommend to the irradiation profile in terms of advice for either processors or at the production end.

DR. BRANDT: Thank you all very much. We appreciate your being with us and thank you for the information. We will now move onto Anne Depman, who is a Science Policy Analyst, who will talk about the FDA Modernization Act of 1997. You have an outline of that in the stack of material that was put at your place.

FDA MODERNIZATION ACT OF 1997

MS. DEPMAN: Good morning. My name is Ann Depman. I am a Science Policy Analyst with the Executive Operations Staff at CFSAN. I am here to discuss the food provisions of the FDA Modernization Act of 1997.

Before I go through the food sections specifically, I would like to try to give a little background to explain why this bill was able to pass through Congress this

past session.

In July 1996, Dr. Diane Robertson of the Executive Operations staff came to an advisory committee session to discuss the provisions of the FDA reform bills currently pending at that time. I would like to pick up at that point.

In 1996, the 104th Congress, FDA reform bills were introduced in the Senate and the House. The Senate bill had many agency-wide provisions, food provisions, in particular, including food contact substances and health claims. Three bills were introduced into the House, one dealing with drugs, one, devices, one, foods. Many of the food provisions included admissions statement, national uniformity, health claims, food content substances and a Declaney clause fix.

The House bills were never marked up. The Senate bills never came to the Floor for a vote. This was, in particular, in the

Senate due to Democratic opposition, and it was also an election year. They just ran out of time for these bills.

The 105th Congress began in January of 1997 with a very different spirit. There was the knowledge that the very popular Prescription Drug User Fees Act was going to expire October 1, 1997. The sessions opened with Senator Jeffords and Representative Bliley making it clear that PDUFA, the Prescription Drug User Fees Act, would not move through Congress unless it were tied to a general FDA reform bill. This told everyone that they had to actually go through with the process this particular past year.

Senator Jeffords introduced a bill in June. This was favorably voted out of committee. It addressed drug, device, food and agency-wide issues. Some of the food specific provisions included health claims and nutrient content claims. There was a lengthy Floor debate in the Senate in

September, including a two week filibuster by Senator Kennedy.

In the House, just as in 1996, three bills were introduced: One, drugs; one, devices; one, foods. Representative Whitfield introduced the foods bill on September 11th. Eventually, the drug, device and food bills were combined into one, H.R. 1411. Foods provisions in the House bill encompassed a broader range than the Senate bill. It included nutrient content claims, disclosure of irradiation and the pending irradiation petitions.

Both the Senate and the House bills came up for votes on the Floor, and they were both passed. Because the bills were different, they went to a conference committee. The conferees met for three weeks to iron out the differences between the two bills. Eventually, they came upon one version of the bill that was acceptable to everyone. This bill was forwarded to

President Clinton for signature, and he signed it on November 21, 1997.

This is the enactment date of the bill. However, the bill did not go into effect completely at that time. There was a three month delay period built into the bill, so the effective date for the majority of the sections of the bill is February 22, 1998.

PDUFA's provisions are an exception to this rule. One went into effect immediately that dealt with meat irradiation petitions, and one will go into effect 18 months from the signing of the bill, as food contact substances.

For the specific food provisions, I'm going to be discussing sections and using section numbers. On the outline provided, there are some section numbers. Those are sections of the FDA Modernization Act, not of the Food, Drug and Cosmetics Act.

In particular, I want to start off with Section 305. This is Section 305 of the

Modernization Act. It amended Section 403(r)(2)(B) of the Federal Food, Drug and Cosmetics Act. Within each section of the Modernization Act, it says what was amended, if you'd like to follow along in your books.

First, nutritional claims. There are some substantive aspects for nutritional claims, beginning first with the referral statement, section 305 of the Modernization Act. Under the NLEA of 1990, a referral statement is required where a food label contains a claim regarding the level of a nutrient, such as fat free. The label was required to contain a statement, referring to the nutrition facts statement.

I have an example to try to make this a little clearer, and I can pass these around. This says it's a fat free food. Directly underneath it, it says, "See side panel for nutrition information." This refers the consumer to the side panel. This is the requirement of the NLEA from 1990.

The NLEA also required disclosure statements. This is where a food contains a nutrient that increases the risk of a disease or a health related condition that is diet related. The disclosure statement must identify the nutrient.

An example of this is sodium. On this, there is a statement on this label that says, "See side panel for information about sodium and other nutrients." This is a disclosure statement. Whereas this box has two referral statements, in fact, the fat free food and also about sodium.

Section 305 of the Modernization Act eliminated a requirement for the referral statement. However, the disclosure statement, which is on this soup can, is still a requirement. That's the explanation for that section.

DR. CLYDESDALE: Could you do that again just very quickly?

MS. DEPMAN: Sure, I'd be happy to.

Section 305 of the Modernization Act eliminated the requirement for the referral statement. This is the statement that all claims regarding the level of a nutrient be accompanied by this referral statement. However, the disclosure statement, which is now required when the claim on the level of a nutrient is made and the Secretary determines that the food contains a nutrient at a level that increases the risk of a disease or health related condition, this will bring added attention to this disclosure statement, to the sodium or possibly if there's cholesterol in the product, this will bring added attention to that.

The consumers who have very wholeheartedly adopted the nutrition facts panel no longer need to be told to refer to the side panel for every item.

The next section, Section 303 of the Modernization Act. The NLEA of 1990 also established a pre-market review process for

health claims. Under this process, a person may petition FDA for approval of a claim. Section 303 creates the modernization pre-market notification process for health claims. This is based upon an authoritative statement of certain scientific bodies of the United States Government.

A notification may be made if a scientific body of the federal government or the National Academy of Sciences has published an authoritative statement and the statement is currently in effect regarding the relationship between a nutrient and a disease or health related condition.

The process for filing this pre-market notification is a person submits at least 120 days before marketing a notice that contains the information which has been specified in the statute, Section 303 of the Modernization Act. This includes the exact words of the claim, a copy of the statement relied upon and a balanced representation of

relevant scientific literature.

The claim that is the subject of the notification may not be made after this 120 day period until FDA issues a regulation prohibiting or modifying that claim, or in an enforcement action, the court finds the requirements of the statute have not been met.

Section 304 of the Modernization Act created an identical pre-market notification system for nutrient content claims. The original NLEA created petition system is still in effect. This was not altered. This pre-market notification system is simply an added mechanism to allow some claims to get to the market faster.

There are some procedural aspects of the nutritional claims' sections of this Act.

Flexibility regarding claims, Section 301. This provides an additional procedural option for regulations for health

claims and nutrient content claims. FDA may make a proposed rule effective upon publication, pending comment and final rule. This provides consumers with information regarding nutrition and healthy dietary practices, or it allows FDA to ban or modify an authoritative determination claim that has been made through this notification process.

Deadlines for Agency action on health claim petitions were also established. Section 302 created certain deadlines for actions on health claim petitions. If FDA fails to make a filing decision with 100 days, the petition is deemed to be denied, unless the petitioner and FDA agree to an extension.

Secondly, if FDA fails to issue a proposed rule within 90 days of filing the petition, the petition is deemed to be denied, so there is a 100 day period for FDA to decide to file. Once FDA files, there is now a 90 day period for FDA to issue the

proposed rule.

The third deadline that was established is if FDA fails to publish a final rule within 540 days of receipt of the petition, this goes back to day one now. FDA is required to provide the relevant House and Senate legislative committees reasons for such a failure.

The next section of the Act that I'd like to discuss is food contact substances, Section 309. Food packaging material, such as plastics, and paper and components, such as adhesive sanitizing coatings, are regulated as a food additive. For this box of pudding, the food contact substance is the package on the pudding mix.

Section 409 of the Federal Food, Drug and Cosmetics Act, the existing Act that was modified by this Modernization Act, provides that food additives are subject to FDA pre- market approval under the petition process found in Section 409.

A food contact substance, this food packaging material, though not without risk, has very low exposure to food, so it presents very little risk. Despite this, the processing of these petitions for food contact substances absorbs a large amount of FDA food additive review resources.

FDA has engaged in a discussive process with food contact substance industry to develop a new system to regulate these food contact substances. This new process is found in Section 309 of the Modernization Act.

A food contact substance under this Act established a notification system for food contact substances. This is similar to the health claims and nutrient content claims notification system.

These food contact substances are still food additives, so they are still subject to the same safety standard under 409, which is reasonable expectation to do no

harm except in carcinogens.

Under this new section, a manufacturer notifies FDA 120 days before marketing of the identity and intended use of the substance and the manufacturer's determination that the use is safe under 409. The notification becomes effective and the substance may be marketed 120 days after the submission of the notification unless FDA determines that based upon the data and the information submitted, the use has not been shown to be safe.

In this Modernization Act, there was a very convoluted appropriations method that was created for funding of this program. It requires the President to make a yearly budgetary request for the program to go into effect. The first year for the program to go into effect is FY'99. However, the FY'99 budget did not include the minimum $1.5 million request. Therefore, the status of the section is a bit unclear at the time.

This is one of the two food sections that has a different enactment date from February 22nd. This is a delayed effective date of 18 months in order to create the implementing regulations needed to implement this program.

Now, some miscellaneous provisions. Disclosure of irradiation, Section 306 of the Modernization Act. Prior to the Modernization Act, FDA regulations required that any food that has been irradiated bear a disclosure statement, "treated with radiation" or "treated by irradiation." It must display prominently and conspicuously a logo reflecting the fact that the food has been treated with radiation.

Under Section 306 of the Modernization Act, the radiation disclosure statement cannot be required to be any more prominent than the declaration of ingredients. The change that was created in this section simply limited the size of the

disclosure statement. Before in the regulations, there was no limit to the size. Now it says it can be no larger.

Unfortunately, I don't have an example to show you of a product. Most of these products are in the Midwest, radiated spices. I wasn't able to get one.

What this section means for the logo is unclear. That was not addressed in the section of the Modernization Act for the size of the logo. In the regulation it specified that it must be prominent and conspicuous, and that was not addressed in Section 306.

Another miscellaneous provision is the meat irradiation petition. This is the other food section that has a different effective date. Under the definitional section of the Federal Food, Drug and Cosmetics Act, radiation is defined as a food additive. When the Modernization Act passed, a petition was pending before FDA requesting

approval of the use of radiation on red meat.

As you know, radiation had previously been approved for certain uses on ground spices, pork and poultry. Section 307 of the Modernization Act requires that the Secretary make a final determination on the meat irradiation petition within 60 days of enactment, therefore, by January of 1998, or to provide the appropriate legislative committees of the House and the Senate an explanation as to why the action was delayed. The final rule approving meat irradiation was published on December 3, 1997. This is well within the 60 days.

Another miscellaneous provision is glass and ceramic ware, Section 308. Heavy metals, such as lead and cadmium, are often used in enamel paints. Such metals, if consumed in large enough quantities, may be toxic. When metals are used on food packaging or food serving materials in the lip and rim area of a glass or a mug, such

metals are subject to regulation as food additives. However, a food additive cannot be approved for use unless it has been shown to be safe.

Section 308 of the Modernization Act restricts certain possible regulatory activities of FDA regarding lead and cadmium enamels. The first section of 308 imposes an one year delay on the implementation of any future ban of lead and cadmium based enamels in the lip and rim area of glass and ceramic wares. The second section, which is referred to as the shot glass exemption, prohibits any ban as an unapproved food additive, the use of lead and cadmium based enamels, on small glassware prior to January 1, 2003, and imposes certain restrictions on any ban imposed thereafter.

The final section I would like to discuss is Section 413, which is the study of mercury compounds on drugs and foods. Under this section, FDA must compile a list and

provide a quantitative and qualitative analysis of drugs and foods that contain potentially introduced mercury compounds.

FDA, subject to appropriations, shall conduct a study on the effect on humans of the use of mercury in drugs and dietary supplements also.

Thank you. I'd be very happy to answer any more questions.

DR. BRANDT: We have time for a couple of questions, if anybody has one. Dr. Harlander?

DR. HARLANDER: What are the practical implications of the health claims and nutrient content claims provisions? How do you see that playing out?

MS. DEPMAN: It gives people an opportunity to have a shortened review period. When there is an existing authoritative statement by one of these government bodies, they can use that statement. It's support that has been

specified by the Act, and in 120 days, mark it their claim, as opposed to going through the full petition process, because the scientific research has already been reviewed. It is out there; it is an authoritative statement. It has undergone the review process.

DR. HARLANDER: It doesn't necessarily meet the significant scientific agreement standard?

MS. DEPMAN: Yes, it does.

DR. HARLANDER: It does meet the significant scientific agreement standards?

MS. DEPMAN: Yes.

DR. HARLANDER: Thank you.

DR. BRANDT: Dr. Clydesdale.

DR. CLYDESDALE: After the 120 days, if someone says puts that on their label, can that be recalled?

MS. DEPMAN: Yes, sir. It can. FDA is allowed to issue a regulation modifying or removing the claim from the

market.

DR. CLYDESDALE: At any time?

MS. DEPMAN: After, yes.

DR. CLYDESDALE: It's never really approved?

MS. DEPMAN: They can use it. It can go out in the market 120 days, unless FDA prevents them from using it before the 120 days, but then afterwards, it has to be pulled off the market.

DR. CLYDESDALE: My mind says when something is approved, it means it's on and can stay on, I guess. That's not a legal definition. That's a Clydesdale definition.

MS. DEPMAN: The notification process is a bit of no news is good news. Once the 120 days is up, we still have the opportunity to give some bad news later, but it's to withdraw, instead of to prevent from going out into the market.

DR. CLYDESDALE: That would generate a recall of those labels then?

MS. DEPMAN: I'm not sure about a recall. I don't know the details of that.

DR. CLYDESDALE: At least a recall to change the labels.

MS. DEPMAN: It would definitely cause a change in the labels.

DR. BRANDT: Dr. Larsen has something to add to that.

DR. LARSEN: I would suggest that if you want to discuss some details about this, whatever details we can discuss, that we hold off until tomorrow and try to put Chris Lewis on the spot. It's the Office of Special Nutritionals and the Office of Food Labeling that are trying to deal with the practicalities of this provision of the Modernization Act.

DR. CLYDESDALE: I had the privilege of hearing Chris present something like this about a week ago and that's what triggered the question.

DR. LARSEN: We are putting her on

notice now.

DR. BRANDT: Let's take a 10 minute break. We are running way behind. A 10 minute break, that means by my clock getting back here at 10:20.

(Recess)

DR. BRANDT: Ladies and gentlemen, if everybody will come to order, please, we are ready to start again.

It is my pleasure now to introduce Mr. Joe Levitt who is the new Director for the Center for Food Safety and Applied Nutrition. You have an 1 page summary of his resume, telling you about him. I think it's fair to say he's a long term employee of the FDA, 20 years is a long time. We would now like to hear from him. Please.

INTRODUCTION OF CSAN DIRECTOR

MR. LEVITT: Thank you very much. I feel comfortable sitting right here and not at a podium, if that is all right. I'm happy to be here. I have just been in the job

right now less than 2 weeks. With your permission, I'd like to try to both help you catch up on your schedule and try to cover three main points.

Number one, I'd like to just introduce myself a little bit, tell you a little bit about my background, things that aren't necessarily on your one pager.

Number two, I want to really reinforce the importance of this committee, and this kind of process, and the significant help that you give us as we do our job.

And finally, I wanted to just tell you a little about the priorities, at least as I see them, in the very near term.

Number one, you will see I say three things, and then I'll go right down them. I'm not that difficult.

Number one, Dr. Brandt is right. I've been around FDA long enough to remember very well when you were Assistant Secretary for Health, and Mark Novich would trot down,

and meet with you regularly, and really valued the leadership that you provided. When I saw that you were chair of this committee, I said, what could be better? I know just in looking at the CVs and the background of everybody around here, we have just an enormous breadth of expertise.

In terms of myself, I have really been fortunate, worked on a lot of different parts of FDA, in general counsel And, in the Commissioner's office, in medical devices. I think what is significant or valuable for my current job is that I have had really just a wonderful opportunity at FDA to work at all levels. I've been functionally a division director, an office director, a deputy center director, a deputy commissioner. I worked in a lot of different areas. I've also worked pretty extensively in the foods area in some ways, especially in food labeling. I was very involved in the launching of the initial food labeling initiative and really got to

know a lot of people in the foods program through that way.

Notwithstanding that, it is clear that there is an enormous amount to learn, there is enormous breadth and array. I think probably one of the most significant things that I bring is a background that also has a broad array and is willing to try to take a step back, and see the big picture, and try to make things fit within a coherent hole to the extent that makes sense.

I am enormously both gratified, and I must say, somewhat humbled by the invitation and the opportunity to be the director of the Center, but there is a lot of good work to be done, a lot of important work to be done.

That's a little bit of who I am, where I come from.

The second point I want to make is again to really reinforce the value of this committee. Back when I was in the

Commissioner's office and even a little before that or around that, when Dr. Brandt was downtown, there was no Food Advisory Committee. We always both wondered why and hoped there would be, and sure enough, one has been established and, indeed, a fine one at that.

I've seen some of the work and have already been told of some of the good work you have helped us on, things like folic acid, things like BST, things like Ephedra, important significant issues.

What I will be trying to stress, and I think it fits exactly within the framework of this kind of committee, is really four general principles.

Number one is we need to stay focused on our mission. As even the name of our Center says, Food Safety, Applied Nutrition, which I'll paraphrase as disease prevention, these are the things we really have to be focused on. It's easy in a world

of so many different activities going on to stray a little, but we have to really keep focused on what our mission and what our goals are and be sure they are health and safety related.

Second, we need to base our decisions on sound science. You won't ever hear anybody from the FDA who doesn't say that, but I want to say very candidly, I know I'm not a scientist, and that, if anything, makes the importance and the value of good *bona fide* scientific advice even more important. I know I need to surround myself with good scientists, to be a good listener, and to rely on expert judgment. I will try to know what I know, and know what I don't know, and rely on others to really lead the way. We need scientific bases for our decision making if it is going to have credibility.

Third is openness. No matter where I've worked, FDA is the one. You're a black

box. We don't understand you. We can't penetrate you. That's true. I can say from working inside it's hard also; so for people outside, I know it is astronomically or exponentially harder to do that.

I will try to bring openness to the process, both openness internally to the staff, which I can tell you, I've got in a resounding salute and happiness towards. And this committee and this kind of process is one of the ways that we will try to bring openness to the proceedings.

I think it is very important that we have broad input, that people understand what's going on, that we hear from the scientific community, from the consumer community, from the industry community, so all that can be brought together and try to make coherent and rational policy.

Finally, efficiency. We have a lot to do. We don't have a lot of time to sit around not getting things done. I'm not sure

people would normally associate a public advisory committee with efficiency. We usually think of that as an internal thing, but I'm a big believer that the more important issues that are brought open, out front, in advance, the more that is going to help our long term efficiency. There is nothing that is more counter productive than to keep everything inside under cover, spring it on everyone, have it blow up in your face, and then you are spending a lot of time back tracking.

When you go back to focus on our mission, basing on sound science, and open process, and an efficient process, and all the ways you know you can help us with that, we will be looking forward to it. We will need your advice on new products, on emerging science, on implementation of new programs, and you are clearly an advisory committee I've been very pleased to see that doesn't just meet four times a year. You are a

working group; you are engaged; you are hands on, and I just think that's terrific, and it's delighted to be able to come to a job that has a system that is working so well.

Finally, priorities. Early on, as I said, this is probably about my tenth day or so, so you will forgive me if everything is not lined up, but it is very clear our highest priority is the President's Food Safety Initiative.

In my 20 years at the FDA, I have to tell you, I cannot think of another time when the President of the United States is out there saying go out there, go forth, do good work, protect the consumer; we need to enhance the safety of our products. It is an invigorating experience for those of us in FDA.

You heard some of the presentations this morning. There is a lot going on. I have been, I'll say, honestly amazed at the amount that has happened so quickly, even

with FDA. When I've gone over to the Medical Device Center, I worry very much about what's happening over in Foods. Just the initial briefings I've got on what is happening in a public education campaign to fight back on public meetings to deal with a produce initiative, on a whole series of implementation of seafood HACCP, and extending it to juice, and on and on down the line.

I will say it's a little chaotic still. There is a lot going on, but it is also a lot happening. I had the opportunity yesterday to be down at the Old Executive Office Building for a meeting with the head of the FDA, Mike Friedman, the Undersecretary for Food Safety at Agriculture, Kathy Ridecki, and others, that had a meeting to present the `99 budget where the President is asking for an additional $100 million for food safety. Think about it. For FDA at least, $100 million for food safety is really

a significant, significant statement that the Administration says we need to do better on food safety.

It is significant for us, and we are going to be putting all our force and effort behind that.

Beyond that, in my first couple of months, I'm going to spend a lot of time just being oriented, notwithstanding having been here 20 years as I said. There's a lot going on that I don't know about, a lot of people. There are some old acquaintances and friendships reinforcing, but a lot of new people I need to meet, understand, and get to know, both within the Center, within other parts of government. It's clear that the food safety program is a government wide program, USDA, EPA, CDC, and others.

We are going to work hard to forge those together, but I'm going to spend a lot of time just going around meeting with people, meeting with consumer groups, meeting

with industry groups, meeting with people in the Center, just to try to get a sense of what this is.

Finally, I'm going to spend a fair amount of time on recruitment. I'll be asking you for advice and suggestions. We have two significant positions right in the Center Director's office that are open. One is the director of the new Food Safety Initiative. We will be looking for somebody with strong scientific credentials, preferably a background in infectious diseases, preferably a medical background if we can find the right person for the job. Again, the focus is on food safety. We need to bring the best leadership, the best science to that.

If you have suggestions of people, please forward them to me, to Lynn Larsen. Let me know if you want to talk to me about some ideas. Please call me directly. I'll look forward to doing that.

We also have a deputy director for what's called the deputy director for programs, which really is, again, a significant position that has responsibility over food additives, over food labeling, over a whole host of programs within the Center.

What that also means, I have to tell you, since you see the slate is not full, is that people who are there are working double time, triple time, quadruple time.

Janice Oliver, who is also a deputy center director and is functionally now the deputy center director until I really get going, is just doing a fabulous job.

Bob Blake, who is the policy director, again, long, long experience in FDA. I'm very fortunate to have them at my side teaching me, showing me not only the ropes, but literally running the Center in this time.

My goal, I would say a year from

now, is to have a full team in place, a clear set of priorities. We will be having our own internal priority setting process, and we will be sharing that with you and getting your advice along the way.

With that, I think the way I would best summarize, and when I met with the senior staff the first day, I said, you know again, you look at, sometimes programs go in cycles; sometimes you feel you are on the up; sometimes you feel you are on maintenance; sometimes you worry you are slipping a little bit. This is a program on the rise. This is a program with a bright future. This is a program where there are a lot of needs and a lot of work to be done.

As I said, I look out in the Center, and all I see is opportunity. It's a great time to be in the foods business. I'm thrilled that you are all here to help, and to teach, and to lead, and help me learn.

With that, let me thank you. Thank

you for your attention and mostly thank you for your hard, and continued work, and support.

DR. BRANDT: Are there any questions? We have him at our mercy right now. We will give you another week to sort of find out what's going on; then we will quiz you.

We are glad you are here. We appreciate your being here. We hope you will attend some of our meetings, if not all of them.

I guess I have the most seniority of anybody, since I've been here since the beginning. I think somehow or other I have tenure as chairman of this committee. I don't know. Some strange thing happened.

MR. LEVITT: We could raise the notion of a lifetime appointment.

DR. BRANDT: Yes. We have had some interesting meetings, I must say, pickets, the old bit at times. Welcome. Feel free to

call on us any time we can help as individuals. I'll volunteer all their individual efforts, as well as my own.

Let's go then to the White House Commission report, Dr. Robert Moore.

MR. LEVITT: With your permission, I'll stay and listen a little bit.

DR. BRANDT: Please. We hope you will stay. Dr. Moore?

WHITE HOUSE COMMISSION REPORT OVERVIEW

DR. MOORE: Thank you for the opportunity. I have slides. While they are getting those started up, the introduction ones probably aren't too relevant.

In 1994, Congress passed and the President signed the Dietary Supplement Health and Education Act of 1994, hereafter referred to as DSHEA. Among other reasons, it was the intent of Congress to amend the framework used by FDA to regulate supplements, primarily to promote the availability of information that consumers

could use to make informed decisions about the use of these types of products to promote and maintain their health.

Among the other changes brought forth by the amendments, two related directly to this idea of increasing the amount of information available to consumers. First, it provided an exception for dietary supplements that enabled them to make certain claims on the label and, in their labeling that prior to that time, would have subjected the product to regulation under the drug provisions of the Act. Generically, these types of claims are commonly referred to as structure function claims.

The amendments also provided an exception that would enable certain types of published materials to be used in the promotion of a supplement and not be considered labeling. This is relevant, in that labeling can be used to establish the intended use of an article under the Act and,

perhaps, subject it to regulation under the drug provisions.

Therefore, it appears that the primary intent of the Act was to provide certain types of health related claims that didn't go as far as health claims, or disease, or drug type claims to be used for dietary supplements.

However, in establishing this new statutory framework for claims in dietary supplements, Congress also recognized that much was still not understood about the type of information that would be most useful, enabling consumers to make informed decisions, both about the type of information that would enable them to decide what types of supplements may be useful for their particular circumstances or lifestyle, but also what information would be useful in enabling them to avoid products that might also be inappropriate given their individual circumstances.

Thus, DSHEA contained a provision to establish a Presidential Commission on dietary supplement labels, herein the Commission. It's mandate was to study and develop recommendations to the Secretary for the regulation of label claims and statements on dietary supplements, the use of literature in connection with the sale of supplements, and procedures for the evaluation of such claims.

In developing these recommendations, the Commission mandate was to consider how best to provide truthful scientifically substantiated and not misleading information to consumers that would enable them to make informed decisions on the use, benefits, and limitations of the use of various supplements.

The Commission was enpaneled in February 1996 and released its final report on November 24, 1997. The report provides guidance and recommendations over a broad

range of subjects, including safety, the type and presentation of information on the label and in the labeling, the treatment of health claims under the Nutrition Labeling and Education Act, the scope of the so-called structure function claim, and the substantiation necessary for them, and the treatment of the so-called third party literature used in association with the sale of the products.

It also separately treated the issue of botanical supplements under DSHEA, and how a separate framework may also be appropriate for them under the drug provisions of the Act.

Guidance in two areas of the report address areas directly related to the mandate of the Commission, that is, what information do consumers need? And how do they use it to make purchase decisions? And second, how to assure that consumers have information as to what products may not be best for them.

It recommended that FDA work with outside entities to address these needs. It is these two areas that the Agency is asking the committee today to consider.

First, how can FDA work with industry and other interested parties in identifying and sharing information on emerging safety problems in the market place, and then work to rapidly resolve them to the consumers' benefit.

And second, how do we develop and execute studies to gain a better understanding of what type of information is most helpful to consumers in making purchase decisions and adjusting the Agency's regulatory framework towards dietary supplements to accommodate such findings.

Today, I'd first like to summarize the overall findings contained.

The Commission addressed three broad areas of information labeling, nutrition information and format, health

claims under the Nutrition Labeling and Education Act of 1990, and the scope of structure and function claims, and I'll touch on each one of these briefly.

On September 23rd, the Agency published final regulations that would implement the nutrition labeling and nutrient content claim provisions of DSHEA. These regulations become effective in March of 1999. In essence. DSHEA provided for slightly different presentation of information on the labels. For example, within the facts box, foods can only list nutrients that have a daily value established by the Agency. They cannot list the source of the material that provides that nutrient.

DSHEA amends that and, for all practical purposes, allows nutrients to appear in the supplement facts panel that don't have a DV established by the Agency, and they are allowed to identify the specific ingredient in the product that provides that

nutrient.

The Commission, in general, did not offer specific guidance regarding labeling and supported the Agency's rulemaking incorporating these requirements into the regulations, and except for a few technical areas that will have to be revisited, the regulations as published will go into effect in approximately 18 months and become the mandatory labeling for supplements.

Under NLEA, it was provided that manufacturers could make certain claims referred to as health claims about the relationship between a substance and a disease and labeling, if there was significant scientific agreement that the claim was scientifically valid, and the Agency had authorized the use of that claim prior to its being incorporated into the labeling.

The Agency published implementing regulations which treated conventional foods

and dietary supplements the same, even though the statute provided FDA the flexibility in treating health claims on these two categories of food products differently.

The Agency concluded that because of these claims and their relationship to associations between substances and serious chronic disease processes for which diet is but one possible factor, that the standard should be the same as to create a level playing field, and promote dietary changes, and minimize consumer confusion, if the Agency had established different standards and processes for the two types of food categories.

The Agency also believed at that time that the significant scientific agreement standard that was based on the totality of the publicly available information was appropriate for both foods and supplements.

The Commission report generally

agrees that this approach was sound, and that sound public policy in the interest of consumers had been best and continue to be best served by adhering to a rigorous scientific standard for the validity of health claims.

As recently discussed, the FDA Modernization Act of 1997 will result in a somewhat different framework for the authorization and use of health claims, but that is beyond the scope of our discussions today, and the Agency will address those issues in some future rulemaking.

The Commission did express, however, some concern about the process that FDA has used in the past to review health claim petitions and felt that it could be improved to include more input from experts and bodies outside the Agency which could serve to broaden the expertise in evaluating the given set of evidence.

As we heard earlier, that issue in

part will be addressed by the issue of authoritative statements from government bodies in the future.

DSHEA also added Section 403(r)(6) to the Act, and what this did was provide for dietary supplements to make certain types of claims, which the amendments term statements of nutritional support, but if you will, in street language, have been referred to as structure function claims in their labeling under a set of prescribed conditions.

First, it had to be acclaimed about either a classic nutrient deficiency disease, or a claim about the effect of a substance on a structure or function of the body, or the mechanism by which the substance affected the structure or function of the body, or a claim about general well being. Such claims are permitted without prior authorization by FDA, provided they meet other requirements in that section.

First, that the manufacturer have

substantiation that the claim is truthful and not misleading. That the claim contain a disclaimer that is stipulated in the statute and that the firm makes notification, notifies the Agency that they are using the claim within 30 days of making the claim.

However, what constitutes such a claim and where the line between an acceptable and unacceptable claim, if you will, is not clearly delineated in the statute.

The Commission considered this issue in some detail and felt that such information should provide useful scientifically valid information, which I'll touch on in a minute.

Second, they felt that such claims should not suggest disease prevention or treatment. Under the Act, claims about treating, preventing, mitigating, diagnosing, curing disease, cause the product to be subject to regulation under the drug

provisions of the Act.

Thus, the question of when a structure function claim crosses an imaginary line to become a disease claim is important with respect to information that can be placed on the label and in the labeling of dietary supplements.

The Commission felt that claims could include mention of organs, tissues, et cetera, and not be disease or drug claims within the meaning of the statute. However, they noted that such claims clearly must be within the ability of consumers to evaluate the claim in the context of any underlying implied relationship to some type of disease or abnormality.

In general, they concluded that claims such as restoring normal or correcting abnormal could be interpreted as to be implied disease claims and subsequently may cause a product to be subject to regulation under the drug provisions of the Act.

The Commission also agreed with the concept that structure function claims are distinct from health claims and drug claims, and that they should not state or imply linkage between the supplement or its ingredients and the prevention and treatment of disease, including explicit use of the words, treat, cure, prevent, mitigate, in the absence of any other linkage to a disease or abnormality.

The Commission also provided guidance on the type of information necessary to substantiate a structure function claim. It recommended that a person establish files, but it did not address the issue of whether such information should be available to consumers desiring to know the basis of a claim being made by a manufacturer or other responsible party.

The Commission believed that such evidence should include experimental or clinical data or findings of authoritative

bodies. It felt such information should be balanced, that it should be evaluated by an individual qualified by training and experience, but it also concluded that historical use could be cited as evidence for a statement, although it noted that the product must correspond to the composition of the historical product, and that such claims must be in their words carefully qualified to prevent misleading consumers.

However, it should be noted that there was considerable discussion between the commissioners, and it is reflected in the report as to what would constitute the appropriate balance between scientific and historical data for the purposes of substantiating a structure function claim.

The Commission also stated in their report that the safety of the product was a key element that should be included in the substantiation of any product claim, but it did not elaborate on the appropriate balance

between -- again using the ordinary meaning -- the risk and benefit in considering safety in relationship to any purported benefits of the product.

DSHEA also included a provision under Section 403(b) that provides for the use of published literature in the sale of dietary supplements. Literature used directly in the sale of a product is generally considered labeling under the Food, Drug and Cosmetics Act. Such information can be used to establish the intended use of the product for purposes of determining whether it is subject to regulation as a food or under the drug provisions of the Act.

DSHEA provided an exemption from being considered to be labeling certain publications used in connection with the sale of a dietary supplement. These provisions apply to specifically a publication, including an article, a chapter in a book or an official abstract of a peer-reviewed

scientific publication that appears in an article and was prepared by the author or the editors of the publication, and which is represented in its entirety.

Generally, this seems to mean that literature in its native form, native, undoctored or unaltered form, may be used, but that summaries and similar types of literature preparations can't be without risking being considered as labeling within the meaning of the law.

The statement of agreement that accompanied the Act seems to bear this out in that it states that this provision doesn't apply to summaries of a publication, other than an official abstract of a peer-reviewed scientific publication.

The exemption thus can be claimed if it meets five pre-conditions established in the statute. One, that it is not false or misleading. Second, that it doesn't promote a specific brand or manufacturer. Third,

that it is displayed or presented such that a balanced view of the available scientific information is there, which has generally been interpreted to mean that it prevents both the positive and the negative, not that it has to include all of it, just a representative piece. Fourth, that it is physically separate from the supplements, if it's displayed in a retail environment, and lastly, does not have appended to it any information, which in the ordinary sense of the meaning of the word would mean doesn't have a company logo or call-me-to-buy-it type information, that it is strictly a neutral document.

However, it left a number of issues unanswered and unresolved. The Commission report, while pointing out that these factors remain unresolved, did not offer any bright line definitions that would serve to clarify what constitutes a publication, and going to the third one, where the use of third party

literature, that is, documents that would summarize the scientific evidence that would be prepared by someone other than the manufacturer or the scientist and then made available to consumers, what constitutes a balanced presentation as far as the quantity of the positive and negative material and the spin put on it thereof, whether or not this information can be provided to consumers without subjecting the manufacturer to the possibility that if references of some of the information in there is related to diseases, would then represent it being used against them as representing it for other than food use within the meaning of the drug definitions, and then finally, whether or not promotion of a product, whether a manufacturer who prepares this information and includes it with his materials, whether that is with the product or physically separate.

This is important, not so much only

in the retail environment, but in mail order and catalog sales type stuff, where proximity isn't physical as much as it's spatial on the piece of paper.

Moving from claims, botanicals formed a large part of the discussion of the Commission, but will constitute the smallest of my comments here. Most of the issues are outside the area of responsibility of the Center for Foods.

Botanicals were noted to be a particularly complex issue. The Commission generally felt there should be a provision within FDA's regulatory approach to botanicals to at least enable many of these products to be marketed as either a food or as an over the counter drug product.

In part, this reflects their view and, I think, the common perception of most, that many of these products derive their consumer interest because of their use in traditional medicine systems.

The Commission recommended that FDA consider alternative regulatory frameworks to accomplish this guidance, that botanically derived ingredients have an opportunity to be marketed as either OTC drugs or as dietary supplements, and included in their guidance, the possible use of disclaimers to advise consumers that these were not supplements, that perhaps their evidence of substantiation was less than for traditional OTC drugs or an approval mechanism outside of the OTC monograph system.

In moving towards this, the Commission felt that a study of alternative approaches used elsewhere in the world to regulate such products may be helpful to the Agency in moving towards consideration of these recommendations.

As I said, the issue of how to treat drugs under the OTC monograph and under the drug provisions of the Act would be the responsibility of FDA's Center for Drug

Evaluation and Research, and thus, I won't attempt to comment on what their approach may or may not be.

Finally, before I move onto some of the other more germane subjects for today, the issue of research on dietary supplements was addressed. DSHEA also established an Office of Dietary Supplements in the National Institutes of Health, and they have the primary charge of coordinating federal efforts of research into the health and therapeutic benefits of dietary supplements and then offering advice to the Secretary, and the Commissioner, and other pertinent persons within the department on how best to apply this information and knowledge.

However, the Commission also addressed that there were a number of barriers that applied to the generation of supplements, that it may be that the Agency might be able to consider, as far as promoting better and more research in this

area, both by the government and by the regulated industry.

First, it noted that economies of scale were significant, that many firms -- this is an industry that to a degree is dominated by relatively small businesses. These are not the Merck's and Proctor and Gamble's of the world. Thus, individual firms may lack the resources to conduct the types of prospective control clinical studies necessary to provide a level of substantiation, either to support OTC use or to provide a level of scientific substantiation as it is commonly understood by many.

Thus, it was felt there may be opportunities for the government and the industry working as a group to come up with a different mechanism for joint funding or cooperative funding of research programs that would both substantiate claims and be useful in advising consumers of the appropriateness

for use of these products.

The nature of the research is also an issue. Many of the claims for supplements as noted are based on their use in traditional medicine. Many of the outcomes for both ethical and practical reasons are difficult to subject to a perspective placebo control type of study paradigm, and thus, there was some discussion in the report that the government could facilitate developing some guidance and some types of cooperative projects that would obviate the need for these types of controlled intervention studies and disease states, particularly in developing guidance and practical applications, in deriving some types of information from perspective or case control type studies, like epidemiologic studies and the like.

Finally, one of the issues raised was the development of government initiatives to stimulate research. One of the options or

suggestions was that the Agency consider a mechanism that would enable, if a certain degree of substantiation was met, that a firm would have the option of, for example, not including the disclaimer required under the statute as part of its claim.

It is unlikely that FDA on its own could choose to ignore a statutory provision of the Act, and as the Commission points out, in certain instances, a legislative fix is what would be needed, and perhaps both the Agency and other public health agencies within the government as well as the industry, it might prove useful to explore certain types of incentive mechanisms that would both encourage the conduct of basic research studies to substantiate claims in the private sector and explore both regulatory and legislative approaches that would both stimulate and codify those.

The major portion of the early part of the report, and part of it which bears

directly on today's committee deliberations are safety issues related to the use of dietary supplements in the market place.

The Commission stated in their report that they considered it axiomatic, that marketed supplements should be safe, and in its report it separated out four general issues related to this:

First, responsibility both of industry, government, and consumers in addressing this issue; surveillance for emerging problems; actions by the government against unsafe products; and appropriate use of warning statements and directions for use on the labels and in the labeling.

The Commission felt that manufacturers bear the primary responsibility for marketing safe products and in lieu of this, it should be noted that one of the provisions of DSHEA was a removal from coverage under the pre-market approval provisions of the food additive regulations

for dietary supplements.

The burden under DSHEA is on the manufacturer to assess the evidence that they have, to make it as the basis for a conclusion that a product is safe.

However, the report is largely silent on the Commission's interpretation of the term "safe," and what it meant it to mean. The report mentions that the government also is obligated to have in place adequate GMP regulations and other mechanisms to alert the public to safety problems and to initiate re-calls.

In line with this, in February of 1996, the Agency published an advanced notice of proposed rulemaking dealing with good manufacturing practices for dietary supplements. The second part of the Commission's deliberation after this will be considering a couple of the issues raised in that GMP rulemaking that was initiated at the industry's behest after they came in with a

proposed GMP framework for consideration by the Agency.

It should also be noted that FDA has no mandatory re-call authority over foods and thus, a limited enforcement tool with respect to re-calls is court action to seize a product or to encourage voluntary re-call by a firm who may have a product with safety problems.

Finally, the Agency does have mechanisms to disseminate information to the public when safety problems or dangers arise in the market place.

The Commission encouraged and reminded the Agency that it was its responsibility to take prompt action against unsafe products. Under the Act, FDA has the authority to remove unsafe products from the market place, primarily through its legal authority to initiate seizure proceedings, but in the case of dietary supplements, the burden is on FDA to prove that the existence

of significant or unreasonable risks exist under the labeled conditions of use or under ordinary conditions of use for a dietary supplement before it can argue that it's an adulterated product.

This is a resource intensive undertaking, particularly if it involves multi-ingredient products or novel ingredients for which there is not a lot of medical or scientific information available, and there is little practical knowledge of the ingredients used in humans or, at least, under the conditions of use that it is being entered into the market place.

The Commission recognized these issues, the relative paucity of information on certain ingredients, a lack of analytical methods, and in many instances, the difficulty in doing trace backs with dietary supplements and separating out effects in multi-ingredient products, that resource constraints may exist to limit the ability of

the Agency to develop the evidence necessary to take action against certain unsafe products, but the Commission also stated that the industry must accept its share of the responsibility for ensuring the safety of the supplements before they enter the market place, and when unexpected actions may appear in the market place, that they take the necessary steps under their ability to recall products, to remove unsafe products or products for which there may be questions of safety.

Under DSHEA, safety is linked to dosage and directions for use, even if higher doses may be harmful. The Commission concluded that consumers should be provided clear and adequate dosage recommendations. Moreover, they felt that a warning should be utilized when the need for a warning is indicated for the safe use of a product.

For example, if a product may be subject to abuse or there is risk of adverse

effects, dosages in excess of the recommended usage on the label, or if there were certain subpopulations that may be particularly at risk or have a narrower tolerance, the Commission suggested that if manufacturers were not adequately providing warning about potential hazards, FDA should use its authority to require a warning statement.

While the Agency has in the past and continues to consider the use of warning statements on products, for products that don't meet a standard for which a ban would be an appropriate remedy, it must be remembered that the process that must be used by the Agency, notice and comment rulemaking, is to a degree not a process that lends itself to rapid resolutions of eminent hazard type concerns, and while certainly the Agency has the authority and will continue to use it with regard to warning statements, this is an area that the Commission recognized that both industry and the Agency can work together to

probably find a better approach than simply relying on reactions to emerging market place problems and resolving them through notice and comment rulemaking.

The Commission urged FDA, industry, the scientific community and consumer groups to work together to improve post-market surveillance systems, including reporting systems to ensure rapid identification and correction of emerging safety problems.

The Commission recognized that current systems are passive in nature, that there is no authority of FDA to mandate the reporting of adverse events or safety problems to the Agency. It also noted that a number of systems exist independently, poison control systems, the Agency's MedWatch and its food adverse event reporting system, the USP has a system for products to meet its requirements. That coverage is limited and, in some cases, only for certain uses of a given product.

The Commission noted that all of these systems have inherent weaknesses. They are voluntary, and thus, they are likely to under report emerging safety problems in the market place. The reports need critical review, which may not always be timely and may not always get reported. The quality is uneven both through the various systems and depending on the originating source. Some may originate with consumers. Some may originate secondhand. Some may originate out of emergency rooms and have a fairly detailed record.

Finally, time lags may exist largely because the reports are coming into many sites collecting the information, into a Center database, to identify emerging problems. Nonetheless, the Commission recognized that these types of systems can provide wide coverage and are relatively cost effective.

The Commission felt that the

post-market surveillance could be improved, however, and it urged FDA, industry and others, including the medical community and consumer groups to work together to improve the systems, including information collection and to ensure that safety problems that arise are identified and corrected promptly.

Thus, part of what the Agency and the Center is asking the committee to consider today are the broad issues related to the Commission's guidance with regard to post- market surveillance systems.

First, the Commission noted that post-market monitoring is more than adverse events. It includes impurities, contaminants, safety, and although unsaid explicitly, product quality. As noted, reporting of adverse events, consumer complaints, product problems, is not mandatory under the Food, Drug and Cosmetics Act.

Moreover, the Commission repeatedly

stated that industry as well as government has an obligation to ensure the safety of marketed products with problems, which presumably includes the identification of emerging safety issues. Thus, to assist industry and the Agency in meeting its responsibilities, one of the things that we are asking the committee to consider today is to identify the medical, the toxicologic, and the communications principles and guidance that can assist both us and them in establishing a system that is more comprehensive than the current -- "hodgepodge" is the wrong word, but the current spread out system among many players to collect, evaluate and report potential safety problems, such that interventions can be undertaken.

The second charge in the general sense is that the Commission emphasized the obligations the government has to identify safety threats and communicate them to the

public and to the regulated industry in case they have not identified them independently.

The Agency accepts such responsibility seriously and is asking the committee to consider mechanisms that would enhance the Agency's ability to share its post-market surveillance information with consumers, industry and others to provide a more real time and a more comprehensive treatment of the information that the Agency has in its databases.

The Commission also addressed a number of issues related to the provision of information to consumers and other users of supplements, namely health care professionals, but the Commission recognized that there is little research on what information they use, where they get their information, and how they apply it to their purchase decisions.

The evaluation of consumer information needs relating to the use of

supplements is important, but it is an area where a paucity of information exists. The Commission raised several questions that are critical in developing policy or regulations on what specific information or format would be most effective in getting information to consumers.

How do consumers view current label information? And is it adequate to meet their needs? And does it vary among groups, perhaps older adults versus younger persons who are looking for different types of information or perceive certain claims in a different light, depending on their own circumstances?

We also don't know how non-label information is used. For example, do consumers rely on books and other media to make purchase decisions relative to a primary reliance on labels and labeling? Or do they rely on advertising in commercials or other types of information?

Finally, what is the extent of understanding and use of currently allowed label statements? Do consumers distinguish between health claims and structure function claims and the underlying basis that goes along with each one? Do they understand the difference between the substantiation and evidentiary standards underlying the different kinds of claims, or are all claims perceived in the same light and thus the current framework doesn't really meet the statutory goals of providing information that consumers can use to make informed decisions?

The Commission also addressed the guidance provided by some professionals and organizations on the use of supplements. The Commission argued that such advice maybe colored or biased by negative pre-conceived notions and attitudes on the parts of the person providing the advice or information, and that consumers may be better served if more and better information were available to

professionals to interpret and apply into their various practices.

The Commission urged professionals to become more knowledgeable, but recognized that limitations on the availability of information for them in relationship to their specific specialties exist, and thus it isn't at all clear what types of information and where they would get it would enable health professionals to better advise whoever their clients may be on the use of supplements.

The Commission recognized a lead role for industry in this effort. It encouraged industry to develop summaries of evidence and make them available to consumers. It also recommended that publicly available databases could be developed alone or in cooperation with the government and other interested parties that would enable consumers and professionals access to the latest information that they could use to then make their purchase decisions.

It also urged industry to consider establishment of an expert panel to provide scientific review and guidance regarding the safety benefits and appropriate labeling of dietary supplements.

Thus, the Commission recognized that little is known about consumer use of information and how various types of information are used in their decision making, but the Commission report recognizes that a public/private partnership will likely be needed to best undertake how to best understand how consumers use various information in their purchasing decisions and then to implement public and private practices to develop and convey that information.

Thus, FDA is asking the committee to consider what current research information is available on consumer use and understanding of currently available label information. What type of data is currently

available on consumer use of nutrition information in making purchase decisions and what type of information is likely to assist consumers most in making decisions about using dietary supplements? What gaps, if any, exist in data on how consumers use and understand the various claims presently in the marketplace, i.e., drug claims, health claims and structure function claims? And finally, do consumers understand and are they able to differentiate between the meanings and intended uses conveyed by these different types of claims that are authorized by the statute?

That's the end of my comments. I can address any questions.

DR. BRANDT: Are you going to be able to stay around for a little bit?

DR. MOORE: Yes, I can stay as long as you need me.

DR. BRANDT: I think what we will do is to get Dr. Castro, Dr. Elizabeth

Castro, to give her presentation, and then we will put both of you up there on the griddle.

DR. MOORE: Okay.

PERSPECTIVE ON WHITE HOUSE COMMISSION REPORT

DR. CASTRO: Good morning. My name is Elizabeth Castro. I'm with the Office of Disease Prevention and Health Promotion. I had the privilege to serve as senior research fellow for the Commission on Dietary Supplement Labels. I am standing in for the Executive Director, Dr. Kenneth Fisher, who sends his greetings and wishes he could be here with you this morning, but I am very happy to do so.

I see there is one of the former members, a scientist, Dr. Annette Dickinson in the audience, and I would like to greet her and acknowledge her.

It's hard to follow Bob Moore. He gave a very in depth analysis of the Commission, its report. What I would like to do is give you some of the highlights of the

Commission findings and then probably go into perhaps a little more detail of several issues that I was told were very important to you this morning.

I should reference this by saying that the executive director and the chair, the former chair of the Commission, put forth the idea that the Commission's report, and I believe you all have a copy of it, would stand on its own, and that interpretations, reading between the lines, et cetera would be unnecessary. Most of my comments are going to be very straightforward ones, and perhaps your questions can help bring out some other ideas that you would like to know about.

As I said, Bob did a very outstanding job of summarizing, but these are highlights that I guess should be presented, particularly knowing what was on the Commission's mind in devising this. First of all, safety was the primary concern, we will come back to that in a moment, in terms of

public health. The approval process was deemed should be similar for conventional foods and for dietary supplements.

The Commission proposed guidelines for statements of nutritional support. They reaffirmed that botanical products should continue to be marketed as dietary supplements. They came out as determining that balanced and misleading summaries of the evidence substantiating statements of nutritional support and product safety should be available to the public, and that the Agency should establish a review panel for over the counter claims for botanical products when manufacturers wish to make claims of preventive or therapeutic uses.

Finally, two ideas came forward under the framework of research that the Office of Dietary Supplements should be the focal point for health research and that Congress should fund at the level authorized by DSHEA, the office and the activities of

dietary supplements.

The critical nature of the points that are raised here were arrived at in a very long process, and it is the perspective of the staff that the Commission did an outstanding job of taking its charge from DSHEA, addressing many very difficult issues that are very complicated, and reaching a consensus and providing some input and outcomes for in depth analysis, of which you are involved now. They advanced for us the whole environment of the learning curve for dietary supplements.

Now, what I'd like to do just very briefly is give you some insight on the issue of consumer research and post-marketing surveillance, which I know you are tasked with straight away.

The Commission looked at consumer research on two different times. First of all, from the standpoint of use and demographics, who uses what, how much, what

are the product descriptions, et cetera. Secondly, consumer information needs and assessment of consumer understanding.

Under that first one of use, the Commission recognized that information on the research into vitamins and minerals is very well documented. The staff assembled for the Commission data from the NHANES studies, the 1980 FDA vitamin/mineral supplement intake survey, the national health interview surveys in HIS cancer risk factors supplement, unpublished studies from FDA, market studies from industry, all of these being viewed as being very critical to the overall thrust of understanding consumer use and describing the consumer themselves.

Also, as requested by the Commission, the staff met with a staff of the National Center for Health Statistics and discussed features in previous NHANES studies and future NHANES studies, giving credence to the fact that the Commission felt very

strongly that these sources of information were extremely critical, should be continued, and should be supported.

Another idea arose that I think is worth noting. I said that vitamin and mineral research was very well established and should be continued in their view. It was also thought that research beyond vitamins and mineral supplementation is very important and worthy of critical research, so that research on consumer use of botanicals and non-nutritive substances should be considered or should be supported strongly because there is a very large gap in comparison with the more traditional research on vitamins and minerals.

In summarizing this, the Commission felt a strong continuing need for assessment of data on who, how much, what types, and also beyond vitamins and minerals.

Also, I think it would be fair to say that there was an interest in defining

methodologies and improving the precision of the description of products that would be very important for the consumer, given that a large percentage of consumers use dietary supplements, and it would be impacting on their total nutrient intake, which is often a very critical part of many research areas separate from dietary supplements.

A second type of consumer research that the Commission put its attention to was assessing consumer understanding and consumer information needs. It was brought out in the report, if one can make the analogy between foods, other than dietary supplements, and dietary supplements and claims on each one, that for foods other than dietary supplements, it was difficult for consumers to distinguish between nutrient content claims and health claims, and the reference was given in the report.

If that fundamental difference is difficult for consumers, then what else is

difficult and how can this be assessed? In fact, there are some professionals in the field who have difficulty in determining the difference between nutrient content and health claims. The same would be true with statements of nutritional support.

Many questions arise. What we are trying to do for the consumer is very laudable and very important. Is it useful for them and how will they use the information.

This guidance was given by the Commission. The Commission urges that dietary supplement labeling be evaluated in additional consumer research to determine whether consumers actually want and can utilize the information provided by existing FDA regulations, by the regulations of DSHEA, and in the recommendations of the Commission.

The Commission recognized that consumer understanding of statements, of nutritional support and health claims, as

well as consumer perceptions of dietary supplements use, based on literature at the point of sale, are important aspects of the use of information and really do require additional and continual assessment, because there will be a dynamic system in which we are working. It will be changing, so continual assessment should be there as well.

There was a corollary to this research that the Commission raised, which is that research is needed on the attitudes of health and nutrition professionals towards supplements and the extent to which these attitudes are sufficiently informed and specific.

The Commission felt the reason this is important is because these health professionals, and they encompass many fields, are advising consumers, providing information to consumers, so they themselves need to be evaluated, their level of knowledge assessed, and how can information

be more readily available to professionals in order to help consumers is another area of study.

An idea that was perhaps lightly touched on by the Commission's report, but given, nonetheless, some significance, was what might be behavioral correlates of dietary supplement use. What could be developed into studies, such as lifestyle studies and dietary use, should be continued and encouraged.

Another idea that was raised and is in the report is that the Agency should be encouraged to take the initiative and any instances that are feasible in cooperating with the Office of Dietary Supplements and use that focal point for the Agency's vantage point.

I'm going to leave consumer research for a moment, and maybe we will come back to it if you have questions. I just would like to say a word or two about

post-marketing surveillance. This was, of course, addressed in the realm of safety, which was the number one priority of the Commission. The Commission recognized the importance of voluntary systems as Bob listed, and there are many of them.

These passive systems are very necessary components for public safety, but the weaknesses inherent in them are pointed out in the report, and it was hoped that there will be some mechanism or mechanisms by which these disparate groups, with a common interest, can be linked and can be perhaps coordinated and to share their information. Details were not given. Specifics were not given, and I think in deference to the experts in these different areas and in these different systems. However, the need was acutely recognized.

The guidance that the Commission gave, I won't repeat because Bob gave that to you, urging the sharing of information and

the coordination of post-marketing surveillance.

With that, I will conclude. If you have further questions, I'd be happy to address them.

DR. BRANDT: Thank you very much, Dr. Castro. If you and Dr. Moore could come down here and sit by each other and share that one mike now, we will open it up to questions of either Dr. Castro or Dr. Moore.

QUESTION AND ANSWER SESSION

DR. BRANDT: Dr. Harlander?

DR. HARLANDER: I'm wondering if the Commission discussed what data would be required for establishing dosage instructions for consumers. That seems like it would be a difficult area to deal with in terms of, particularly, claims that would relate to general well being. I guess I'm particularly interested in botanicals, not so much where we have a nutrient deficiency disease or we

have end points and bio markers and things.

DR. CASTRO: Specific dosages, no, weren't discussed at any length. There was a linkage of dose and dose information to perhaps the extent and the level of substantiation, so in other words, substantiation of a statement would be relevant only to a dose that was intended before a dose that was given on packages. That linkage was made. Other than that, I don't recall more specifics were given.

Safety, of course. The dosage with respect to safety is always linked, and there was a discussion that they would want to always have a linkage of the two, safety as opposed to the level of dosage.

DR. BRANDT: You are talking about the dose that the manufacturer recommends in the package?

DR. CASTRO: Both, that for certain, because that's the information given to the consumer, and that the statement

should support that.

DR. BRANDT: Her question was how is that established, does that have any meaning?

DR. CASTRO: Established by extensive research I think is how the Commission -- research from various sources so that it is balanced.

DR. BRANDT: Dr. Benedict?

DR. BENEDICT: I have just a couple of questions. The first one is, as I read the Commission report, it could be I overlooked the way it was phrased, but it seems to me that most of the definitions of "consumer" is someone who is interested in reading labels and who is interested in paying attention to this sort of thing.

I'm wondering, first of all, did the Commission discuss at all the non-informed consumer in addressing things that they might need to learn, people from lower socio-economic backgrounds?

DR. CASTRO: I would say that wasn't a general point of discussion, literacy levels for information, et cetera. I believe that might have been given or deferred to by those that would be expert in trying to reach difficult populations. There really wasn't a substantive discussion about that.

DR. BENEDICT: The second question is, as I read this, there are several references to flexibility that the consumers would like to have on labeling, to the mandate for making sure that information on dietary supplements becomes available to everyone.

I'm wondering -- I realize this is a hot issue -- I'm wondering if there are some brief thoughts you could render on emerging science as it relates to things that don't quite reach significant scientific agreement. It seems this Commission calls for a way to address that without actually

providing a way to address it.

DR. CASTRO: It's a thorny issue, the extent of substantiation of different types of use. One idea that kept running through was that the level of evidence required for a certain statement is linked to that statement. It's driven by the type of statement that is made. Recognizing there are different levels of statements should be a trigger that there should be different levels and rigor of the criteria. Other than that, I don't have any more specific insights to offer.

DR. BRANDT: Dr. Clydesdale?

DR. CLYDESDALE: Thank you. Everyone applauds the Commission on the movement towards more science and more rigor. I guess my question is, if one is going to consider post-market surveillance, I think the thing that has to come before that is assurances of GMPs. It's very difficult to do a post-market surveillance on a product if

you are not certain what's in it. It's very difficult to do post-market surveillance on a product if the active component is not regulated at least at a certain level.

I guess I find it had to talk about post-market surveillance unless I'm assured that there will be good GMPs.

DR. MOORE: I'd love to give you that assurance, but I'm not sure it's possible. Certainly, the intent is to move forward with GMPs, but it's not clear how much authority the Agency has. We don't have the legal authority to prescribe formulations for products. Ultimately, it will rest on each manufacturer to decide, if you will, what quality he wants, and if he wants 1 percent of an active ingredient or 90 percent, that ultimately will be up to him, because we don't have under the Act the authority to prescribe composition or formulations. The authority we have to do that for conventional foods comes out of the

food additive regulations, which dietary supplements are exempted from.

DR. CLYDESDALE: I'm sorry. Do you have the authority to say that if they have 1 percent or 90 percent, they have to at least label that, and GMPs have to assure that at least that 1 percent or 90 percent is present?

DR. MOORE: Certainly. That comes under the general mis-branding provisions. If they make a label statement, then the product has to conform to whatever statement that is. Where the potential problems lies, I think, is going back to where you are coming from. If someone wants to sell extra active herb X and chooses not to put the percentage of whatever active ingredient or whatever you want to call it, the inherent material, in there, that label statement is true, and he doesn't necessarily have to put it there.

There is not a mechanism for us to

say if you are selling a ginseng extract you have to disclose the goings-on sides. That only becomes required within the rubric of whether there are other claims on there that would make the disclosure of that material fact.

DR. CLYDESDALE: May I give you an example? When we had the Ephedra hearings, product lines that FDA analyzed varied from 0 to 600 milligrams of the active component of the same product, and I guess my question is, you can't do any meaningful post-market surveillance if there is a variance of 0 to 600 milligrams of the active component in a product.

Will the FDA have the authority to enforce that so that kind of thing stops?

DR. MOORE: I think where there are safety issues, there is probably a mechanism that can be done. You can set tolerances, and the example is what was proposed in the Ephedra proposal, that in an instance where

the concentration of some type of substance may present a risk to the consuming public, then you can probably establish limits or tolerances if that's necessary to ensure that the product doesn't pose a significant or unreasonable risk, but there is no mechanism under the statute that we can simply say you need to disclose all of the -- I'm struggling with the word because it doesn't exist -- the quality indicators of whatever your botanical or your substance is.

It's really an issue of whatever the manufacturer elects to put on the label as the quality he wants to meet, then that's all he's required to disclose. Unless there is a safety issue, we don't have the authority to require more.

That's terribly unfortunate; isn't it? The post-market surveillance would have to be used to find out if there is a safety issue.

DR. BRANDT: Dr. Wang?

DR. WANG: I have two questions. One is, there are four post-market surveillance systems presented in that document here. How is this information made available to consumers? Are they published somewhere so consumers can follow, and also is there an attempt to coordinate these four systems combined so that you have some type of alert system?

DR. MOORE: Those specific points are going to be covered in one of the later talks, and it may be better to leave it until then.

DR. BRANDT: Other questions? Dr. Rodier?

DR. RODIER: This is about the new Office of Dietary Supplements. NIH already has intramural and extramural programs related to nutrition. I'm trying to envision what the role of this new office would be. I understand that it's going to be the authority on supplements, if funding is

provided. How is that going to be related to the work that's gone on for many years at NIH?

DR. MOORE: I don't know, because I don't work at NIH. I was looking around to see if Bernadette Marriott was here. The flippant answer I can give is just what the statute envisioned is that there would be one federal office that would serve as a coordinator for the federal government's research into dietary supplements across both agencies and across the discipline lines with NIH.

DR. RODIER: Is the distinction that it is only going to deal with products as opposed to human health issues?

DR. MOORE: I think it is going to deal with substances as they relate to human health that may be marketed as supplements. Again, we are not over there, and their strategic plan isn't done, so I don't think anyone knows exactly where they are going.

Its statutory mandate is simply to coordinate and encourage sound research on the use of supplements and health, regardless of how they might get commercialized later.

I say that, because if you are doing research on a botanical as a cancer cure, then obviously when that gets commercialized, if it's a supplement, it's not going to be commercialized as a cancer cure because of the claims.

What their mission is, that's really beyond FDA, because they are not part of FDA. What they do is to a degree none of our business, and we have no say on it.

DR. RODIER: I don't mean to be flip either, but it sounds as though it's going to be an office of profitable nutrition as opposed to an office of scientific nutrition.

DR. MOORE: That I don't know. Like I say, it's not part of FDA. That was assigned to someone else.

DR. BRANDT: Dr. Harlander?

DR. HARLANDER: Elizabeth, I want to see if I understood you correctly, that there would probably be different kinds of statements, different language of statements that would reflect the different levels of substantiation of claims. I have a vested interest in this, because I'm working with the emerging science working group for this group. We have struggled with how to come up with a kind of language that would be understandable to consumers, that they would know this is something that's based on emerging science versus something that there was significant scientific agreement on.

Did I understand you correctly, that you actually have come up with language that's understandable to consumers, that claims are based on emerging science versus something that's been --

DR. CASTRO: No, I didn't mean to imply that it was already a set type of level

language. Actually, what you just said is the reverse of what I tried to imply, that manufacturers have the flexibility of making different types of claims, and the types of claims in an ideal world would be linked to the level of substantiation, whatever those levels are going to be defined as.

Whether the product is going to be marketed as a dietary supplement with this type of claim, nutritional support, or if it's going to try and move up to the level of over the counter product and make this type of claim, then it moves into another level of substantiation needs.

DR. BRANDT: Other questions? Dr. Clydesdale?

DR. CLYDESDALE: I'm sorry, I just have to get back to what we were discussing. I understand this is DSHEA. It's not you. If one is making a structure function claim for efficacy, and then one is also making a claim for safety, again, just so I

understand, there's no requirement to have assurances that the bioactive component that the structure function claim is based on is present at a certain level, nor any assurances that's there always at that level for safety issues. Is that correct?

DR. MOORE: Yes, no, and maybe, all at once. I think if there was general scientific agreement, and again, no legal meaning attached to it, that a certain -- for instance, the effects of garlic on blood lipids. If there is general agreement that it's due to a specific substance, and there is the market place, and it contains none of that substance but still makes the claim, then one could argue it is mis-branded, and it's an illegal product, and we could take action.

The burden would be on us to prove that was false, the claim was false or misleading because it was missing that "active" ingredient.

Certainly, at the present time for many products for which claims are made and the underlying physiologic or pharmacologic mechanism isn't known, it's very possible that there could be a substance out there with no ability to effect whatever the claim is, and no one is going to know.

There's no requirement under the Act. What it says is they have to have substantiation to support the claim. It doesn't say they have to have clinical evidence that their product necessarily does it. Certainly, there is an implicit understatement, I think, in the statute that if they are making a claim, there's a basis to support that claim, but they can rely on literature. They don't necessarily have to rely on individual clinical trials of their product.

DR. CLYDESDALE: One could, with the garlic example, have a structure function claim based on garlic, and they could have a

3 percent extract or a 90 percent extract, and that wouldn't have to be stated, even though we didn't know the single bioactive component, there could be in one case a 3 percent extract of garlic or a 90 percent extract of garlic.

DR. MOORE: It's not a simple answer. This is the one part of the final labeling regulations that is probably up in the air. Supposedly, extracts have to identify -- there has to be some identifying nature of what it is, 3 percent or what. We have run into a buzz saw that the reg isn't worded real well, and we are going to have to re-visit the issue.

All they would have to do is it would have to be a 3 percent garlic extract, whatever that means. They don't necessarily have to say 3 percent garlic extract containing X parts per million or X milligrams of substance A.

DR. CLYDESDALE: Thank you.

DR. BRANDT: One last question. Dr. Benedict?

DR. BENEDICT: Just to follow that, and I think I already know the answer, but it would be interesting to hear your comments, and that is, it's one thing, of course, to say there's a certain content, and you have already commented on that, but I never see anything about bioavailability as well. At what level does the authority extend to allow someone to ask about bioavailability?

DR. MOORE: What the law requires is that it be there. Whether it's available is a moot point, except if they make a claim about its availability, or if they claim to meet a compendia standard that has an availability requirement buried within it. Right now under our statute, all that's required is that it be there.

DR. BRANDT: Thank you all very much. We will watch this with great interest, I can assure you, as things

develop. We have discussed this in the past. We still are left with a lot of questions about how to determine effective dose; how do you determine an end point; how do you determine what concentrations are necessary, bioavailable, all those kinds of issues, none of which seem to be answered at the moment. Thank you.

We are going to look at consumers for a moment. Ms. Richardson, we expect you to chip in on this one; if you will. We have with us Dr. Brenda Derby and Dr. Alan Levy, who do not have prepared remarks, I am told, but want to lead us into a discussion. Come on, folks.

CURRENT STATE OF CONSUMER RESEARCH

DR. LEVY: I was told I should lead a discussion on the current state of consumer research with respect to the dietary supplements. I actually can endorse a lot of what Elizabeth talked about, that we really don't know very much about certain things,

particularly the things that are probably most relevant to the issues raised by DSHEA.

Most of the research that has been done related to supplements to this point consist of asking people in various kinds of surveys what their usage of dietary supplements is. We describe their behavior, and then we can classify them in terms of how much they use or whether they use at all, and then we can identify the distinctive characteristics of those people who use and how much they use in terms of their demographic characteristics, attitudinal characteristics, and to some extent, motivation.

From this research, I think we have a picture of dietary supplement users as information seekers, people who tend to inform themselves about the health effects of supplements. That's their motivation for using and buying supplements, that they want to achieve these health effects that they

expect these products to provide.

We understand that it's an uniquely information driven kind of consumption behavior. There is no experiential characteristics associated with supplements, they don't taste good, they don't give you a lot of pleasure, other than the fact that they provide these health effects.

What we don't have for dietary supplements is the kind of information that has been collected in the last 8 or 9 years with respect to food labeling, which was inspired by the NLEA, where we actually show people labels and product labels, not just ask them whether they like this or whether they buy the product, but we actually try to measure aspects of how people can use the information on the label, to what extent it facilitates the purposes they have for label information, nutrition information on foods, and that has to do with to the extent they use it for identifying whether the product is

high or low in specific nutrients, how it fits in their diet, or how it should be used in a balanced diet. People have different purposes for this information.

This is the kind of stuff that we don't have for dietary supplements in general, because we haven't actually looked at what information people use on the label and how they use it. We haven't really defined the different purposes that people have. We haven't really defined what the different types of information are available versus those understood by consumers and how they are used.

This kind of information was not generally available about food labeling 8 or 9 years ago, and it was only under the impetus of the NLEA which focused attention on certain issues and raised issues that made it possible to come up with focused questions that could inspire consumer research that we actually generated this kind of information.

Apparently, I think what stage we are at with respect to supplements is sort of like we were 8 or 9 years ago with respect to food labeling. We have something very similar to NLEA, a mandate to think about these things, a lot of uncertainties about how to proceed, and these uncertainties are going to raise fairly specific and focused consumer questions, consumer behavior questions, and that's going to allow us to design research to answer those kinds of questions.

My understanding is your mandate is to help us in that task and tell us what kinds of focused questions we need to address to deal with the issues that are being raised by DSHEA.

DR. BRANDT: You said these are information seeking people. Where do they get the information?

DR. LEVY: They tend to get it from reading.

DR. BRANDT: Reading what?

DR. LEVY: Health magazines, books, material that represents the state of the science to them. That's what they tend to do. They tend to be actually somewhat distrustful of traditional sources of information, doctors. They actually have --

DR. BRANDT: Science.

DR. LEVY: They read those books that represent what the state of the science is and claims about the efficacy of various ingredients.

DR. BRANDT: Dr. Harlander?

DR. HARLANDER: I think the information you have generated on health claims was extremely enlightening to all of us that heard it here for the FDA Advisory Committee. I think despite the fact that FDA has regulated food labels, consumers thought the food industry regulated the front panel of those, despite all of the education we have had around food labeling and all the

discussion we have had about health claims, and structure function claims, and nutrient content claims to learn that consumers don't really distinguish a difference between them and do not understand that FDA regulates those.

My hope is that will guide some of the research that we do on supplements as well. I think going into that research, I probably wouldn't have predicted what came out of it. Consumers, we really do need to rely on what consumers' perceptions and understandings are when we come up with language that might mean something to us, but mean something totally different.

I think the work that you both have done will help us in designing research going forward, and I hope we will look to that.

DR. LEVY: The one thing I would say though, I think it is very important research, and the unexpected findings from the things we have done is really a testament

to how important the research is.

One of the things I would say though, is I'd be very cautious about generalizing from the findings in food labels to dietary supplements. It's true that a lot of the things that we have said about the food labeling, the important difference between the front and the back panel, the problems in trying to assert authority in your statements and trying to say this is really authorized, and the difficulty of doing that, that may well generalize to dietary supplements, but I would not assume that without research.

DR. BRANDT: Ms. Richardson? She is here representing consumers, so fire away.

MS. RICHARDSON: You indicated there is not a lot of trust for traditional sources of information. Was there any explanation as to why that trust was lacking?

DR. LEVY: Not directly. The supplement users tend to be active

information seekers about the health effects and the product characteristics of supplements. They tend to get that information from the available sources. They are somewhat distrustful of traditional medicine.

There is an element of alternative treatment aspects in dietary supplements. You have to be a little careful. Half of the population uses supplements. It's actually very, very common behavior. Only about a third of those people are really heavy, serious kinds of users. They have distinctly different characteristics, more of this information driven, information seeking people actually read things.

MS. RICHARDSON: Of this 50 percent that are using, did you elicit from them an understanding about what is a supplement and what they expected? This is a discussion we have had before.

DR. LEVY: No, as I was trying to

say, most of what we know now comes from these interviews where we don't actually ask them directly about supplements. We ask them what supplements do you use? We get use characteristics, how much, if at all, do you use them. We don't actually show them a supplement and say, what do you think of this? We haven't actually done very much qualitative research where we just sit down and talk to supplement users and ask them some of these questions, which I think would be very enlightening.

One of the things I think we found in the food labeling thing is it turns out it is very useful, particularly when you start getting into some of the issues about how to represent science in an authoritative way. You need to talk to people face to face and actually just have conversations with them about it and see what they say.

People's failure to make distinctions about health claims and nutrient

content claims and their great reluctance to think of foods as drugs comes just from these conversations. You can easily pick up these things just by talking to them. That is one of the great gaps in what's currently available about supplements. Perhaps the industry has some proprietary information about this, but I'm not aware in the public literature any qualitative stuff on dietary supplement users, how they use information, how they factor in all this other information they have, how that relates to how they use what's actually on the product label. It's a key issue.

MS. RICHARDSON: With the people that you interviewed, was their understanding of a supplement the same as our understanding of what a supplement is? Did you ask them at the beginning if they used supplements, what do they understand that supplement to be?

DR. LEVY: We defined for them what a supplement was, a vitamin/mineral

supplement. We actually asked them about herbal supplements and herbal teas. We asked them specifically about things that contain amino acid. In order to elicit a response, we have to describe what we are talking about, and we did not really try to get to their understanding of what they think supplements are and what the limits are.

DR. BRANDT: Dr. Wang?

DR. WANG: I have a suggestion when you talk about the source of information, probably the consideration of the cultural background. I have friends that they treat ethnic herbal products as ethnic medication tied. They won't take that, but then their understanding of supplement is kind of confusing. They may get information from the health food stores or from friends.

Another area is to target the elderly population. There appears there is a network there to educate, or somehow the information reaches the elderly population.

My interpretation of their distrust of traditional science, or whatever, is their lack of knowledge of science. It's very difficult to explain to them what we perceive as science and what they perceive as beneficial to their health.

Another thing you might want to consider is cost. It's amazing that anything that's a benefit to their health, the cost consideration. Some complain it costs then $2 or $3 for a certain product, and yet they can get it cheaper, or some of them would prefer to buy more expensive for knowledge of what they are getting.

DR. BRANDT: Dr. Clydesdale?

DR. CLYDESDALE: If you were asking for suggestions as to what to ask, I would be very interested in finding -- I don't know how you would do this -- if there was a way to ask consumers if something appeared on the label assuring them of purity, or content, or availability, or efficacy, if something was

on the label voluntarily, would that make them buy one product over another.

I think we have an industry that in some places people are trying to do scientific things, and others are not within that industry, because on the label it isn't mandated that certain things be on the label. If we could find some consumer triggers that would give people some motivation to put things on the label, knowing that consumers would choose that product over another product, I think that would be very helpful to get around a law that doesn't mandate science, but would maybe have more responsibility on the producers of the product.

DR. BRANDT: Dr. Fennema.

DR. FENNEMA: Thank you. If information on emerging scientific issues is allowed to be placed on labels, what is your feeling, based on the way you have described the users of dietary supplements, wouldn't

they be unusually susceptible to accept these kinds of statements as facts, more so than the public in general?

DR. LEVY: That's an interesting question. That's quite possible. In our most recent research related to this, we had information use characteristics with respect to food labeling, and we looked at the characteristics of dietary supplement users in terms of how much they relied on front label claims, but with respect to foods, not dietary supplements.

One of the things we found was that dietary supplement users were more likely to rely on front panel claims of food. That would be certainly something to explore for dietary supplements, and in general, I think these people want good information and they are susceptible to good information. If we could give them clear signals of good information, I think that would actually have some impact.

DR. FENNEMA: You were also suggesting that they don't have much confidence in traditional sources of good information.

DR. LEVY: Right.

DR. FENNEMA: This worries me a little about putting information that is emerging science which they may very well regard as good information, since it is not a traditional source, so to speak, as factual.

DR. BRANDT: One last question or comment. Dr. Chassy?

DR. CHASSY: Have you collected data on that, I guess, any more narrowly dividing dietary supplements into categories? We sort of have a catch all phrase here that we are using. I have a suspicion that there are differences in behaviors between people that take vitamin pills and people that take botanicals. If you are not doing that, I think we ought to be doing that before we generalize.

DR. LEVY: We make a distinction between the multi-vitamin type products and the specialized products, which tend to only have one or two nutrients or minerals between botanicals, herbs, herbal products, and amino acid products. Those are the four that we have discriminated in our work, and there are probably many more distinctions that you probably would want to make.

There are clear differences in the types of people that are going to use -- the patterns of use depend on the type of product. People who use herbals or the amino acid products tend to be heavy users, or heavy users are people that are defined as using three or more products.

People who are light users only use one or two products. They almost always use at least one multi-vitamin product. The heavy user is someone who uses a multi-vitamin product, maybe at least one, and then multiple specialized products. Both

herbal and amino acid people tend to be, even more likely to be, heavy users. You have that kind of understanding, and you could probably develop that more.

DR. BRANDT: For those of you that have suggestions to make for them as they do more consumer research, get it to them. Dr. Larsen will be happy to transmit them if you get them to him, so that we can perhaps get the kind of information we need.

We are going to talk about it some more this afternoon, but all this talk about food and diet and everything, it's probably time that we see whether or not we can metabolize.

We will reassemble at 1:20. It is now 12:20.

(Whereupon, at 12:20 p.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:20 p.m.)

DR. BRANDT: If everybody will get seated, we can get started and try to stay reasonably on schedule this afternoon. We will welcome Dr. Clancy who has joined us. We are glad you are here.

We are going to begin this afternoon talking about post-market surveillance. We will begin with our good friend, Dr. Christine Lewis.

POST-MARKET SURVEILLANCE FOR DIETARY SUPPLEMENTS

DR. LEWIS: Thank you very much, Dr. Brandt. I want to just take a few minutes to talk a little bit about the course of all of this. I think from this morning's presentations, there was a lot of information given. I'd just like to spend a minute or two talking about the focus that's of interest.

Clearly, this food advisory's

session is focusing on dietary supplements, and it's focusing on the White House Commission report on dietary supplement labeling, and in a little while, it will focus on the notion of GMPs.

There are a lot of issues that are brought up by both of these documents. The reason for picking the three or four that we have developed into charges for the committee I think goes back to the theme that in all of the cases, the charges in some way or another look at the idea of collaboration.

The White House Commission report founded the theme of collaboration, and in many ways, when we looked at the response to the GMPs, we could see the need for collaboration, collaboration with industry, collaboration with scientific bodies, public health communities.

As we are going through all of this background material for you, and there will be more background material on post-marketing

surveillance, I think it's important to keep the idea that the charges for the Food Advisory Committee deal with this idea of collaboration, and if there were a theme to sound, I think that would be it.

Backing up then to this idea of collaboration, if we look at the White House Commission report relative to post-market surveillance, it does say work together to voluntarily improve passive post-marketing surveillance systems to ensure that safety problems are identified and corrected. That "work together" refers to the industry, to scientific communities, to public health communities and FDA, seen as a collaborative group.

Just as a background, what you are about to get in the next hour or so is a flavor for post-marketing surveillance across a lot of different issues and a lot of different regulatory frameworks in the sense of at least a couple.

The notion of post-market surveillance is not only what a lot of people want to talk about, which is adverse event reporting, but it's also product monitoring. We need to raise consciousness in your mind for both of those.

In the case of the adverse events reporting system, it does vary across the Agency. We have a couple of people here today from FDA who will address this.

I think an important notion in all of this is that sometimes it's voluntary reporting, and sometimes it's mandatory reporting. That's due almost exclusively to the regulatory framework for the particular product or for the particular center.

In the case of dietary supplements, which is the issue really before the Advisory Committee today, there are a couple of themes in post-marketing surveillance. I think you will hear those from the next three or four speakers. Because of the nature of the

regulations, it's clear that the system that is available to us is a passive one. There are no mandatory requirements for reporting. We want to emphasize repeatedly this is a very invaluable monitoring tool. It has been very useful to us, and it's something we support wholeheartedly, but there are a few hitches in this that sometimes make addressing safety a little more problematic. This again is going back to the White House Commission report, back to the idea of how can we collaborate to improve it.

You have heard already from Bob Moore and a little bit from Elizabeth Castro that not all of the events and problems are captured, because this is a passive system. There are lag times between the event and the reporting.

Information formulation and directions for use on these various products are hard to come by. I believe Dr. Litovitz from the Poison Control Center will also

emphasize the point that many times in the case of dietary supplements, we are not exactly sure what the product is that we are dealing with. We don't have a lot of information on the product.

Overall, just as a state of affairs, there is very limited product monitoring itself, separate from the adverse events system.

For today's presentation, again, this is to give you a flavor of how post-marketing surveillance is done. Not all of the speakers that follow me will deal specifically with dietary supplements, but often times it does come into their purview.

We have today a representative from one of the other centers at FDA, the Center for Biologics Evaluation and Research. The speaker is not Dr. Susan Ellenberg but --

DR. LARSEN: Dr. Marcel Salive.

DR. LEWIS: We also have a representative from the FDA MedWatch system.

We at the Center for Foods do use MedWatch. It's an umbrella type of surveillance system which cross cuts FDA. We do have Dr. Litovitz today to give us a little bit of a description of the poison control centers.

I will come back and try to talk a little bit more specifically about what we are doing at the Center for Foods in terms of post-marketing surveillance in general and then raise a couple of questions for dietary supplements.

That's to set the context and the tone. However you'd like to proceed, I'll just sit quietly here.

DR. BRANDT: Thank you very much for introducing the issue. I hope you do get your vacation soon.

We will now hear from Dr. Marcel Salive on post-market surveillance experience in other areas.

VACCINE ADVERSE EVENT REPORTING SYSTEM

DR. SALIVE: Thank you. I tried to

give handouts to the committee.

DR. BRANDT: I forgot. Let me interrupt you. You have a bunch more handouts at your place. Those of you on the emerging science working group have something that is in your chair. That will allow you to follow along. Go ahead, I'm sorry.

DR. SALIVE: I can work on some of the themes introduced by Dr. Lewis. Dr. Ellenberg couldn't be here today because of a family situation.

In CBER, the Center for Biologics, we do also use the MedWatch system, but we also use a system called the vaccine adverse event reporting system, and that's what I'm going to be talking about today. I would be happy to chip in on questions on the MedWatch system as well with the following speaker, but I'm going to focus on the VAERS, as it is now called.

As Dr. Lewis alluded to, the regulatory framework does have some

implications, and theirs was established in 1990 in response to the National Childhood Vaccine Injury Act of 1986, as HHS response to that. That covered pediatric vaccinations, those that are recommended by the Director of CDC.

At FDA, however, we expanded it to cover all licensed vaccines, so it does cover a broader scope than what was in the original law. All adverse events following all licensed vaccines is the focus for VAERS.

It is a joint project with CDC in the national immunization program. Certain reporting is mandated by law. As you will hear in MedWatch, drug manufacturers are required to report to FDA about adverse events they hear about, but the only instance where there is actually mandated reporting by physicians comes under this Childhood Vaccine Injury Act, where certain events are mandated to be reported into VAERS following certain vaccines. There is a table of events. I'm

here to say they are not police that go out and enforce those laws, but they exist, and we take them seriously, but it's a very tricky issue, I think.

As with most passive surveillance systems, reporting systems, there is a Freedom of Information Act piece, which allows the data to be available to the public. Those can go out. The NITS sells it, so it's an entire data set minus the identifiers can be obtained by members of the public or interested parties, or more narrow requests can be made under FOI to our office.

I should also mention that touches on the theme of collaboration. I didn't bring my slides on it, but the VAERS project is a collaboration with CDC. It's a very close collaboration there, but also for vaccine safety, we collaborate with the NIH, with the Health Resources and Services Administration for the vaccine injury compensation program, with the manufacturers,

with the other FDA centers. We collaborate on methods issues regarding epidemiology, and post-marketing surveillance, and certainly the MedWatch program. We do collaborate with industry to some extent.

Passive surveillance is kind of the theme. The objective, as far as for product adverse events, in this case, vaccine adverse events, it can be simply stated, the main objective is the previously unknown adverse reaction, and new knowledge about product safety is really the prime objective.

There are other secondary objectives. I think these are valid, but they are definitely lower, I think, on our list, and that is understanding known reactions in terms of their severity, whether there's an increase in the frequency of those events and also the prognosis for the patients who have those events. They are always interested in knowing the natural history of the adverse event. This in some

ways serves as a registry for those types of studies.

Looking at risk factors or preexisting conditions that may promote the reactions for biological products, where there may be variability by lot, we are interested in the safety of the product lot; a large batch of the product may have an unique set of characteristics.

Because the vaccines are such a high profile issue, we, in some cases, have established active surveillance, but that is much more costly, and that deals with higher levels of ascertainment of the events, or in our case, we try to link administratively between vaccine administration and uniformly ascertaining the outcome of the events.

I have given you the VAERS form, so I'm not going to discuss too much about the form itself. We do have a simple set of data elements, the patient identifiers which are needed by us to do follow-up, should such

questions arise, the nature of the reaction, the nature of what product was being used. We have a very detailed set of elements there for how the vaccine exposures can be described, exposures that might have occurred.

You are dealing obviously with dietary supplements. Dr. Lewis alluded to, we do occasionally receive reports where the person was getting dietary supplements and a vaccine, and there's some question about that, about what might have been a confounding factor.

Those are the main elements on the form, I think it's fair to say.

Passive surveillance has some draw backs. The prime one that we see is under reporting, although in some sense, this is a mixed blessing. We wouldn't necessarily want to hear about every known reaction that ever occurred. It might swamp our system. Certainly, the known and well characterized

reactions like rashes, fever, it might be a big waste of time for people to fill out lots of forms about those.

That leads to bias, potential biases in the system, but it does have the strength of serving as a signal. Sometimes boxes are left blank on the form, and you are not sure what that means. Does it mean they didn't have a past medical history? Or does it mean the person just missed that box and didn't fill it out? Missing data is sometimes ambiguous.

We have noted over time reporting biases, such as time after the event, if there is a long lag between the exposure and the event, people may not make an attribution of the event to that product and not report that in. We tend to receive only reports about events within the first 2 weeks after vaccination, for example.

There are sometimes geographic clusters, and sometimes these are based on

publicity, or sometimes local knowledge or local concern over certain events that may have occurred. The publicity effect, I think, is well known, and publicity stimulates reporting such as "60 Minutes" or the "Now" program, just articles in the newspaper.

A major issue is lack of exposure data, how many people got exposed to the product during a period of time, and also lack of controls.

There are some major advantages, one of which is the cost. It's not that expensive. It covers the entire U.S. It does serve as a signal generating mechanism so we can quickly recognize problems. We do receive the reports quickly. They are processed quickly and can be examined quickly. The data are readily available. We can look back because we enter everything. We can look back and see if this signal has a history of previous reports that are similar

in our database. Now that we have 8 years of data in the VAERS, it's becoming quite useful for sort of a repository of events. We have had useful findings, which I'll touch on a bit later.

I think VAERS is a little bit unusual in that we have multiple sources of reports. Obviously, they all go back to the patient, and the physician, and in this case, the parents of the patient, but the route that they get to FDA can be a bit circuitous for some.

As you see, a quarter come from the health care professionals, nurses, doctors' offices, and about a third come from the clinics in the state health departments where vaccine is administered through the state health departments, and those reports are routed through the state health departments. Because of our CDC tie, that serves as quite an useful reporting source, and really only a small percentage come directly from patients

and parents, but it is becoming more well known. I think we are getting more direct reports. This also affects the quality of the reports as well.

How many reports do we get? We get about 10,000 per year. It goes up; it goes down. Right now, we are at about 12,000. The 1997 number is about the same. We classify them using a regulatory criteria for what is serious, but it's comparable to a clinical definition of serious. It's regulatory in the sense that that way, we can mandate to the companies if it meets the criteria for serious and it's not in the package labeling, that should be sent to us right away, within 15 days, so we can look at it and make some assessment of it.

As I've said, many of the reports are commonly known reactions about rashes, fever, injection site swelling and redness, but we do get a fair number of serious reports and some fatal cases that are

associated in time with vaccination. These have been looked at in depth, and the Institute of Medicine concluded these were temporally associated, but not causally associated. Nevertheless, we have a high priority for reviewing and doing follow-up on those reports.

The FDA VAERS staffing is listed here. It has actually more than this. We have four medical officers, including myself, a nurse, a couple of computer people, a secretary, and some fellows who are conducting special studies under funding from the national vaccine program office.

CDC has about four or five people working on this, and the data entry contractor has actually around nine people working to collect and process the reports, and enter them into the database, and track them, and conduct some of their follow-up.

I think it's fair to say that at FDA, this is the most intensive scrutiny of

surveillance data that comes in on a routine basis in terms of if you compared this to some of the MedWatch pieces or other centers' surveillance systems. That's based on the priority that is accorded to vaccine safety in the Public Health Service.

What do we do with all of these reports? Quite a lot actually. The contractor sends letters out and conducts written follow-up for recovery status of all the serious cases after 2 months and after a year, to determine that.

Our staff does telephone the reporters of all fatal cases and selected other cases to obtain the sort of core set of information that can be compared over time.

We also, as a matter of policy, put high priority on new vaccines. There is a list here of some of the vaccines that have been approved in the last 3 years, which are receiving a lot of scrutiny because they have been -- I should say Hepatitis B was

originally for health care workers and then in 1991 was recommended for universal neonatal administration. Hepatitis A and vericella, chicken pox vaccine, were approved. Those were both approved in 1995. The Pertussis, a cellular vaccine, has been approved over the last several years, but now is used in infants. These were put into wide scale use in recent years, so those receive high priority.

We look at the lot specific data every week. We look at the serious reports every week, and every month we do have a meeting with other vaccine scientists in our Center to discuss current ongoing projects and specific cases, kind of like a rounds, if you will.

We have discussed some of the limitations. One I wanted to highlight. I think this is an important one, causality assessment. It's a very difficult issue with single case reports or collections of case

reports. In our scenario of vaccine exposure, sometimes you can conclude causality, but it's quite rare. You need these criteria to be filled at a minimum, and that is obviously the exposure had to precede the event, and in some cases, you have an unique vaccine association, like vaccine associated paralytic polio that can be isolated from sites in the body like the cerebral spinal fluid, where it shouldn't be, and then you can say, ah, this is a true causal relationship. CDC focuses a lot on that particular entity.

Another example is positive re-challenge, and that is simply the fact that the event occurred after the administration, and then reoccurred again after the administration a second time. That makes it much less likely that any event would be due to coincidence and might be causally related.

We have seen that in the case of

hair loss, where that provides some evidence of causality that's stronger than just simply this temporal association, once, where it might be due to coincidence.

The last criteria known to be drug related and no other confounding factors present. I think there are rare instances of that. We don't see that too much in vaccines.

Very few cases meet these criteria. A lot of the reports we get are "possible." We don't do causality assessment on our reports as a general practice, but if we did, this would be our problem. This is really why we don't do that.

There are a number of other considerations, and I think these would apply in the area of dietary supplements, many things are going on in the world. People are taking medications. They are getting vaccinated. They are eating. They are taking supplements. In our case, they get

multiple shots at the same time, thanks to the CDC's recommendations, which are sound, but this makes the issue of confounding very serious, and certainly the vaccine schedule is set up in a certain way. It's published every year. You can look at it. Certain vaccines are given once if you are a baby, and twice if you are over age 12. There are various things that are complexities.

In terms of lot safety, the size of the vaccine lot varies, so the number of events per dose varies or may be constant, but the size can be tenfold bigger; that lot may look like it has a lot of events versus other lots with very few.

We do get duplicate reports where the physician will send a report, the health department may send a report, the parents may send a report. I think we do have a record that we keep on these. It happens, and it varies, I think, depending on the seriousness of the event and the knowledge about

reporting that people have.

That is one of the reasons why on the VAERS form we have a lot of identifiers, so we can try to weed out these duplicate reports. Having identifiers raises some privacy issues, so there are trade-offs that are present here.

Normal variability, I think, is just saying that certain things happen in life. They may not be associated with the vaccine or as well, you know, there has to be a lot with the highest number of reports because that's the nature of statistics, I think.

There are changes over time. CDC's advisory committee is meeting right now too. They are considering possible changes potentially to the schedule. Certainly, there are new combination vaccines on the horizon that might be approved by FDA.

We have some challenges which I've alluded to, and one of them is definitely

risk communication, which I think is in your charge for the committee, where you have high scrutiny of common exposures that everyone can relate to that have adverse events. Certainly, the causality issue raises these as well. If you can't disprove that the product was involved, people may assume it was involved.

We have a lot of cases of sudden infant death syndrome, and if you are getting vaccinated every 2 months, a certain number of those will occur in proximity with the vaccinations.

We have found a number of findings from VAERS, which I'm not going through. I mentioned hair loss. It's not an exciting story, but it did get published in JAMA. We have collaborated with follow-up studies to study some of these signals in more depth, more rigor, using epidemiologic methods.

What impact have these had from our point of view at FDA? We revised the

labeling in conjunction with the manufacturer. We work with CDC's advisory committee, with their labeling for public health care providers. We provide information to physicians. I think Dr. Goldman will talk about this in more detail. We present to the public. We have a Web site.

Just to sum up, I have this diagram. The circle represents the real world in practice. People are getting vaccinated. A certain amount of them have adverse events. Some of those get reported. We can do more systematic epidemiologic studies to look at those in more depth. All of that information feeds into FDA actions, regulatory, such as inspections or re-calls, labeling changes, information communication to the public and physicians, and that ultimately has results and impact in the population.

I'd be happy to answer any

questions.

DR. BRANDT: I want to try to save all the questions on this.

DR. SALIVE: I am going to have to leave.

DR. BRANDT: If he has to leave, let's fire questions at him right now, if you have any.

DR. SALIVE: Otherwise, you can ask Steve all my questions.

DR. BRANDT: We will defer to him. That will be fine. Dr. Stephen Goldman will talk about MedWatch.

DR. LEWIS: I might add parenthetically that I didn't mention that Dr. Goldman is the associate director for medicine and in charge of MedWatch.

MEDWATCH SYSTEM

DR. GOLDMAN: I was asked, I think, to fill in on some aspects that maybe more global than specific for dietary supplements, but Dr. Salive actually has shown a couple of

my slides, showing great minds think a like, Dr. Salive.

I think it's always worth noting why we have post-marketing. One of the things I always like to go over is the inherent limitations of even the best design, best performed pre-marketing clinical trials, and the predominant limitations you have that are inherent to the system and inherent to way trials are done is short duration, in that even the longest trials generally don't approximate people taking medications or any other medical product chronically.

Now it's a population in which they are studied as soon as an agent comes out on the market, the populations in which they will be used are much broader and much more general than the populations in which they are generally studied.

Thirdly, a narrow set of indications that is generally studied during the pre-marketing phase, when a medication

comes out, as you are all aware in the United States, prescribers can use an agent that is felt to be clinically appropriate for an indication other than for which it has been approved, particularly drugs, in that sense, and the actual size.

Those are the power limitations of the pre-marketing clinical database. They do not ascertain the serious adverse event by virtue of the fact that they are simply not large enough to do so.

MedWatch is the FDA's medical products reporting program, and it is an educational promotional program, and I'll explain what I mean. MedWatch was started in June of 1993 with the express purpose of enhancing the effectiveness of post-marketing surveillance of medical products that are regulated by the FDA. What does that mean?

We have four basic goals. One is to increase the awareness of what was originally stated as drug and device induced

disease; it's all medical product induced disease, anything regulated or watched over by the Agency, all medical products.

A clarification of what needs to be reported to the Agency, facilitating, making it easier to report to the Agency, and fourthly, something which came up this morning in listening to the discussions, to better inform health professionals about regulatory actions that are taken by FDA in response to the reports we receive.

When we talk about reporting to MedWatch, we mean that the people should report when there is a suspicion that a medical product may be related to a serious adverse event. That is, causality is not a prerequisite for a MedWatch report. You do not have to be certain that the event in question was caused by the product or products in question.

In addition, something we always like to clarify. Dr. Salive touched on this

with the VAERS. We do not want increased reporting of all events. MedWatch is designed to increase the reporting of serious events. We are not seeking a report on every adverse event that occurs. The reason for this is fairly basic. We are trying to keep a system with as little noise as possible. We are trying to find the serious unexpected, unknown events to the national post-marketing surveillance system.

This is how "serious" is defined for the MedWatch system, and again, we are talking about voluntary reporting: Death, the most serious of all; life threatening; hospitalization, either hospitalization being initialized by the event in question or a prolongation of hospitalization due to the event or events in question; disability; congenital anomaly or an intervention being required, a medical or surgical intervention, to prevent permanent impairment or damage.

As you can see, any single event

could perhaps entail more than one category. People are perfectly welcome to choose more than one box when they send in the form, hoping to avoid the worse box of all, death.

These statistics are from early in the program. MedWatch was launched in June of 1993. This is a gauge as to how well we are doing when it comes to serious adverse events. I just need to make a couple of points on this slide. It's from approximately 3 years ago. The "serious" definition here is died, hospitalized or disabled. It does not include intervention required to prevent permanent impairment or damage.

If you notice, there was an increase in the relative percentage of serious versus non-serious reports. This has held. We run somewhat over 50 percent total serious reports since the MedWatch program started by virtue of the statistics we have available.

I would mention for drugs, it's closer to two thirds, that the reports that come in aren't serious adverse events. Other products, somewhat less.

We feel we are running at a fairly plateau level of over 50 percent. We'd like to make it higher if we can, but we feel we have had some success in increasing the percentage of serious events being reported to the system.

The bottom line is, in doubt, report. This is what we tell health professionals. This is what we tell consumers. This is what we want people to understand, that you do not have to be certain the event was caused by the agent or agents in question.

To reiterate what Dr. Salive was saying, with the exception of certain adverse events associated with specified vaccines, the ones covered by the VAERS program, health professional adverse event reporting in the

United States is voluntary. This is a very important point, because with a system that's voluntary, you are beholden in some ways to make it clear why you are asking people to report, and I'll talk more about that as we go along.

We have a single form that hopefully people have seen. This is it. Any agent can be reported on the MedWatch form. Obviously, vaccines, we recommend the VAERS form. Once again, sending them onto VAERS.

This is to reiterate that we would like to receive reports on any medical product other than vaccines on the MedWatch form, including what you are looking at today, the special nutritional products. They all go on one form.

Confidentiality. In a voluntary system, as you can imagine, this is a very important consideration for people to report. The patient's identity is held in strict confidence and is protected to the fullest

extent of the law. The reporter's identity may be shared with the manufacturer unless requested otherwise. There is a box on the form you can check.

FDA will not disclose the reporter's identity or identifying information concerning the person upon who it is being reported to requests from the public pursuant to the Freedom of Information Act, and I'd like to read that. In addition, this was strengthened on July 3, 1995, when a regulation went into effect extending this protection against disclosure by preempting state discovery laws regarding voluntary reports held by pharmaceutical, biological and medical device manufacturers. There it is, the yellow form.

Contrary to the slide, we have three ways at the moment. We have the form itself, which is postage paid. You can phone in a report. This is for health professionals only. We have a health

professional, a pharmacist, clinical pharmacist, taking reports over the phone.

If a consumer should call, the report is not taken directly, but we provide a MedWatch form; we provide instructions, with also a recommendation that they either work with or have their health professional, generally their doctor or pharmacist, work with them or fill out the form, but they don't have to. They can fill out the forms themselves.

You can fax them in at this number. Modem, we no longer have available. However, in the near future we will have a fourth way. That is reporting by Internet. We are very excited about this possibility of enabling people to literally go to our Web site, which I'll talk further about, and report that way.

What should be reported? I am currently in the midst of re-writing, revising the instructions for completion of both the mandatory reporting form and what's

relevant to this meeting, the voluntary, the 3500 report. We are trying to make the instructions as clear as possible. We are getting input concerning special nutritional products via Dr. Laurie Love of CFSAN, to put more wording in there to let consumers and health professionals know specifically what kind of information is needed with regard to special nutritionals. We are working on that now.

One of the things that we always try to make clear is that these reports are only as good as the information provided. As a clinician myself, we always try and make clear to put down both positive and negative findings. Sometimes a negative laboratory finding is just as significant, if not more significant, than a positive finding. People are welcome to include as much as they feel is necessary to get across what was done clinically. These reports are then evaluated by the health professionals who read them and

assess them. As Dr. Salive pointed out, the quality of these reports varies tremendously.

In addition to the adverse event reporting, there is also product problem reporting. Product problem is defined as a defective or malfunctioning medical product about which there is a concern about quality, performance or safety.

What are some examples? Here they are: Inaccurate or unreadable product labeling; packaging or product mix up; suspected contamination; questionable stability; particulate matter and injectable products; defective devices, and others. You can report on the same form. As an example, for drug quality, the reports go to the drug quality reporting system, the DQRS, and in addition, you can check both boxes. There are times that product problems cause an adverse event.

I thought you might be interested in who reports and what kind of reports we

get. This data is from the end of August 1996. This has generally held. About three quarters of the adverse event reports are on drugs. The rest, medical devices, a fair proportion, the drug quality problems I mentioned, DQRS, and there are food reports, biologic, and even early in the program, veterinary reports.

Who reports? The majority, that is more than 50 percent of the reports come in from pharmacists. A sizable proportion, although less, come in from physicians, and from other health professionals and consumers, non-health professionals, who are welcome to report under the MedWatch program.

This is to give you an idea of the difference between health professionals, as to what is reported. This data from May of 1996 showed that more reporting by nurses actually was on medical devices versus drugs. This has flipped. They are still the two most predominant reports by nurses, although

drugs are slightly higher now than devices.

This kind of information helps us to target when we educate as to the kind of reports we are getting from certain professions. Physicians, and this still holds, are predominately drug reports, although there is some reporting on medical devices. As you can see, on others, including foods, to a small percentage and in nurse reporting.

I'd like to mention the Joint Commission on Accreditation of Health Care Organizations, their stance on post-marketing reporting. They require hospitals to monitor for adverse events that involve pharmaceuticals and devices. They require that medication monitoring be a continuing collaborative function, and that medical product adverse event reporting should be done for applicable law and regulations, including those of state and federal regulatory bodies.

Well, that's interesting, because there is no mandatory reporting concerning these agents, other than medical devices. The only user facilities, and that's what these are, hospitals, nursing homes, outpatient treatment, and diagnostic facilities, and ambulatory surgical facilities, they are mandated reporters for device adverse event. However, and this is a little confusing, the health professionals within these user facilities are not mandated reporters, but the facility themselves are. Concerning drugs and biologics other than vaccines, as mentioned by Dr. Salive, the reporting is voluntary.

Concerning the holder of the NDA, that's not voluntary. That's under the Code of Federal Regulations. I won't belabor this. The 15 day alert reports, the most serious reports concerning serious and unexpected adverse events, as defined in the regulations, in addition, there are periodic

adverse event reporting. There are scientific literature reporting, results of post-marketing studies. These are mandatory reporting again for industry, for those who hold NDA.

Over the counter drugs. Reports are only required on those OTC products that are marketed under an approved NDA, including those prescription drugs that get switched to OTC status. Reports are not required for other OTC drugs, and as mentioned, there are many biases that can affect all the drug ingredients that are marketed without an NDA, although we certainly encourage voluntary reporting on those.

Spontaneous reports. Spontaneous reports are defined as all unsolicited reports from health professionals that we receive at FDA by either the voluntary or mandatory route. The reason why we mention that is when we tell people to report, we tell them to report to FDA, the manufacturer

or both. They have options. They don't just have to report to the Agency. They can report to the manufacturer.

These are clinical observations that originate outside of formal studies, and it's the combination of the adverse event information that is generated by all reporting that makes up the post-marketing surveillance database we have at FDA.

Dr. Salive went through this very nicely. I'm not going to run through it again. I'm simply going to mention two words that you may have heard in relation to that, that is numerator and denominator. The numerator is the actual number of reports that you get. Obviously, with under reporting, that number is affected, and as Dr. Salive mentioned, accumulation of numerated data.

The denominator data, the actual number of people exposed to an individual agent, is information often not available.

In that case, there are mechanisms and ways that we have to approximate the denominator data. Numerator and denominator considerations and the limitations involved make computing an incidence rate based on numerator and denominator data through a spontaneous reporting system problematic. That's always a concern you have.

In addition, we mentioned before the quality of the reports varies tremendously.

What are the advantages? Again, Dr. Salive mentioned these. It's large scale and cost effective. I'm not going to belabor that. I will make the same point Dr. Salive made, that the whole theory behind the spontaneous reporting surveillance system is to make the best possible use of the data that is obtained, to generate hypotheses, and to force suspicions based on what comes in in these reports, and to look at the signals of potential problems that are generated by the

post-marketing surveillance system.

When a report comes into FDA through the MedWatch program, it is sent onto the appropriate center. In the case of devices, CDRH. Foods and special nutritionals go to CFSAN. Medications, if there is a product problem, it goes to the drug quality reporting system, DQRS. Biologics go to the Center for Biologics. Drugs obviously go to the Center for Drugs. It is sent to the appropriate center.

MedWatch, that is the actual MedWatch program in which I work, we are not to report evaluators. That is done by the individual centers by their post-marketing surveillance specialists.

You probably cannot see this in terms of the actual numbers. It's almost pointless. What this slide shows, you will have to take my word for it, is the relative number of direct reports versus the relative number of reports that come in from the

manufacturers. The great majority of reports come from the manufacturers because by virtue of the mandatory reporting. A much higher percentage of the direct reports are serious versus the reports that come in from manufacturers who are mandated to send in the reports of which they are aware, serious or otherwise. That's why the percentages vary. Again, what is done with these reports is done in the individual centers.

This is basically just a printout of which reports -- the direct reports are the ones that come through the voluntary system. The 15 day manufacturer alerts and the periodic reports, which still make up the bulk of the reporting.

This is to let you know that we have what's called the MedWatch to manufacturer program, by which companies, manufacturers, can sign up and get serious direct reports sent to them that come in through the MedWatch program. This is not

automatic. Companies must sign up with us to receive the serious direct reports. I won't belabor the particulars. I will note that these are reports that we have criteria set up for, and the companies sign on with us, unless someone has stated they don't want their report shared with the manufacturer.

This is the essence of the program. We need to let the health professional community know that their report makes a difference. How do we do that? Based on careful analysis of spontaneous reports, FDA can initiate various actions, such as producing a Dear Health Professional letter from the manufacturer, making labeling, name or packaging changes; conducting further epidemiologic investigations; requesting manufacturer sponsored post-marketing studies; conducting inspections of manufacturers' facilities; or records; or working with the manufacturer regarding a possible withdrawal of a medical product from

the market.

Feedback to health professionals, which was brought up several times in the morning session. This is one of MedWatch's bailiwicks. We have the MedWatch partners. We have 130 health professional organizations who have signed on with MedWatch to agree to work with us to promote post- marketing surveillance.

These organizations include the American Medical Association, the American Psychiatric Association, the American Society of Health System Pharmacists. We have physicians, specialty, nurse specialty, pharmacist specialty, dental specialty and others who have signed on with us, from small organizations to some of the country's largest organizations. They work with us. They are notified along with the others we have.

The Drug Information Center, which has over 70 drug information centers, as soon

as a notification of a safety related notification has gone out from the Agency, of which MedWatch is made aware, we notify by E-Mail list serve all of the partners and the drug information list serve to let them know something new has come out.

We put this on our Home Page, any new Dear Doctor letter, Dear Health Professional letter, safety alert, from any of the centers that comes out which MedWatch is made aware of, it goes up on-line and is available to anyone who can get on the Internet.

We depend on our partners and on the drug information list serve to disseminate that information to their members, because we simply cannot do it ourselves. We rely on them to be our information extenders.

In addition, we publish in the medical literature, as Dr. Salive pointed out. We all do that. We have the FDA

Medical Bulletin, which is also available on-line, to which MedWatch makes a significant contribution in terms of material. We have the FDA on Internet, the FDA MedWatch Home Page is WWW.FDA.Gov/MedWatch. We post, as I mentioned, safety related notifications from all centers. We post safety related drug labeling summaries the month following when the change is made. That is available. We have been doing that for 18 months now. We post other publications that come out of FDA.

We like to think we have a wealth of clinical safety related information available to anyone who knows how to use or access or have someone else download from the Internet.

In summary, the effectiveness of any national post- marketing surveillance program depends on health professional participation. Pre-marketing clinical trials have inherent safety related limitations that

all of us in post-marketing surveillance recognize. The medical product safety profile of any medical product is an evolving ongoing process that's contingent upon post-marketing clinical experience. Spontaneous reports data have limitations and strengths. That problem identification and subsequent dissemination of safety related information begins with health professionals. And that we ask that health professionals review adverse event reporting as a professional responsibility.

I should also note we have a continuing education program by which health professionals can get continuing education credit. You have an example of one of them, the clinical impact of adverse event reporting that you were distributed today was one of our CE articles. That's good, I believe, for another month and a half, for doctors and pharmacists, and when CE runs out, we'd like to think the information is

available and is still good.

In closing, what we try to make clear to people, both health professionals and consumers alike, if it's serious, we need to know. Thank you.

DR. BRANDT: Thank you very much, Dr. Goldman. We appreciate that. Are you going to be able to stay around?

DR. GOLDMAN: Yes.

DR. BRANDT: Thank you, sir. Now, let's go to Dr. Toby Litovitz from the American Association of Poison Controls. She has given us two publications plus this reporting form.

POISON CONTROL CENTERS

DR. LITOVITZ: To follow this lecture, you are going to need both of these handouts, and there are lots of them in the back just outside the room, if anyone doesn't have it. I know the committee members have them at their seats.

Good afternoon. What I'd like to

do is describe to you today the American Association of Poison Control Centers' TESS post-marketing surveillance system, which is the toxic exposure surveillance system. It was piloted in 1983, widely implemented in 1984, embraced by most poison centers in the United States today.

If you turn first to the 1996 annual report, the white handout, this first table shows the growth of the system from a quarter million cases in 1983 to 2.1 million reports in 1996.

There are currently 75 poison centers in the United States; 67 of those poison centers participated in the TESS in 1996, and those centers serve 87.2 percent of the U.S. population.

Of the 67 participating centers, 49 are certified as regional poison centers by meeting minimum national criteria for the operation of a poison control center.

For those of you who are not aware

of what happens in poison centers, let me describe the basic criterion for a certified poison center. That includes 24 hour operations with dedicated staffing.

By dedicated staffing, we are not referring to the attitude of the staff members, but rather the fact that what they are doing on the job is just poison control. They are not also filling prescripts in the pharmacy or seeing patients in an emergency department. These individuals are highly trained. They sit for a national examination and become certified as specialists in poison information. The background is either a registered nurse or a pharmacist.

They have 24 hours a day Board certified medical toxicologists back up for consultation in more difficult, less routine cases. They do follow cases. Poison centers are handling telephone calls about poison emergencies. Lots of these come in from parents, but about a quarter of them are

involving health professionals.

The initial call is not the final contact with the patient. There are calls back to find out whether the symptom has resolved, what the final clinical effects were, and to continue to provide advice as the clinical course evolves.

There is comprehensive charting on each of these cases, with a full clinical history and documentation of recommendations.

There are other services of poison control centers, including poison prevention education for the public, which is delivered through the media, through presentations, attendance at health fairs for the distribution of materials, and professional education for health professionals in the poisoning treatment and in the diagnosis of poisonings.

How are the data currently collected? About a third of the TESS participants, and that's the poison centers

that submit to TESS, enter the data on a standardized report form. One of these forms was provided for you. This contains a detachable perforated medical and data form. It tears down the center. The data record is completed with a high carbon marker. It's bubbled, just like you would the old SATs, and then torn off, scanned through an optical scanner, which is programmed to check for information consistency and completeness. Cases are rejected if they don't meet the minimum consistency and completeness requirements, and they are corrected and re-scanned.

The other roughly two-thirds of TESS participants enter data using one of several computerized data collection programs.

What data are collected by these centers? If you turn to the next page in this annual report and look at table 2, you will see that we capture data on the site of

the exposure and the site of the caller. The vast majority of reports, in fact, are cases of poisoning that occur in the patient's own home. About 13 percent of calls originate from health care facilities.

Turning to table 3, you can look at the age distribution of poison exposure cases reported to the system, and you see that children under the age of six comprise 53 percent of cases. Remarkably, they comprise just 4 percent of the fatalities, even though they are the majority of the poison exposure reports. Sixty-one percent of poisoning fatalities actually occur in 20 to 49 year olds.

Take a look at table 5. Here you will see that more than one substance is implicated in 7.2 percent of cases reported to the system. We code up to two substances to brand, if the brand is known, and then we have the ability of analyzing the data for cases that are reported with a single

substance or cases that are reported with concomitance, depending on whether we are looking to focus on the toxicity of the substance implicated or total number of reports involved.

Table 6 shows you the reason for the exposure. In most of the cases, about 86 percent are unintentional. In contrast, most of the adult deaths, about 79 percent, are intentional. There were 123,000 therapeutic errors in this database in 1996 and 32,000 adverse reactions to drugs.

Table 9 shows the route of exposure. Multiple routes can be coded for a given case. Most exposures are ingestion's.

Table 10 shows the management site. Most cases are managed at home or at the exposure site, about 74 percent. We code the highest level of care which is provided. For example, if they are seen in an emergency department and treated and released, that will be coded as treated and released. If

they are admitted to an ICU, that would be the highest level of care, and that would be coded instead.

Table 11 shows variations in the outcome distributions from product to product that are key to identifying the hazards that are associated with the individual products.

We capture our outcomes in two ways. One is the definitive outcomes and the non-definitive outcomes. The definitive outcomes include no effect, minor effect, moderate effect, major effect, and death. Major effect is life threatening or resulting in permanent disability, and minor effect is limited to the GI tract or the skin, minimally bothersome and resolves without much treatment at all, and the moderate effects are usually more systemic and more prolonged than minor, but are not life threatening, so they fit in the middle.

There are actually specific coding definitions for the individuals who code

these cases who are the specialists who actually are handling the calls originally in the poison centers, and certain symptoms, for example, would force a case into one particular outcome category.

On Table 13, you can see that we also capture the duration of the clinical effects.

Table 15, certain therapies are collected, but these predominately are tox related interventions. They are the administration of specific antidotes. They are not general medical therapies for the most part.

If you turn to page 472, Table 21, what you will see is part of a long compendium of all the fatalities that were reported to this system in 1996. The substance implicator is reported for each case, along with the age of the patient, the chronicity, the route exposure, the reason for the exposure and where it's given, the

highest blood level that was reported of the substance that was implicated, and the time post exposure where that is known for the level.

On this page, you see two cases that involve dietary supplements. The first is Case 591, and this is a death from Ephedrine, an unidentified herbal, and EDTA. A 63 year old taking multiple herbal products and EDTA from Mexico for several years developed hepatic and renal failure. One of the products was a capsule containing high concentrations of Ephedrine. Post-mortem showed diffuse hepatic necrosis with viral studies.

Further down on the same page, Case 608, shows a death following the intravenous injection of an herbal tea preparation. This patient is actually abstracted on page 499, where we have pulled out an abstract of the cases that we feel will be generally of interest to medical toxicologists. In other

words, they are cases that aren't typical.

This patient had actually taken a native legend tea that was intended for oral use, and it was given intravenously to the patient. The patient had leukemia. It was used as a treatment for the leukemia, and reportedly there were a whole host of ingredients. None of these ingredients of course could ever be verified for sure, and she had previously received intramuscular injections without adverse effects, but then after the intravenous injection, there was immediate cyanosis, cold sensation, agitation, weakness and diarrhea, and she went on to die.

This data collection system wasn't set up to capture information on dietary supplements or botanicals, so we have been involved in a host of re-coding in the last few months. Where dietary supplement information was previously listed by its use or by what it was made from, you could have

found dietary supplements in the plant category, under miscellaneous drugs, under hormones, stimulants, cough and cold medications, sedatives, diuretics.

The intention is to move all these things into a category which is labeled dietary supplement/homeopathic. With that, we will be able to come up with at least some evidence of the total number of cases reported to our system with time. At the present time, we don't have a handle on that, because we have to go through and lump all of these together. We can, however, look at individual products.

The computerized compendium of product information that the poison centers rely on for product data to manage individual cases is called Poison-Dex. With one glaring exception, every major U.S. manufacturer, distributor of pharmaceuticals and household products, chemicals, and pesticides, voluntarily provide ingredient information to

Poison-Dex. The exception is the botanical industry. Only a small percentage of available botanical products and dietary supplements are listed in this computerized compendium by brand name.

The poison centers use Poison-Dex product listings and ingredient information to make treatment recommendations when patients are poisoned. In the absence of ingredient information, the patients are either over or under treated, and poisoning outcomes are obviously worse. It's always more difficult to treat a poisoned patient when you have no idea what the substance is that's involved in the case.

In addition, when a substance is not listed in Poison-Dex, it's difficult or impossible to do effective surveillance. Thus, a given brand name product can't be determined to be safe or unsafe unless the distributor ensures that the product is listed in Poison-Dex. Since many botanical

products are currently not listed, TESS data are much less accurate and much less useful for botanicals than would be for standard pharmaceuticals.

In addition, the surveillance of botanicals is complicated by the fact that the ingredients are often unknown, the toxicity data is often non-existent, the ingredients may or may not be accurately reflected on the label, the ingredients of a given product may change from time to time. Multiple ingredients may occur in a single product, often with obscure substances, about which little tox data is available anywhere.

The toxic effects can be due to contaminants, and there is no registry of products with reliable ingredient information.

If the botanical industry and the dietary supplement industry were to list their products in Poison-Dex or some other registry, then the TESS would become an

effective hazardous surveillance tool for the industry, allowing safe products to be recognized as safe, and unsafe products to be rapidly identified as unsafe.

My single most important message I think to this group is that without information on product ingredients and without a registry of products, no one can do effective surveillance in the United States, no matter how much money is put into improving or developing existing or new surveillance systems.

If we could turn to 22B, let's look on page 485, what you see here is a listing of all pharmaceutical categories with the number of exposures, the age distribution, the reason distribution, the use of health care facilities, and the outcome, where that outcome is definitive.

About 42 percent of the TESS database involves pharmaceuticals. Although this data is lumped by categories, you can

use the TESS database to look at an individual product by brand, because the data is coded by brand. We obviously couldn't possibly publish brand name information. It would take more than half of one journal.

That information looking by brand, just to give you an idea how that is done, if you will turn to this other handout, the blue one, which is titled TESS, and look at table 3 on page 9, the first thing that you can see is that we do capture specific symptom information. This is just a subset of the specific information, specific symptoms that are captured there, about 120 of them in total. They are determined to be either related, not related, or unknown if related.

If you look at table 12 on page 14, you can see that each case is given in a log type of listing, and for each case, you can determine the specific symptoms associated with that case.

TESS data have been used to support a number of regulatory actions, change in labeling and packaging of iron with OTC switches. TESS data has been used to support the OTC switches of enfads, of H2 blockers, and nicotine patches, and to support the EPA cancellation of the registration of several pesticides, and the CPSC requirement of child resistant closures on dibucaine, lidocaine and acetonitrale type of products.

I will close at this point and take questions later.

DR. BRANDT: You will be around?

DR. LITOVITZ: Yes.

DR. BRANDT: Thank you very much. Now, we will go back to the beginning, come full circle, to Dr. Lewis.

CFSAN'S CURRENT POST-MARKET SURVEILLANCE MECHANISMS AND SYSTEMS,

DR. LEWIS: What was intended with the last three presentations was to give the committee a sense of post-marketing

surveillance. Certainly, there are also other kinds of products and what not that are surveyed. That was to give you a flavor. I think one of the purposes we want to accomplish a little bit today, but more in the working groups when you do convene, is the idea of how dietary supplements specifically are handled now within CFSAN for surveillance, and then perhaps some more in depth review of the existing system as we go through the working groups.

We do have within the Center a system for adverse events reporting, which is the one a lot of people have been focusing on. We also need to talk briefly just about product monitoring, because I think a theme that's coming through is the idea that it's not just a matter of getting to adverse events, it's also a matter of looking at the products themselves and getting information about the products.

Overall, CFSAN has a central

processing and assignment unit. All incoming reports pass through a single office, and then the individual program offices subsequently monitor the products under their area of responsibility.

In the case of dietary supplements, they do go to the Office of Special Nutritionals.

Just as background, we at CFSAN have tended to group adverse events into four broad categories. Under Special Nutritionals, we have dietary supplements, infant formula, and medical foods, but we also do adverse event monitoring for products such as cosmetics and food additives, as well as what we would call traditional foods, such as seafood.

Depending upon what topics are hot, we see periodic increases and decreases in this type of reporting. It is, of course, characteristic of a passive surveillance system.

There are a couple of special considerations that we need to emphasize for the Center for Foods, but I think you have heard them in the other presentations as well.

This surveillance system plays an important role in the case of dietary supplements, because there is no pre- market approval, review or registration for these products. Our surveillance is not pre-market; it's post-market. It is as we have mentioned about 100 times before, a passive voluntary system, and there is no mandatory requirement for reporting. That means we do have to do often times follow-up to clarify.

As came out in Dr. Litovitz's presentation, the product information that is needed, almost no matter how it happens, there is not enough to exactly pin down the problem, the source, the issue, what was involved. This means follow-up is needed on

the product itself, the ingredient label, directions for use, what was actually in there, those types of pieces of information often are missing initially.

Also, in terms of getting to the heart of the adverse events, you need medical records and often times interviews with families and friends. Once the report comes, in many ways, it's the beginning as opposed to the end.

In terms of how these adverse event reports get to the Center, and again, I'm distinguishing that from the product monitoring, but how these adverse events relative to consumers get to the Center, the vast majority of ours do still come from the field. There's a special report that people in the field who receive these calls or other contacts can report the adverse event back to the Center. That's the majority of ours.

It's followed fairly closely by reports from the MedWatch system. As you saw

in Dr. Goldman's report, the MedWatch system does have a majority of its cases focusing on drugs, but there were some on foods and dietary supplements, and those do come to us.

We also get reports through the consumer hot line. We do run an 1-800 number at the Center for Foods, and consumers can report directly there. Then the last component is kind of a hodgepodge. We can get them from states, other government bodies, the poison control centers, also can report to us.

One of the tasks we didn't accomplish today was actually getting an on-line presentation of the kinds of reports that come in and the nature of the reports. I think, Lynn, you and I were talking about in the working group actually doing a demo so that the people who will be addressing the charge to the committee can get a sense of the kinds of data and the way in which they are presented to the Center.

In lieu of that, I thought I would just go through a couple of examples of products and food components, dietary supplement components, food components, that have involved closely activities with the adverse event reporting system.

In the case of tryptophan, which perhaps many are familiar with, several years ago, L-tryptophan supplements were found to cause a serious illness known as EMS. We had about 100 deaths or debilitating disease from this particular product. The supplement was being recommended by physicians for treatment of a mental illness in depression. However, most of the marketed product contained a contaminant due to inadequate quality control.

The AERs, the adverse event reports, gave us and CDC the pattern that we needed to help us nail down exactly what was happening, and it also helped us to convince the industry to voluntarily re-call this

product.

Another example involved potassium in a medical food. We had a report from an ICU that they were having problems with a complete nutritional product, a so-called medical food, in their unit. It turns out that patients with transient kidney and bladder impairment following trauma and surgery were ending up with hypercalcemia. The hospital on its own analyzed the product and found that it had over 200 percent of the labeled potassium. They notified us, and we followed up and identified it as being a problem of poor quality control in the manufacturer's plant.

In the case of infant formula, thanks to the AER system, we had clusters of complaints about infant formula products from a certain company. The complaints were generally mild, things like spitting up, crankiness, some diarrhea and vomiting, but they were clustered. The frequent clustering

suggested batch problems, some type of quality control problem.

Finally, after two clusters in quick duration, which we had field inspectors in the plant, it was discovered that the complaint clusters were associated with a breakdown in the production-line. The product was basically sitting for 24 to 36 hours. This resulted in a warning letter from us, and the problem cleared up.

I will mention just briefly the plantain digitalis issue, although this will come tomorrow again with GMPs as an example of how there are ways in which we can work with the industry to get at these types of problems. There was a 21 year old woman who was hospitalized with digitalis poisoning. She was not using any digitalis containing products, and she was not responsive to the usual treatment for digitalis toxicity, which suggested that the course of digitalis was other than a drug form.

FDA investigated, and it was found that a herbal cleansing product was associated with this woman's condition, and when it was analyzed, it was found that the plantain labeled product contained digitalis lanata. This is a botanical containing a digitalis like glycoside.

It was chased to a raw bulk ingredient which had been imported, and as a result, there has been a voluntary recall of these products.

The REO hair color, I mention only because it's not a dietary supplement issue, and I wanted to let you know that the adverse event reports at CFSAN do deal with other products. In this case, it was supposedly a hair coloring product, and it was the opposite of Rogaine, more or less, all the hair fell out.

I've got a flip set of slides here, what's being done and what's not being done. Currently, with the adverse event reporting

system, we do log in obviously all the ARs that are received. However, we must monitor manually for patterns and problems. We do use it for some limited research. The Office of Women's Health has taken a look at some of the ARs to consider some research problems. It is used primarily as a trigger or a support for regulatory actions, and we do use it to meet Congressional requests for information.

It is there and to the extent that we can, we try to make the information available, but what is not being done, due to limited resources at this time, is a couple of things that I think would be helpful and address some of the concerns the committee has already raised and questioned.

At this point, we do not have routine printouts of what's in there. I might add parenthetically that we are working frantically to get a form of the adverse event reporting system on the FDA Web Page so

that interested persons can access it, and there is a search system for that particular database.

It's not yet ready, which is why we are not demoing it today, but hopefully in the future, for the expert panel, we will be able to demo it.

We can't follow-up on all the incoming hot line calls. If it comes to us through the normal adverse event reporting way, of course, it gets logged in, but we aren't doing as much follow-up, especially when there is a lot of media coverage.

Thirdly, we are unable at this time to provide feedback to states, public health communities and the industry. There is interest in this. We don't have a system in place. Again, this feeds into this notion of collaborative efforts, the overarching theme perhaps of this particular working group meeting.

If we put adverse event reporting

to the side for a moment and think more in terms of product monitoring, we do have a very small limited program at CFSAN, and I would like to describe that to you. I think as you consider the charges to the committee, you may want to look closely at the kinds of things that are being done here.

Basically, the product monitoring falls into two categories, a surveillance program and special assignments. In the case of the surveillance program, it focuses exclusively on label accuracy. It does not have a safety component. It focuses on vitamin/mineral products. It does not deal with botanicals or animal based products such as glandulars. The special assignments, we will review in a moment.

Let me talk just a little bit more about the surveillance. The surveillance program is conducted by the field. We plan for a total of 60 firms being inspected, of which we hope the inspectors will pull about

150 products a year. In all candor, we don't hit that number. We don't come terribly close to it.

Each field district is asked to inspect and collect vitamin/mineral products. They are then analyzed for their content and checked against label declarations. That is the sum total of the surveillance program.

The heart of our safety product monitoring really comes down to special assignments. These are samples that are collected when there is reason to believe there is a problem. Most of this is triggered by the adverse event reporting system, so the two are married in a way, when you see some problem or issue being focused on by the adverse event reports, then there is a special assignment made to the field to go and collect the problem product.

They do locate it. They do collect it, and it is analyzed. It is our primary safety activity, but clearly it's reactive,

it's not proactive to a problem.

I've thrown a couple of wish list items up here because, for a previous presentation, we had to sit down and think about some of the things that we would like if we could get them. It was interesting. The first item on our wish list is one that is clearly sounded in a lot of the reports and advisory recommendations made to the Agency, and that is, we would like more coordination and collaboration. We'd like it with the industry. We'd like it with health professionals. We'd like it with state and public health communities. We'd like it with related programs, for example, such as those with the poison control centers.

That's our wish list in terms of a generalized approach, and then we, of course, have a wish list that has a lot more to do with resources. We would like better in place coding systems. I think we need to think about that coding system being one that

would allow us to work with other centers or other groups, because there is no point inventing a coding system that doesn't allow us to hook into other types of data that would be out there.

This is another wish list related to resources. Again, this is strictly a matter of better software, better hardware, electronic transfer of data and staffing. I think a monitoring system where we could respond to the kind of questions you had, how are you making this available to consumers, how are you making it available to the industry, we would definitely like to accomplish that, but running parallel to this is the notion of the need for methods development for composition and identification.

Dr. Litovitz also touched on this. It doesn't do us a lot of good to get information about something if we don't know what's in it, we don't know how it's made and

we don't know exactly what it's doing. We do need some of that.

Those are some overarching themes in terms of how it's handled at the Center. In terms of the charges to the committee and how the working groups might further pursue this, I think we need to come back and periodically re-visit what it is the Center for Foods and Applied Nutrition does exactly with dietary supplements.

The intent today was to give you a flavor, and I am not the center's expert on this type of surveillance. I'm a pitch hitter today. I am going to rely on the other people who gave some presentations, as well as others in the room to help answer any of the more general questions you might have.

DR. BRANDT: Thank you very much. I wasn't responsible for the telephone ringing.

DR. LEWIS: No, I think it was my supervisor.

QUESTION AND ANSWER SESSION

DR. BRANDT: Dr. Goldman and Dr. Litovitz, if you all would come join her there at the end of the table, please, we will now open up for questions, comments, et cetera. Dr. Applebaum?

DR. APPLEBAUM: This is a question for Dr. Litovitz. If you would, please, and Dr. Lewis just echoed it, and I wrote it down, so if I paraphrased it wrong, please correct me. Again, you essentially said that you can't do effective surveillance if you don't know what you are looking for or you don't know what you have.

Could you elaborate on that a little bit more? I might have a follow-up question.

DR. LITOVITZ: The typical call that comes into a poison control center about a dietary supplement involves someone who has taken one or many different preparations and

has a symptom. Chances are 50/50 that we will know what's in that supplement, what's supposed to be in that supplement. Where we think what might be in that supplement, who knows what the chance is that we are right?

For us to capture data as we capture data on everything else that comes in, we know how many exposures to Clorox there were. We know how many exposures to Tylenol there were. We know exactly what the distribution of lesions and adverse reactions and symptoms. We are capturing data really on some product which may or may not have a name. And we may or may not know the ingredients, the intended use and what the toxicity is.

It's that inability to have the database that has a listing of the products with their ingredients and with the information about the toxicity of the ingredients that really paralyzes us in the acute management and the surveillance

problem. There is no product listing that's stable. You don't know what's in a product at a particular moment in time.

DR. APPLEBAUM: The usefulness of this type of information is what? I mean, fill in the blank.

DR. LITOVITZ: For some substances, it's fine. If you go in and you look for St. John's Wart, chances are that's what you got. For other things, it's worthless. We have no way of managing the patient. We have no idea what we are capturing.

DR. APPLEBAUM: I guess what I'm trying to get to then, and I'm just wondering because of the various committees that are identified, consumers, GMPs and post-market surveillance, for post-market surveillance, you need to know what you are looking for. And I'm just wondering, in terms of the questions posed to those who are going to be looking at post-market surveillance, is it a little bit like putting the cart before the

horse?

We are talking about post-market surveillance, but at the same time, there isn't any certainty as to what is there because of GMP issues. I'm raising this question because it just triggered me to think even more, what are we going to aspire to in terms of recommendations if the basic information is questionable?

DR. BRANDT: That is, of course, an issue that Dr. Clydesdale worries about a lot too. It was a major issue when we held the Ephedra Mawong hearings, because nobody knew what was in that stuff, except that we knew Ephedrine was in there. It ranged from 0 to 600 milligrams of Ephedrine, depending on the bottle you picked up.

My own opinion, which I will now give you free, is that they ought to go in hand and hand. We have to know more about what's in this stuff, and at the same time, we have to have some surveillance system out

there that will allow us to begin to detect adverse events and, therefore, leading to all the other chain and the manufacturing issue too.

We have the whole set of problems. It's the age old issue of trying to solve a problem when you don't have any data, which I love to do, by the way.

Dr. Fennema?

DR. FENNEMA: Yes, this is about serious adverse effects. Given the fact that the Food and Drug Administration has a responsibility for assuring the safety of dietary supplements, and given that the dietary supplement industry has what I would regard as less dependable systems for assuring the safety of their products than do the food industry, would it be unreasonable to require, make mandatory, the reporting of serious adverse effects by the manufacturers of dietary supplements and by health professionals?

DR. BRANDT: Who is going to take that on?

DR. GOLDMAN: I'm going to defer to Dr. Lewis.

DR. BRANDT: I don't blame you.

DR. LEWIS: As you know, the statute provides that the first step in determining the safety of the product is the manufacturers. They are not required to come to us for that type of review. Therefore, because there is no pre-market approval and the safety does rest with the manufacturer, the FDA responsibility is in the area of this post-marketing surveillance. When safety problems arise there, then it's very important that we take action.

As far as requiring mandatory reporting, of course, the statute does not provide for that. I think in many ways your question was rhetorical. Where the recommendations are pushing us, and we are going willingly, is this idea of what can we

do collaboratively. Clearly, they have something that can help us, and we have something that can help them. How best do we bring these two together?

DR. FENNEMA: You can't very well do a good job on post-market surveillance if the manufacturers and health professionals are not required to respond to incidents of serious adverse effects.

DR. LEWIS: We would indicate that complicates the situation, yes.

DR. BRANDT: That's a nice bureaucratic answer.

DR. LEWIS: I'm well trained.

DR. BRANDT: Dr. Wang?

DR. WANG: I'm glad that L-Tryptophan was brought up. When we talk about serious adverse events here, we are talking acute, and after the diagnosis or the newspaper announcement about L-Tryptophan, we started getting a lot more calls of people who had chronic views, and then they

developed this chronic symptom they didn't identify.

The question I have for poison control is, the way I understand it, people get poison substance exposed, and who made the diagnosis? When they call up poison control centers, they want help. How do you get them to tell you it is probably a dietary supplement they have taken or something unusual they have taken?

DR. LITOVITZ: The caller to the poison center, first of all, when they first call, they think it's an anonymous call, although it doesn't evolve into an anonymous call. Eventually we get their name and number. But they are calling with a question, and the question is usually about a substance. That information about what is implicated is offered right up front. We know immediately what they think is the product, but we may or may not know what's in it.

DR. WANG: It is the consumer who thinks what it is. It's just like food poisoning, when they say, well, I have stomach cramps, who diagnosed that as food poisoning could have other --

DR. LITOVITZ: That's right. It's the consumer calling with the question, and then it's the poison center that will make an assessment as to whether it's related. If they call with something we know couldn't possibly cause those symptoms, or it's a preexisting fever, and then they had the medication, we try to sort that out, but obviously, it's not perfect.

DR. BRANDT: Dr. Clydesdale?

DR. CLYDESDALE: Does FDA have any information on the number of companies and/or associations that are listed in the report that recommend there be an 800 number for customers to call? Do we have any idea of how many companies or associations, supplement associations, recommend to their

constituent memberships that at a minimum, they have an 800 number for them to call?

It would seem to me that minimum would begin this area of collaboration and cooperation. There is no way to enforce that.

DR. LEWIS: No, we don't have it specifically. We need to roll us into the idea that dietary supplements are foods, so we don't have GMPs or those types of things for foods either. Companies with adverse events in conventional foods are not required to report to us either, and how many of those have 800 numbers also, I'm not sure. We don't know.

DR. BRANDT: Nobody else has their hand up, so I have a question, unless there is objection from somebody on the committee to my saying anything.

There is sort of a perception, and indeed, some claims that dietary supplement safety is not really an issue because poison

control centers don't get many calls about dietary supplements, and yet what we heard from Dr. Litovitz was part of that is a coding problem. I would suspect or would postulate that somebody who gets sick and has been taking only a dietary supplement would rarely associate that dietary supplement with their illness. Is that a reasonable assumption?

DR. LITOVITZ: It's definitely true that the fact that the public believes the dietary supplements are safe influences the data. For example, you don't see any suicides with dietary supplements. People don't believe they could kill themselves with them.

DR. BRANDT: We have had some kids who committed suicide with some of these Ephedrine containing substances for sure.

DR. LITOVITZ: I really shouldn't say it that way. When I compare, for example, hypericin with the other

antidepressants, I look at a 57 percent suicide rate with the traditional antidepressants and a 7 percent suicide rate with hypericin in our database. It's that belief that you can't kill yourself that keeps people from even bothering to try. Obviously, it's a bias in the data system.

We have noticed the comments in the press about how our data shows that there are no problems with dietary supplements. Those quotes did not come from us.

DR. BRANDT: I wasn't accusing you of anything. Any other questions? Dr. Benedict?

DR. BENEDICT: Do you have an idea about the demographics, the type of people who actually call the poison control center? Are there not people who just get over it and don't call, or people who get ill and are adversely affected? I'm trying to get a feel for what sampling of the population you are getting.

DR. LITOVITZ: Unfortunately, I have no way of knowing what sampling I'm getting, but you are unequivocally correct. If they don't make the association, they will not call. Even if they do make the association, if the symptoms are minor, they also may not call. It's not like an acute poisoning event, where you just saw your child stick something in their mouth and you are in a panic state. A dietary supplement phenomenon would evolve over some period of time, and people would have more time to think about whether it's necessary to query.

DR. BENEDICT: The reason that I'm sort of asking is, is it the opinion of the collective three wise persons that this is the way to go to get post-market surveillance on dietary supplements? Do you think this will be an effective way?

DR. LITOVITZ: I think it is one approach to capture some of the cases. I think that a passive reporting system is

going to be a whole lot cheaper than going out and asking every single person who takes a dietary supplement, or a sample of persons what kind of effects they had as a result of that.

DR. BENEDICT: Would you argue that education might be a more important factor than just passively waiting?

DR. LITOVITZ: Education?

DR. BENEDICT: Of the consumer.

DR. LITOVITZ: To do what?

DR. BENEDICT: To watch out for dietary supplements, in the event that they OD or whatever happens.

DR. BRANDT: They can't report it if they OD.

MR. GOLDMAN: I think I can make a couple of comments as a clinical pharmacologist, not necessarily as an FDAer in this sense. The reason why Dr. Salive and I in particular always like to point out both the limitations and strengths of

post-marketing surveillance is these are known. These have been known for years. Any system you have, whether it's a system that is set up in Europe or the systems we have here, have no limitations and strengths, which we have enumerated.

I'm going to focus for a minute on education. One of the most important aspects to get someone to think about an adverse drug event, as an example, and diagnostically, is to think about a differential diagnosis, that common things occur commonly, and making the attribution at the bed side that something someone is taking is showing a clinical syndrome rather than a disease state, separate from whatever medical product you have taken, as you know, is actually a fairly sophisticated thing. You must educate people, and you can't just educate them once as second year medical students or as pharmacy students. This is a continual process. You must educate.

This is one of the things that frankly we do at MedWatch, knowing this as health professionals ourselves, that this is something you must constantly reiterate. I think it impacts whether it's Toby's system, in terms of poison controls, or it's a system we have, whether it's Dr. Salive's VAERS, or the MedWatch system for the other products, I think there are general principles irrespective of product that have to be acknowledged.

Having said that and given my admittedly limited knowledge of dietary supplements versus drugs, you seem to have some particular difficulties that Dr. Brandt had alluded to and I think Dr. Applebaum had said, about the actual products you are dealing with.

I would like to make a clinical pharmacology point, that many of the adverse events that we pick up, the serious unexpected events that we see in

post-marketing, are not always ones that you could have predicted because of pharmacokinetics. They are pharmacodynamic. This is a very important point to make, because whether or not the strength is 200 milligrams or 2,000 grams, or whether someone is taking one blood level versus another, you cannot always predict a priori what you are going to find clinically.

I think this is one of the reasons why these are the nuances and shadings that come up when you do post-marketing surveillance.

DR. BRANDT: We thank all three of you, Dr. Goldman, Dr. Litovitz and our friend, Dr. Lewis, who we see a lot of. One more question.

DR. RODIER: I just wanted to drive Dr. Lewis crazy.

DR. BRANDT: Okay, go right ahead.

DR. RODIER: I know the whole goal here is to get consensus and get

collaboration, but one way to educate the public, if a product has no requirement for having any known ingredients or anything that might offer protection if you take too much of it or whatever, it might be possible to educate the public by having an instructional label that says this product, the ingredients in this product are secret; you should take this into consideration before you ingest it.

I think FDA is going to put itself in the position that they say they are doing post-marketing surveillance, and they are not doing post-marketing surveillance. In fact, it's a total void. I don't think you ought to rule out the possibility of something that's fairer to the public. We are always complaining about how the public, everyone is science illiterate and people believe anything.

I think it's perfectly reasonable of the public to assume that if we say we are going to post-marketing surveillance, that

that's what we mean we are going to do. To say we are going to do it when we know it can't be done, I think that is really mis-information. That's how I'm going to drive her crazy.

DR. MOORE: Dr. Brandt, I think I need to clarify one thing. You have the mistaken impression that they don't have to declare their ingredients. They do have to declare their ingredients on the label. What they don't have to do, and what Dr. Litovitz was saying, is there is no requirement that they tell the poison control centers, Poison-Dex or whatever. They don't have to register their product. They don't have to tell them what the formulation is.

The product that is in the market place, while we may not have a quantitative formulation, we know the ingredients, but we have post-marketing surveillance with foods. There is no requirement for food companies to disclose their formulations of their

ingredients.

I think there is a mistake to think that supplements are somehow this hybrid animal that is different than foods. We have all the same limitations that we have with conventional foods with supplements.

DR. RODIER: There is one difference, and that is that all the supplements are being advertised as being health providing. Nobody tells you a steak is going to do your blood vessels any good.

DR. LEWIS: I think we can bring this up in the working group.

DR. BRANDT: I think so, too. I just have to comment, Dr. Rodier was pointing out she wanted to drive somebody crazy. One of my colleagues a few years ago was bugging me, and I said, you know, if you don't quite, you are going to drive me crazy. And he said, that's not a drive; it's only a short putt.

Let's take a break and be back at

3:25.

(Recess)

OPEN PUBLIC HEARING

DR. BRANDT: We are now in the public hearing. We have two people that have signed up to speak to us, and others will be given the opportunity. Let me point out to members of the public who are going to speak, you will be limited to 5 minutes. As you approach 2 minutes, I'll warn you with a two. As you approach one minute, I'll warn you with an one. That's where we are.

The first person is Dr. Regina Hildwine from the National Food Processors Association.

THE NATIONAL FOOD PROCESSORS ASSOCIATION

MS. HILDWINE: Thank you very much, Mr. Chairman, members of the committee. I thank you for this opportunity to present our views today. I'm Regina Hildwine, not Dr. Regina Hildwine, although I played one on

TV. I'm Director of Food Labeling and Standards for the National Food Processors Association or NFPA, which is the principal scientific trade association representing the $430 billion food processing industry.

NFPA has three laboratory centers, and we are the leading authority on food science and safety for the food industry. We have been in operation for more than 90 years, and during this time, the food industry has relied on NFPA for government and regulatory affairs representation, scientific research, technical services, education, communication and crisis management.

My presentation today will focus on the issues of dietary supplement safety and identity with special emphasis on post-market surveillance systems.

As an aside, I would like to note that NFPA made two presentations and filed comments with the Commission on Dietary

Supplement Labels. Our focus at that time was on label claims, but safety of supplements is a primary importance to NFPA.

NFPA supports the recommendation of the Dietary Supplements Commission that post-market surveillance for supplements is needed. NFPA believes that any post-market surveillance system should be strong, even if it is a passive surveillance system. A strong and even robust passive surveillance system should be designed so that it is able to respond in a timely and appropriate manner.

The Dietary Supplement Commission offered guidance that this surveillance should be a cooperative effort between government, industry, the scientific community and consumer groups. While these parties are all stakeholders, NFPA believes that the greatest burden should belong to the dietary supplement industry. There are several reasons for this view.

First of all, by law, dietary supplements are part of the food industry. Since the supplement industry no longer needs to prove safety of ingredients prior to marketing, that is since by law, ingredients of dietary supplements are no longer deemed to be food additives. NFPA believes the supplement industry should assume responsibility for the safety of their products after they are marketed, just as the conventional food industry does.

To set the stage for a market full of safe products, the dietary supplement industry would be well advised to review ingredients of dietary supplements under the standard of generally recognized as safe. Many ingredients of dietary supplements have a history of use, so grass determinations should be possible.

Ingredients of dietary supplements should be held to the same grass standard as conventional food ingredients. Grass panels

established by the supplement industry would not be the first instance in which an industry develops it's own grass list. For example, there's a well known one developed by the flavor and extract industries.

With respect to any adverse reports after marketing, the dietary supplement industry is likely to receive regular input from consumers and the trade. Some of these reports may be associated with safety. Most, if not all, of these comments/reports will go no further than the manufacturer or distributor.

Situations involving actual or potential illness or injury episodes are likely to be reported to FDA as part of voluntary product recall procedures. The industry likely will receive more reports than any other entity, FDA, CDC, U.S. Pharmacopoeia, a poison control center, or any other surveillance body.

Furthermore, adverse incidents

involving tampering are likely to be reported to manufacturers first. This is the case now with the food industry. Clearly, the industry is likely to be the first and best repository of these data, and the industry is also in the best position to initiate prompt action.

I'm going to skip a little bit here and talk about identity of dietary ingredients. To ensure consistent formulation, the dietary supplement industry should develop product standards, including identity, potency and quality. While it may not be necessary for FDA to promulgate regulations on standards of identity, industry standards should be in place. The supplement industry can work cooperatively with U.S. Pharmacopoeia or Food Chemicals Codex to develop these product standards. This is a logical component of good manufacturing practices.

NFPA believes that processed

documentation to ensure consistent product is an appropriate part of good manufacturing practices. The conventional food industry typically uses such in process documentation and controls, many of which go far beyond those required in the food GMPs. This is part of the industry's commitment to consumers.

In conclusion, NFPA believes that the dietary supplement industry should carry the burden of monitoring products in the market place to ensure they are safe, and the industry should commit to developing product standards to ensure consistent identity, potency and quality of dietary supplement products.

NFPA supports a regulatory policy which is consistent for all foods, including dietary supplements. We feel this way for label statements related to health and nutritional benefits of products, and we especially feel this way regarding the safety

of products. Dietary supplements are foods, and they should be treated like other segments of the food industry.

Thank you. I'll be happy to answer any of your questions.

DR. BRANDT: Thank you very much. Appreciate your being with us. Our second speaker is Dr. Annette Dickinson from the Council for Responsible Nutrition.

COUNCIL FOR RESPONSIBLE NUTRITION

DR. DICKINSON: Thank you, Mr. Chairman, for the opportunity to make some very brief statements. I am Annette Dickinson. I'm director of scientific and regulatory affairs for the Council for Responsible Nutrition, which is a trade association of dietary supplement manufacturers representing more than 85 member companies.

I was also a member of the Commission on Dietary Supplements, about which you heard this morning.

CRN was established 25 years ago. We are proud to have as our members what we consider to be the *creme de la creme* of the dietary supplement industry. We represent the full spectrum of the industry, including the major product ingredient suppliers, who supply ingredients not only to our industry but to the food industry and to the pharmaceutical industry.

We represent large as well as small finish product manufacturers. We represent companies that market through health food stores, through the mass market, including drug stores and supermarkets, through mail order and through direct sales.

Our companies supported the passage of DSHEA in 1994 along with a number of other associations. We supported the emphasis in DSHEA on GMPs, and following the passage of DSHEA, we immediately got in touch with the Food and Drug Administration to determine whether, as authorized in DSHEA, they

intended to establish specific GMPs for this category. They indicated they wanted to do that, but did not have the internal resources to make it happen.

CRN, through its committee on industry quality standards, took the lead among the industry in developing a draft set of GMPs which go very substantially beyond the existing food GMPs and which we submitted to FDA with a request that it be considered for publication as a rule. We also recruited the support and the assistance throughout that process of other related associations.

That was the document that was published in February 1997 as FDA's advanced notice for proposed rulemaking on this subject.

We continue to be committed to improving and expanding that document, and we are committed to remaining intimately involved in all of the processes that may be undertaken by this committee and by FDA

regarding the GMP document.

We also support the need for surveillance. We worked with FDA for a number of years before the final Ephedra rule was proposed and before this committee took up that consideration in order to determine what could be done to resolve that issue.

I share, certainly, and CRN shares the Commission's view that when problems of this kind occur and problems of this kind are very likely to be identified through adverse reaction reporting systems such as currently exist, we believe that when those problems surface, they should be dealt with more rapidly than they were in the Ephedra case, both on the part of industry and on the part of the Agency. We are prepared to support any kind of action that can facilitate that happening.

Regarding the quality issues, we have been working with U.S. Pharmacopoeia since 1990 in the establishment of quality

standards for dietary supplement products. We are continuing to do that. We also have a commitment not only from our industry quality standards committee, but from our botanicals committee to do some very active work in this coming year on the issue of identity standards and quality standards for these products.

Therefore, whether FDA's final rule is published in the very near future or not, we do intend to both support that publication and also undertake some independent activities in support of that effort.

A number of our companies do have 800 numbers on their labels. A number of those companies also use 800 numbers in their advertising and work very closely with FDA in monitoring the adverse reports that come in.

It's also notable that most ingredients in dietary supplement products are considered grass. Most of these products were on the market well before 1958, let

alone before 1994, and are not new ingredients which warrant the kind of concern that I've heard expressed here today.

Our members are committed to high quality, to safe products, to effective products. They know better than anyone else that if these products don't work, and if there are other safety concerns that are raised about these products in the coming year, that our consumer franchise is going to go away, and it's a very strong franchise.

We have every interest in supporting the confidence that consumers have and deserve to have in the product category that we market.

I have been very concerned during this day at some of the comments that have been made by members of this committee and by what I perceived to be the failure to understand this product category. I hope that you will consider involving some additional advisors as you consider these

issues, as you continue to consider these issues, to provide you fuller input on some of the factual bases for these products and for our processes.

Thank you.

DR. BRANDT: Thank you very much. The material that she was talking about is in tab 7 of your book, for all the members of the committee. That is your proposal that is included in that proposed rule?

DR. DICKINSON: Yes.

DR. BRANDT: Is there anyone else in the audience that would like to address the committee? Seeing no one, we will move on down our agenda.

DR. CLANCY: Can we ask some questions?

DR. BRANDT: We don't ordinarily. You can ask them privately if you wish. We are prepared for Dr. Carolyn Miles to begin the GMP.

GOOD MANUFACTURING PRACTICES PROPOSAL

DR. MILES: I'm Carolyn Miles of the Office of Special Nutritionals at CFSAN and Food and Drug Administration. This slide didn't turn out too well at all.

I've been asked to walk you through the document that you heard mentioned a few moments ago. It was titled "Current Good Manufacturing Practice in Manufacturing, Packaging and Holding Dietary Supplements." I'll refer to it in the future as the GMP.

This was published on February 6, 1997, in the Federal Register, and I understand the committee has copies of it. It's really an advanced notice of proposed rulemaking. As you heard, the dietary supplement industry gave us this GMP framework. It was published as a Federal Register document with some additional questions that FDA thought still needed to be explored relative to GMPs. We are going to get into some of those today, recordkeeping and identification of product.

These GMPs are modeled after the current good manufacturing practice regulations for foods, and that was a part of the statutory mandate of the Dietary Supplement Health and Education Act that the GMPs would be modeled after food GMPs.

A number of the headings that you will see in this document are also headings in the good manufacturing practices for foods found in FDA's 21 Code of Federal Regulation, Part 110, Personnel. The requirements in this ANPR are very similar to requirements on personnel in other regulations.

Disease control, it indicates that if an employee is found by a supervisor's observation or by a medical evaluation to have an illness, some open lesion, sore, et cetera, that may adulterate the dietary supplement, this person needs to be eliminated from that part of the manufacturing until the disease is under control. There are cleanliness provisions on

personnel, and these again relate to general things, such as wearing clean outer clothing, washing hands after going to the bathroom, indicating that the personnel should not wear loose jewelry that can fall off and get into the manufacturing process.

In general, it's just that the person involved in the manufacturing must be clean and not adulterate the product because of bringing unsanitary conditions into the plant.

Each personnel needs to have education, training or experience or a combination of these so that they are fully equipped to do the job they have been hired to do. There is also a provision on supervision, that there must be a supervisor who can ensure that the personnel are meeting all of the requirements that they are required to by the regulation.

DR. LARSEN: Carolyn, you have copies of her slides in the stuff put at your

table this morning, and there were extras out back. Most of the folks in the audience should have copies as well.

DR. MILES: Some people were not recognizing them when I said they had them already. There are six on a slide. People said, oh, I thought it was going to be one per slide, so they didn't notice that.

There is a general area on grounds also. Again, the grounds are kept in condition to protect the product that you are manufacturing against adulteration. This involves the proper storing of the equipment, removing litter and waste around the grounds, cutting the weeds and grass, simply because this can be a harborant for pests, or vermin, or whatever, that you don't want around the manufacturing. Maintain the roads, yards and parking lots. Have adequate drainage areas, again, to prevent the breeding of pests that might adulterate the product. There must be proper operating systems for waste treatment

and waste disposal.

The ANPR also addresses plant construction and design. The plant must be constructed of a suitable size, suitable construction and suitable design to facilitate maintenance, cleaning and sanitary operations. You will notice these words coming up over and over again in the many sections of the ANPR. You are always trying to keep things clean and sanitary. You are always trying to maintain things so that you are producing the product you think you are.

The plant construction and design is also set up to prevent mix ups between raw materials and product, and this really means two things, that the raw materials and products need to be segregated in your plant according to whether they are quarantined because they haven't been tested yet to know they meet specifications.

They should be separated so that the raw materials or the product that have

been approved and are ready to be either used or shipped can be separated, so you know what's quarantined, what's been approved for shipment, and what's still up in the air, whether you are still testing it. This is why the plant has to be of a size that you have enough space for these types of operations.

Again, sufficient space. You want to make sure you don't have the potential for a mix up, which might adulterate your product, because you might release quarantined raw materials to be used in the product because you simply have it mixed up, you didn't have enough space to put them in the plant where they belong.

There's a provision on outside bulk fermentation vessels that I really won't go into right now. I meant to mention at the beginning with the introductory remarks, as we are going through these, you might think about dietary supplements the way the law

defines them, that they come in many different forms. We are talking about capsules, soft gels, liquids. There is just a variety of products or extracts of the products. Think in terms of the different forms that dietary supplements can come in.

The plant and facility have to be constructed so that they can be kept clean and in good repair, have to have adequate lighting, obviously, so you can read what raw materials you are using, to make sure you are weighing things properly. There is also a provision for protecting light fixtures so that you don't have glass breakage that gets down into your product.

The plant has to have adequate ventilation and control over microorganisms, dust, humidity, temperature, vapors and odors, and adequate screening against pests that might get into your plant.

You can see the same idea coming up again, sanitary conditions and in good

repair. That is how you must keep your physical facilities. The cleaning and sanitizing materials that you use, you have to ensure they are free from contamination, and you have to ensure that you keep them in your plant in such a way that they do not contaminate the product, that they are used under special care. Many of these would add to your ingredient something that would be unsafe.

There needs to be a pest control system, and the water supply that you provide to the plant for use, you must have it at an adequate temperature and under adequate pressure to provide the water that you need in your processing, to provide the water you need for the employees to have the sanitary conditions for use of bathrooms, to provide the water that you need for cleaning all your equipment. The water that is going to come directly in contact with the product needs to meet EPA primary drinking water standards.

Again, some other things that go along with sanitation of the building is the plumbing system must be large enough to carry water in the plant and to convey sewer out. There must be no cross contamination of the two lines for obvious reasons. There must be adequate sewage disposal. The toilet facilities must be readily available to the employees, provide the water at the temperature and pressure to encourage the cleanliness that you are requiring of the employees under other regulations, and always kept in good repair and maintained in a sanitary condition. This would include the hand washing facilities in those for the employees or the hand washing facilities in other areas of the plant, simply to encourage employees to always wash their hands at appropriate intervals.

There are requirements on rubbish disposal, and there is also a provision that there be supervision of the sanitation of the

building, someone be in charge of making sure that these regulations are being followed.

The equipment and utensils that are used in the manufacturing are also covered in this ANPR, and again, some of these sound like very logical things you would think to require. The equipment and utensils have to be designed and of a construction that they are made out of material and workmanship that they can be cleaned and maintained. They must preclude adulteration with contaminants, and they must be installed and maintained to facilitate the cleaning and prevent adulteration.

Ways of doing this are by using corrosion resistant materials, non-toxic materials, and considering the environment of intended use of the equipment to make sure that the equipment is designed for the conditions of use.

You are required to have freezer and cold storage compartments for the storage

of ingredients or product that might encourage the growth of microorganisms. On these compartments, you are required to have either a temperature thermometer, temperature measuring device, or temperature recording device. There is also a provision for having an automatic control or automatic alarm system if the temperature on these compartments goes above a particular danger level, so that you would be warned that perhaps your ingredients have been held at an unsanitary level.

Any of the instruments or controls used in the manufacturing for the vast number of things you might be doing, controlling pH, mixing things, I can't think of all of them now, but all the instruments and controls that you are going to use have to be accurate, have to be adequately maintained, and you have to have the correct number of these so that the instruments and controls work as they are supposed to work.

I am going to go into all the records in this document at the end of my talk instead of going through it sort of chronologically or how it is laid out in the regulation. I'll just indicate now that for equipment and utensils, there are recordkeeping requirements on the cleaning and sanitation of the equipment and utensils. This cleaning and sanitation is required to protect against adulteration of your product. You would adulterate the product if you used unclean equipment.

The ANPR requires that there be a quality control unit in the manufacturing plant that has responsibility for approving or rejecting procedures, specifications, controls, tests and examinations or deviations from any of the above.

This quality control unit has the responsibility of approving and rejecting all raw materials, packaging materials, labeling, and has the responsibility of approving the

finished product, that it's ready for shipment and released.

The quality control unit also assures that there are complete production records, and that these are reviewed and evaluated for any errors, and you are going to hear more about that than you want to in a few minutes, so I'll hold off on talking about those further.

There is a heading in the regulation called quality control and laboratory operations. The purpose of this part of the ANPR is to ensure that the dietary product conforms to appropriate standards, and here are words that are used throughout the ANPR also, appropriate standards of purity, quality and composition.

One of the issues we are going to get into later is composition or identity of the ingredients in the product, but you will see this is mentioned a number of places.

The quality control and laboratory

operations also addresses packaging materials. They must be safe and suitable for their intended use. There are some records involved also at this point, but you are going to hear more about those later.

There is a heading in the ANPR called handling and storing of raw and processed materials. This involves the inspection of the raw and in process materials, the segregation of these, again, a point I mentioned earlier. They are segregated according to the stage of processing and also whether the raw materials have been tested and released for use in the product, whether they are quarantined until they can be tested, or whether they perhaps have been tested and found unacceptable for the product.

You must inspect your raw ingredients to see which of these three categories they fall into so you are only using raw materials that have been inspected

by your quality control unit and are appropriate for use in your product. This section also addresses the storing of these products.

There is a section on raw agricultural materials and that they must be washed and cleaned, although this water can be reused if there is no possibility of contaminating the product that you are producing.

There is a section addressing the raw material and in process materials and what temperatures they are held at and the relative humidity. They must be held at temperatures and at relative humidity to prevent adulteration of the product.

There is also a provision on frozen raw materials. They must be kept frozen and thawed in a manner to prevent adulteration before they are used in the product.

Then there is a section further in the same section on handling and storage.

The raw materials that are used must all be associated with a lot number. That lot number indicates whether the material is quarantined, approved or rejected for use in your product.

The ANPR has a provision that you must rotate your raw material stocks so that you are always using your oldest stock first. There is an exception to this provided for in the ANPR under particular conditions, but this would be the general rule.

There is a requirement for retesting and re-examination after a specific time of storage or after exposure to air, and heat, so if it's exposed to air, heat or other conditions, your raw materials may need to be retested or re-examined.

The raw materials need to be examined and tested by the manufacturer, or the ANPR provides for the manufacturer to accept a certification of examination or analysis from another party, as long as the

manufacturer of the product has ensured the reliability of the person providing the certificate. These certificates can be given to indicate that the raw materials are free from filth, insect infestation or extraneous materials. There may be certificates given on microbiological contamination or freedom of the raw materials from such. A certificate can be accepted for aflatoxin or other natural toxins that may be associated with particular products.

The certificate of examination or examination or testing is required to make the identity of your product evident. This is going to come back many times and is one of the charges we are asking this committee to look at, of how to go about ensuring the identity of the product that is introduced into interstate commerce.

There is a heading in the document on manufacturing operations. These address sanitary principles, which you have heard

quite a bit about, precautions that production procedures not contribute to the adulteration of the product. To the extent that it is adulterated, then it has to be rejected, or treated, or reprocessed to eliminate the contamination.

Nothing in the ANPR says that you have to reject the product out of hand and not rework it, but it does have provisions for ensuring that during the manufacturing, if you do reprocess a product, it has to meet certain specifications and certain requirements that it is not adulterated before it can be released.

There are also provisions on the control of the growth of microorganisms during the manufacturing operations of the product.

The sterilization, irradiation, pasteurizing, freezing, refrigerating, control of pH, control of water activity are all addressed in the ANPR. These are there

to prevent adulteration of the product through the control of microorganisms. There are manufacturing procedures on how to handle the work in progress, the in process materials. You must ensure that they are not adulterated during the manufacturing process. There are also some provisions, you must protect your final product from adulteration while it is in the manufacturing facility, such as when it is being transported by conveyor.

During the manufacturing process, the ANPR indicates that all of the containers, processing lines and major equipment that's being used in this processing must be identified as to what it contains and what phase of the processing is going on in that particular equipment.

The manufacturing operations also indicate that you must protect against inclusion of metal or other extraneous materials while you are manufacturing your

product, and it indicates that the rejected or adulterated materials that might be in your plant have to be identified, stored and disposed of.

This same idea comes out in the ANPR a number of times. You must have space so you would be able to do something like this. You must test the product after it has been in the plant a certain amount of time, exposed to air and heat, so you will know whether it should be rejected, and here again, the same idea comes up during the manufacturing operation.

The manufacturing operations also addresses mechanical manufacturing steps to prevent adulteration. It addresses heat blanching, if this is a necessary part of the process. It indicates that during the blanching, you must bring the product to the temperature indicated. You must hold it there for the amount of time necessary, and then you must cool it appropriately to carry

on with the manufacturing process.

The manufacturing operations also address controlling the pH of your product, which would have many ramifications relative to microorganisms, and there is also a provision that any of the ice used that comes in contact with your raw ingredients or your product, the ice must be made of potable water.

There is a whole section of the ANPR that addresses packaging and labeling operations, the filling operation, assembling, packaging and the other operations all must be done to protect against adulterating the product.

Labeling materials are addressed. You are required to store these separately with suitable identifications, depending on the different types of product, the strength of the product, the quantity of content. The way you will store these separately will help to ensure that when you are ready for a

particular label, that you go back and pull the right labels.

Obsolete labels, labeling and packing materials must be destroyed, again, to prevent the possibility that you would go and pull the wrong labels to put on your product.

The packaging and labeling operations also address that each dietary supplement must have a lot number. You have heard some information today about post-market surveillance, indicating sometimes, in the infant formula example that Chris Lewis gave, they were tracking that certain lot numbers of the product were probably the culprits.

The ANPR requires that each dietary supplement have a lot number. This would make the product trackable, and the conditions that the product was manufactured under traceable later, which you will see when I go through the record requirements of

the ANPR.

The packaging and labeled product must be examined to make sure it has the correct lot number on it, and the product must meet specifications before it is either rejected or approved. The product not meeting specifications must be rejected. The converse is, the product that meets the specifications would be okay for release.

The ANPR also has a section on storage and distribution of finished product. It just indicates that the storage and distribution must occur under conditions that will protect against physical, chemical and microbiological adulteration and also protect against deterioration of the product or the container the product is in.

There is also one section that indicates you must have a reserve sample with each lot of product. You retain this reserve sample at least 1 year after the expiration date of your lot of product, or at least

3 years after the date of manufacture. You store this reserve sample under the conditions that your product label indicates the product would be stored under. You are required to have twice the quantity of the lot of product that would be required to do all required tests. This reserve sample is kept in case there is some question later and you need some sample to analyze to see if there was any problem.

That gives you a real quick run through of the ANPR, minus the two issues that we really want to address here.

The first of the two is the identity test. This came up a little bit this morning. You are going to have some in-depth discussions tomorrow on testing for identity of various dietary supplements.

Each lot of a dietary supplement has to have its identity verified. Some of the questions we are bringing to this group is what is the best way to do this. There

are tests with sufficient specificity to determine the identity. These include chemical and laboratory tests, microscopic identification and analysis of constituent markers.

I'm going to leave it at this, because that's all I know about it. The experts in this area are going to talk to you tomorrow.

The final area that I'll mention is the types of records that the ANPR mentions that you must keep. The records are not all in one section of the regulation. There is a production record section, and there is a batch record section, but there are record requiring provisions in other of the major headings that we have already talked about.

Under equipment and utensils, the cleaning and sanitation that we talked about quite a bit when I was going through the requirements of the ANPR, another provision in that section is you must have written

procedures established on the cleaning and sanitizing of your equipment and utensils, and you must follow these written procedures. Then you must keep a written record of the major equipment cleaning and use in an individual equipment log in chronological order indicating the date, the product, the lot number of each batch processed, and the person performing the cleaning.

You will have a list of what lots were done before the cleaning and what lots were done after the cleaning. If you identify a problem with a particular lot, then you would have a way to go back and check to ensure that the equipment was cleaned appropriately, that that's not the reason you are having problems. You will have some marker of which lots were done before and after a particular cleaning.

There are requirements of records for the quality control and laboratory operations. These records lay out the

responsibilities and procedures that the quality control unit is going to use. I mentioned earlier that the ANPR does require that you have a quality control unit, and the records actually lay out what their procedures will be.

The laboratory tests you are going to do also require records. You want complete data on all the specific tests that are performed on the product, identity tests, and some of these others that we talked about a little while ago.

There are also records to support expiration dating, which is also a part of the ANPR, that you must have data and rationale to ensure that the product meets established specifications at an expiration date that the manufacturer would establish. This expiration dating would also consider accelerated stability duties or data from similar product formulations, and the product shelf life would confirm with a real time

study that the expiration dating was appropriate.

I put this at this particular point to indicate that since you are going to collect data here, you are going to have written records on expiration dating.

The two major areas where records are concerned are the master production and control record and the batch record. The purpose of this master control and production record is to assure that you have an uniform product from batch to batch. You basically have a recipe. This is how I'm going to make my product. These are the conditions I'm going to have my equipment under when I make my product. This master production and control record is reviewed and approved by the quality control unit that I spoke about earlier.

In the master production and control record, you are going to have a complete list of all the raw materials that

you have used, designated by their name, and remember earlier, we indicated that your raw materials have to have lot numbers, and here you are going to record the lot numbers at this point in the master production and control record. You have to designate the number and the code of the raw materials that you are going to use and indicate any special quality characteristics. In the batch records, you have to indicate the code of the particular raw materials that you are using.

In the master production and control record, there is a listing of the weight or measure of each of the raw materials you are going to put into your product, name, weight and measure of each ingredient on a per unit basis. I probably left off a key phrase on that.

In the master production and control record, you have a calculated excess of dietary ingredient, if any. Before you have to find out if you have really made a

mistake, you have ended up with more product at a certain step than you meant to have. Is this something you need to check into further?

You are going to have the total weight and measurement of any dietary supplement unit that you are going to make. You are going to have a theoretical weight and measure of the final dietary supplement, and you establish a maximum and a minimum percent of this theoretical yield that would trigger an investigation to indicate what's wrong with my product; I have more here than I should, or I have less than I should. Did I not throw something in?

This master production and control record will have a description of the product container, closure and other packaging materials, and it will have manufacturing and control instructions, such as how long a product is mixed, what pH it is at a certain step, what temperature certain manufacturing

procedures are done at.

This is your recipe of how you are going to put your product together. Then the batch production and control record gives you the information on that specific batch that used the recipe we have just gone through. You have a recipe. Now you are making it up, so you have a batch record of exactly how you did batch 0123.

The batch record is prepared and followed for each batch of product. It gives complete information on that batch. First of all, it's an accurate reproduction of the master production and control record that we just went through. It's a copy of your recipe to begin with. It has each significant step in the manufacturing. It shows that each significant step in the manufacturing was accomplished.

It gives the date, identifies the major equipment and lines used, so if there is ever a problem with this particular lot,

you can go back and see if something was happening on a particular line that wasn't heating to the temperature you expected, or you didn't clean that line that day, or whatever. It would help you trace back problems.

The batch production control record has a specific identification, a lot number, for each raw material or in process material used. It specifies each raw material and in process used, the weight and measure of the raw material used, the quality control results of any testing you did on the raw materials or on the finished product, the inspection of the labeling and the packaging and labeling area.

I mentioned earlier, going through the different provisions of the regulation, you do have to have particular inspections of your packaging and labeling. Here you are going to put the results of that in a record to keep for that batch.

The batch record also gives the actual yield and percent of the theoretical yield. Remember, when we were going through the batch production record, it indicated you have to have established what percent of theoretical yield would trigger an investigation of your product. In the final batch record, you are going to have your yield and what percent of the theoretical yield it was.

You are going to have label control records showing a copy of the label or a record of all the labels used on that particular lot. You are going to have a description of the product container and closure. If there were any investigations or deviations from the described process, this is where you are going to keep the record which relates to this batch. Any problems with this batch will be in the batch record.

Any deviations from written approved specification standards, test

procedures or other laboratory control mechanisms will be also in this batch record.

What you need to determine whether there was a problem with your batch or to trace back a problem later should be together.

I mentioned earlier that there are these two big sections of the ANPR that provide records, but if you read the whole document, you will find there are records in a number of other places. What I have done is sort of pulled these together here at the end to show you there are records in other places.

There have to be written procedures on receipt, identification, examination, handling, sampling, testing and approval, and rejection of raw materials.

We have talked many times today about rejection or approval of your raw materials, having space to segregate the product relative to these approvals. There

also have to be written procedures on how you have treated your raw materials.

There are written procedures on the appropriate tests or examinations used on the product to ensure purity, composition and quality of the finished product. There are written procedures on reprocessing batches or reprocessing start up materials.

There are written procedures on the receipt, storage, handling, sampling, examination and testing to ensure identity of the labeling and the appropriate identity, cleanliness and quality of the packaging materials. This sounds very similar to what we just said on raw materials and on finished product, but it's also on the packaging materials.

Written procedures to assure that the correct label, labeling and packaging materials are used, and there are also records on distribution of the product, if ever the company needed to institute a

recall.

As far as how long the ANPR suggests you keep these records, the laboratory production control and distribution records that are associated with a specific batch should be retained for one year after the expiration date of that batch, or at least 3 years after the date of manufacture, and the raw material record should be maintained for 1 year after expiration date of the last batch of product that used that raw material, or at least 3 years after manufacture of the finished product.

The last area on records that I wanted to mention were complaint files. We have talked about adverse events and post-market surveillance, et cetera. The ANPR requires that the company keep written records on the name and description of the product, the lot number, the name of the complainant, the nature of the complaint and

any replies sent to the complainant, if there was one.

This would be requiring the manufacturer to maintain some type of complaint record. These records would also give the findings of any investigation or follow-up action that the manufacturer took on a complaint.

There would be written procedures for handling all written or oral complaints. There would be a review by the quality control unit of any failure of the product to meet any specifications and determination if there needs to be an investigation.

Remember the batch record we have talked about in some detail has all the information about one particular batch. Then if you can relate your complaint to one particular batch of product, then you are going to have that whole batch record to go back and see if you can identify any type of problem, and the quality control unit would

be the one doing that.

The records of complaint should be maintained for one year after expiration date of the product or one year after the date the complaint was received.

As you can see, there are a lot of record requirements throughout here, and we are going to ask you all to do some review of those as one of your charges.

Thank you.

QUESTION AND ANSWER SESSION

DR. BRANDT: Dr. Rodier?

DR. RODIER: How many producers are there in the U.S.?

DR. MILES: I don't know. Do we know?

DR. MOORE: We don't have an accurate record.

DR. MILES: There is no requirement that they must register with us.

DR. MOORE: It varies. There are

market surveys that indicate anywhere from 1,000 to 6,000 actual manufacturers. Some of those may really be just distributors. Annette may have a better grip on this. I think 4,000 to 6,000 is probably a reasonable estimate.

DR. BRANDT: Dr. Clydesdale?

DR. CLYDESDALE: Thank you very much. I was filled with optimism when I first saw the ANPR and applaud the efforts of CRN and others for putting that document together. However, I must admit your presentation made it vastly clearer. It was much nicer to see it put together that way than to try to read the original.

The question I have is, do you believe the rule will be adopted pretty well as proposed? And secondly, if it is adopted, are the resources available to ensure compliance with 4,000 to 6,000 manufacturers?

DR. MILES: As far as whether it will be adopted, I guess I don't have any way

to know. We have comments back on this ANPR. The next step would be to do a proposed rule addressing those comments.

If you read the back of the proposed rule, we ask, I believe, nine questions that we thought there were other areas that may be needed to be addressed more carefully in the ANPR than what was laid out there. Those nine questions, the responses we got to those may drive other things in or out of the regulation. I think that's why we asked those questions to see what the feeling was. One of those is relative to identity testing. Some others, I believe, are related to records. You can see what those nine questions were.

I think the comments we have received to this and the comments we get to those nine questions will drive which direction we go in doing a proposed rule, and then there will be another comment period that will drive how the final rule would end

up.

DR. CLYDESDALE: Will there be resources in order to try to ensure compliance?

DR. MILES: Well, I need a crystal ball for that. Who knows? It would take inspectors going into the plants. I'm not sure. I don't make FDA's decision on funding.

DR. CLYDESDALE: I was just curious. I think this morning I heard someone said at a maximum, there was 150 samples a year taken. Did I hear that correctly? To go from 150 samples per year total to enforcement of this kind of rule is a step that seems to me like going to the moon, but perhaps not.

DR. MILES: I would think as with most things, you maybe couldn't go to every plant but there would be some oversight.

DR. MOORE: Just an editorial comment. It's important to realize that all

enforcement under the Act is really selective enforcement to encourage voluntary compliance with the requirements of the law. It's not necessary to visit every plant, as through the appropriate application of our enforcement resources, you encourage voluntary compliance and minimize the need to go in and do inspections on every site every year.

DR. CLYDESDALE: I would just like to add to something Dr. Dickinson said. I'm not at all concerned about the manufacturers that are interested in GMPs. There are many out there who really want to establish science and a basic foundation to make this a very credible and vigorous industry. Those don't concern me.

I am concerned about the manufacturers who have a post office box in Florida and who may be difficult to get a handle on, who may ultimately hurt the manufacturers who are trying to make this a

scientific industry.

My remarks are not negative towards the industry. There is a concern that those people who are trying to do the right thing will be assisted in doing the right thing.

DR. BRANDT: Let me see if I can get an answer to an earlier question by Dr. Rodier. Dr. Dickinson, do you have any idea how many manufacturing plants there are in the country?

DR. DICKINSON: No, I don't, but I would be very surprised if it's as many as 4,000 to 6,000, although FDA did a study. Was that number that high?

DR. MOORE: Part of it depends on how you define "manufacturer," of course. That 4,000 to 6,000 number is the number that most often is mentioned in market studies. That number will include a significant number who may do no more than relabel or distribute a product under their own name. I don't know if there is a good hard number of the actual

physical facilities that are actually manufacturing from scratch products.

DR. DICKINSON: Our best estimate is that the number is several hundred, not several thousand. One of the things that may complicate identifying how many companies there are is that in many cases, for example, FDA used, I think it was an NHIS database to do -- FDA employees published an article on the number of products in the market. If one looks at the number of products, that is, the number of different brands, one easily comes up with probably 10,000 or 20,000 products, but it's relevant to know there are half a dozen very large private label manufacturers who make most of those products, who make, for example, all of the Safeway, and Giant, and CVS labels that you see in the stores, along with your national brand name products. Some of our members report that they make as many as 10,000 to 15,000 different labels in one company.

One needs to distinguish between the number of products or the numbers of brands and the number of manufacturers.

DR. BRANDT: I think the question she was really asking was manufacturing sites rather than manufacturers.

DR. DICKINSON: We think that is several hundred.

DR. BRANDT: Dr. Fennema?

DR. FENNEMA: I think the committee would be very much interested in knowing what significant differences exist between these GMPs and the ones in the CFR currently.

DR. MILES: For foods?

DR. FENNEMA: For foods, yes, if there are significant differences, subtractions, additions, alterations to that.

DR. MILES: 110, Section 110 on foods. The areas on sanitation, personnel, equipment, plants, these types of things are very, very close.

DR. FENNEMA: I would think so.

DR. MILES: The identity testing is one area that would be different, because it's obvious what a green bean is. That would be one general area. The records are similar in some ways, and then in other ways there may be more things required.

DR. FENNEMA: Is there a list of these differences readily available or not?

DR. MILES: Not that I'm aware of.

DR. FENNEMA: That would be good to have for the committee.

DR. BRANDT: Are there significant deviations in here from what the CRN recommended?

DR. MILES: No.

DR. BRANDT: I just wanted to be sure. Dr. Wang?

DR. WANG: How about the import of dietary supplements? They will be subject to the same GMPs in foreign countries? How do we verify their master production records and all that?

DR. MILES: That's two questions. I think we would say they would be subject to these regulations, because they are introducing their product into the United States. How we would verify their records is another question related to resources, et cetera.

DR. BRANDT: Dr. Askew.

DR. ASKEW: These were very clear and very helpful, but I had one small question on the handling and storage of raw material which was curious to me. If the purpose of washing raw agricultural materials is to remove a potential contaminant, then why allow them to re-use the water in subsequent batches?

DR. MILES: They say re-use the water as long as it does not contribute to contamination. Once the water is so dirty that it's going to still leave dirt in the product, you can no longer use it.

DR. ASKEW: I'm talking about

things that you can't see, like microbial organisms. They aren't going to know if they washed a bunch of E. coli off strawberries.

DR. BRANDT: Dr. Benedict?

DR. BENEDICT: I have just two questions. One is, and I apologize if I missed this as I read and as you presented, are any of these dietary supplements produced with the use of organic extraction, and if they are, I didn't see any place in there to assess whether there is residual organic compounds left in the product. That's the first question.

DR. MILES: I assume they could be produced that way. I don't know that there's anything to prevent that. You are pointing out there is a deficiency in the regulation, it does not account for there being --

DR. BENEDICT: I didn't see anywhere in there that you were going to assess whether there was a residual organic product.

DR. MILES: I think that's true, other than if you do identity and every little thing that's there.

DR. MOORE: The issue of solvents is on the table. We raised that, the whole issue of naming of solvents in the labeling regulations. It turned out to be less than crystal clear on how to deal with that in the labeling provisions. The issue is being studied. It's really a matter of we had addressed it in labeling, and maybe it needs to be more appropriately addressed in the GMPs.

DR. BENEDICT: The second one, and this may be a misconception on my part, but of those several hundred manufacturers, I would assume there are some that are really rather small, and among those that are pretty small and maybe produce one or two products, there probably is a subset that is very conscientious, that we would offer our respect to, and a subset that maybe is slip

shod.

My question, have we an idea of the economic impact on the small manufacturer who really wants to comply with all of these things, but might go promptly out of business as a result of having to do all of this? And this person may be competing with some foreign manufacturers who might not, as Dr. Wang suggested, we might require some more stringent activity with.

DR. MILES: We will be required to do something like that, to analyze the impact on small business as a part of the proposed rule. I don't think that's been looked at in depth now, but that will be a consideration. I can indicate we did get some comments to this ANPR along those exact lines.

DR. MOORE: We have some initiatives underway to try to develop a better picture of the industry and to get an idea of some of the economies of scale, what types of businesses are there, so we can do a

better job of looking at economic impacts. Ultimately, any regulation goes nowhere until you can adequately address the small business issues nowadays.

DR. BRANDT: Dr. Rodier?

DR. RODIER: Do you have any idea what proportion of the manufacturers already follow GMPs?

DR. MOORE: It's a difficult one, because if we don't have them, it's difficult to say what they are following. We do between 40 and 60 site inspections a year. The vast majority of those come back with either no action indicated, or, if you will, violations or poor practices that can be corrected the day of the inspection while the inspector is there. At least based on the firms we are aware of and the sites we have visited in the last 3 years of the compliance program, the firms inspected at least seemed to be doing a pretty good job.

DR. BRANDT: The next speaker is

Dr. John Kvenberg, Strategic Manager for HACCP.

RECORDS IN AREAS COVERED BY HACCP

DR. KVENBERG: Thank you, Dr. Brandt. Good afternoon everybody.

By comparison to the previous presentation, I think my remarks will be somewhat more brief. I've been asked to discuss records as they relate to HACCP. The discussion will be less complicated, I believe, than going through the entire GMPs, but it's important we discuss GMPs in relation to HACCP to give you an understanding of it.

To begin with, the concept of HACCP, which I think most members of the committee, if not all, quite well understand, has a history that goes back many years to the Pillsbury Corporation's involvement with NASA and our low acid canned food regulations of the 1970s.

The current operating principles of

HACCP were developed by the National Advisory Committee for Microbiological Criteria for Foods and served as the basis for our seafood regulation at the Food and Drug Administration, Food Safety and Inspection Service's pathogen reduction program for meat and poultry, and we have stated such to propose regulations for the juice industry that are HACCP based regulations in their content.

The CODEX Alimentarius Commission of the FAOWHO has endorsed the HACCP concept and its principles, and it is being embraced as a food safety mechanism in the European community and other parts of the world as well.

HACCP in its essence is a science based operation that goes through an analysis and focuses on food safety hazards that are likely to occur and documentation of the preventive controls that are put in place, rather than a reliance on finished product

testing to try to find hazards that are associated with it.

It is also something I think that needs to be stated, that HACCP has to be built on a foundation of good manufacturing practices and, specifically, standard operating procedures such as sanitation operating procedures, such as has been discussed in the general sense under 110 of our regulation in 21 CFR, which does not have a recordkeeping requirement associated with it.

Relative to records, HACCP begins with the analysis of potential hazards, which may be associated with a specific product, that as I said previously, are reasonably likely to occur, and looking at what preventive controls may be applied so that a processing failure or introduction of a product would not result in a hazard.

The definition of hazards we are concerned about covers all those that would

be of a safety concern, be they a biological hazard, chemical or physical in nature.

The principal component in records of the HACCP system is the HACCP plan. This identifies the critical control points that must be established in order to keep a hazard from occurring or to not produce it in a situation where the hazard could cause harm.

The HACCP plan also has within it, within the principles of HACCP, the requirements for, once critical control points are identified, establishing critical limits around which you can measure and monitor, which is another principle of HACCP, the critical limits identified at these critical control points, to assure that the product is under control for these safety hazards.

In addition to that, HACCP calls for a corrective action plan. Normally, this would be pre-thought out on how to bring a process back under control and prevent a

hazard from actually making it to the finished product.

The recordkeeping requirements within HACCP are limited to monitoring of these critical control points, the corrective actions that they take, and for verification of the entire system or an audit procedure going back through the records to assure that what was said on the plan itself was indeed being accomplished, and to further iterate that beyond just verifying that the records were accomplished, the audit function can accomplish the validation of the system, that is, are you accomplishing what you are attempting to do, and that is that the process you have in place will indeed assure the hazard does not occur.

As I stated earlier, the provisions are consistent with international recommendations for Codex throughout the world in various commodities and have been largely microbiological in their initial

intent.

The records that are actually involved in addition to sanitation type GMP records that are the basis of the foundation, the number one record would be the hazard analysis itself, because this provides the rationale and the thought process of the manufacturer's analysis of his product to make a determination of which factors are likely to occur and need to be eliminated.

The HACCP plan itself sets in place these other components, to document where the critical control points are, document what the critical limits are, how you maintain your records for monitoring, and I think very importantly, what corrective actions were taken when monitoring indicated the process was out of control, and periodic audits or verification at the end of the process.

The records that include the HACCP plan, I would mention, is an ongoing document. Once a plan in HACCP has been

established, this verification or re-visiting requires that the plan be periodically updated with new information that comes into it so that the plan can be refined to address unforeseen hazards at first onset.

Other records in the plan include specific calibration equipment and verification for the monitoring procedure itself. That's important from the standpoint that not only are you making the observations to keep the process under control, but also that the observations that you are taking are being accurately done.

Relative to retention period, it depends within the HACCP framework of consideration what the shelf life and how long the consumer would have the product in possession. I think it would be consistent with what you heard previously relative to what FDA is thinking about relative to time.

Relative to imported products on HACCP operations, the way that has been

addressed is putting the burden on the importer of record, relative to the requirement for importing a product that is under adequate control. I think addressing imports in general, it's fair to say this can be accomplished in addition to specific on site monitoring of foreign firms as mutual recognition agreements with other countries, et cetera, but the burden relative to who is responsible at the point of import, the importer would have a record burden under the HACCP based operations as well.

Briefly, the types of records that are in place for seafood, meat and poultry, at this point do include some records for prerequisite program sanitation operating procedures. These are the actual written standard operating procedures themselves that are to be followed, and in some cases, actual records that are associated with how the standard operating procedures are followed out throughout the system, including incoming

material control records, as well as sanitation and on-line information on good manufacturing control processes that deal with operations within the plant.

The HACCP plan itself consists of, as I mentioned earlier, a list of the hazards that have been identified that need to be controlled. I think it's critical in the analysis by the firm itself that is looking at a HACCP based operation that a continual reassessment feed back into the list of hazards that need to be controlled, as well as the records that are maintained on critical control points within that plan, and a reassessment of those critical control points and the critical limits they are associated with are in effect controlling what needs to be done.

The only other actual record that I think could be discussed under the HACCP framework, and it may be somewhat different for dietary supplements, is the question of

consumer complaint and review relative to the complaints that the manufacturer receives back in his operations.

It has been our findings relative to pilot testing of HACCP based operations that by and large, the industry is best able to assess for itself the consumer complaint reviews to make a determination of root cause of the actual association of a hazard, be it something like a piece of broken glass that may be associated with the product or an adverse reaction.

That, in essence, is the overview of the HACCP based regulations, and what they do accomplish in seafood, and where we are moving with them. I guess I would emphasize there is a major burden on the part of the industry to do this type of thinking and hazard analysis. On the other hand, there is a freedom and flexibility in which records are associated with the product and its safety. Rather than proscriptive, it goes

into the process where the processor is making a determination of the hazard.

Thank you.

DR. BRANDT: Thank you. Are there questions?

DR. LEWIS: Could I just spend one second going back to context on this?

DR. BRANDT: Certainly.

DR. LEWIS: Again, the purpose of what we are trying to do here is to give a flavor and sensitivity. HACCP is perhaps one way to address GMPs, but there are others. Today we have talked a little bit about HACCP, but I think the working group would want to look at other approaches as would be suggested by the comments. I think what will happen tomorrow is a little bit more of a flavor for what's happening in the area of GMPs relative to analysis, but I want to bring us back to the idea that we need to deal with consumer research. We need to deal with post-marketing surveillance. And we

need to deal with GMPs.

That's the focus of both today and tomorrow.

DR. BRANDT: Very good. Any questions or comments?

Thank you very much. Are there any comments at all from anybody on the committee about today or any of the material today?

Do you feel a little overwhelmed? A lot of stuff. As there is nothing else to come before this committee, we are hereby recessed until tomorrow morning at 8:30 a.m. in this room. Take your stuff with you, I'm advised.

(Whereupon, at 4:50 p.m., the PROCEEDINGS were continued.)

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