were chemical engineers and we had to break this up into unit operations, and we broke it up into three units. You're going to have to go back and build that machine, and you now have experts--I can say that because this is my fourth year--you now have a group of experts, Dr. Kuzminski is one of them, who are going to help you integrate, because that--there is going to be some need to do that.

But as a member of the committee and as a member dealing with these issues regarding the three--the three responsibilities of the task force, forces, the emerging science, the fact that the emerging science task force was able to come up with a definition, I think that's--that is a tremendous advantage.

The fact that as it relates to you could not reach a consensus on allowing statements, again I harken back to what I said prior to break. That's being discussed and will continue to be discussed. I'm not saying it's in everyone's best interests that these types of disagreements get debated and at least concluded successfully, sometimes unsuccessfully in courts, but that's where that issue is going to be. That's my comment.

DR. BENEDICT: Thank you.

Dr. Larsen has no additional comment on that. Does anyone else wish to speak?

[No response.]

DR. BENEDICT: Okay. Dr. Larsen, perhaps you'd like to state a question that we can ask them about your two issues?

DR. LARSEN: Well, perhaps what you could do is go around and ask the committee whether or not they would agree to keep a comment in with respect to the consistency of the working group report with conclusions of others, and then, without wordsmithing it--and if you have wordsmithing you can pass it on to me, because I think it's the concept that we want to get on the table here--and then, secondly, do you want to keep in any commentary that explains what happened or what was transmitted to us on the working group from the IRS? And then, finally, then that as a package together with the working group report, what your final conclusions are on transmitting that to FDA.

I'm suggesting that. You as Chair have the option of taking that suggestion or not.

DR. BENEDICT: I deeply appreciate your suggestions. The Chair will act upon them almost verbatim. The way I would like to package it, however, is so we don't go around this room eight or nine times with me calling out your names, let's do it, issue one, include the comment or exclude the comment; issue two, include the IRS, exclude the IRS; issue three, the same old thing that we did before, transmit with the comments on the record.

Does that seem logical and clear to everyone? If not, we can certainly clarify it, or we can go around one at a time. Please just let me know whether you're prepared to say "include, include, okay," "include, exclude, not okay," or any permutation of those three answers. If I hear no objection, we'll begin.

DR. APPLEBAUM: I just have a clarification.

DR. BENEDICT: Oh, please, please.

DR. APPLEBAUM: Can you repeat again the comment that's causing concern, whether to include it or not to include it?

DR. BENEDICT: Perhaps just tell us where it is, and we'll all briefly read it.

DR. LARSEN: Okay. It's in, as I have crafted this for you, it's in part two of the Food Advisory Committee report to FDA, and it's the first one there. It talks about the consistency of the IWG report with conclusions of others.

It says: "The committee notes that the IWG report is consistent with conclusions of other groups and individuals on the issue of incentives. Because the IWG discussions did not focus on how others have responded, some members preferred to omit from the report discussions of conclusions by others." And I'm shortening up what it says.

"However, the committee wishes to acknowledge the

conclusions of others in its full report to the FDA, and the consistency of such conclusions with those of IWG."

"Some of the group's views and recommendations echo, rather than respond to, the Keystone report. In addition to Keystone and IWG, other groups and individuals have struggled with this issue. The University of Illinois Functional Foods for Health Program held a workshop in November of '97, attended by the program's industry partners, to discuss incentives. While incentives were considered to be desirable, there was a lack of consensus on what the incentives should be. As noted in the IWG report, Dr. Childs' survey of the food industry did not reveal a consistency of views. Mr. Mike Taylor, a former FDA employee here, prepared a paper for the '97 Food and Drug Law Institute Conference in which he argued that the goal should not be incentives or research for their own sake. Rather, the goal"--and this is a very short summary of what he said--rather, the goal should be to meet critical consumer needs, to maximize the flow of truthful, non-misleading information."

And then this concludes with saying that "The committee submits this report in recognition that the issue of research incentives is not resolved by the report, and that discussion of the issue may continue in a variety of fora."

So that's--there is recognition that the working group was not alone on what incentives are needed, if any incentives are needed, and the dispute between two of the working group members as to whether or not to include this recognition in the working group report, or in this case, as I have crafted it now for you, in your report.

DR. BENEDICT: So are we clarified? All right, then. Dr. Applebaum, who requested the clarification, I'll ask you for three answers. One.

DR. APPLEBAUM: The first include is yes.

DR. BENEDICT: First include is yes.

DR. APPLEBAUM: Second include is yes.

DR. BENEDICT: Yes.

DR. APPLEBAUM: And then to pass this on to the FDA with those inclusions and the commentary from this morning, yes.

DR. BENEDICT: Thank you. Dr. Brackett?

DR. BRACKETT: Include, include, okay.

DR. BENEDICT: Thank you. Ms. Richardson?

MS. RICHARDSON: Include, include, include.

DR. BENEDICT: Thank you. Dr. Russell?

DR. RUSSELL: Include, exclude, okay.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: Include, include, okay.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Include, include, okay.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: Include, exclude, yes.

DR. BENEDICT: Dr. Kuzminski?

DR. KUZMINSKI: Include, include, include.

DR. BENEDICT: Thank you. All right. We are 15 minutes ahead of schedule, which is hardly enough to begin the GMP, don't you think? So why don't we begin lunch and then come back earlier. We'll still take an hour and 15 minutes for lunch.

And before we do that, there's an announcement that we would like to convey to everyone. We may begin to lose members of the committee as the afternoon wears on, and we want to make sure that you have a chance to comment on anything that you've read, that you won't be present for the discussion of.

And so we would like to request that if you are forced to leave us, you transmit written comments or editorial changes to the Executive Secretary, Ms. DeRoever, by--here's the date--July 23rd, which is a Friday, three weeks from today, after which time it will be too late. And so, please, it will be very helpful, if you have statements or comments, to do that.

Now we're going to take an hour and 15 minutes for lunch, which puts us back here at 12:50, by my watch. Or an

hour and 15 minutes by anyone else's watch, and we will start at that time. Thank you very much.

[Whereupon, at 11:35 a.m., the committee recessed, to reconvene at 12:50 p.m., the same day.]

A F T E R N O O N S E S S I O N

12:50 p.m.

DR. BENEDICT: Attempting to be more creative with the tapping of the gavel, we will now be in order. I always wanted to say that.

The next--and I'm so grateful to my tax dollars for affording me this opportunity to live out some fantasies--we are going to discuss identity testing and record-keeping GMPs. Before we do that, a question has been raised, a very legitimate question has been raised, about what we can or should discuss of the proceedings as they have been carried out. And I'm hoping Dr. Brackett appears. Inasmuch as he hasn't, let's press forward anyway, and we're going to ask our Executive Secretary, Ms. DeRoever, to comment on this issue, discussion of what's taken place. Here she goes.

MS. DeROEVER: Thank you. As you can all tell, this is a very open meeting. It is being transcribed. I have not checked, but I assume that the trade press are here and will be covering the proceedings.

At the conclusion of the meeting, you are free to discuss your views on what transpired, to give a synopsis of the committee discussion. The transcript that's being taken will be put on our dockets, and it may in fact be put on the world wide web, so people will have access to that.

This committee has never had a closed meeting. If we did have a closed meeting, there would be guidance and restrictions, in fact not only on who could attend but also on what would not be discussed after the meeting.

We would like, even though this meeting is quite general with respect to the topics we're covering and their application beyond today's meeting, when we discussed, for example, Olestra, that issue was brought to the committee twice. And when we went back for the second hearing, if you will, the second advisory committee meeting on Olestra, we did ask all of our members if they had made any public statements on Olestra that could be construed as a potential conflict of interest for their further deliberations.

So if you would keep that in the back of your mind, if you--does that address your question? And please feel free to call if you have any questions. We're happy to work with you. Dr. Larsen, would you--

DR. LARSEN: No, I think you've covered it adequately. And as Cathy has said, we've frequently--not frequently, but we have gotten calls in the past after especially controversial meetings to have folks clarify with us, and we clarify with them, what it's appropriate to say or not to say, or how far--you know, and what the impact may be on any future deliberations. Feel free to call us.

DR. BENEDICT: Thank you both. And in fact

several of around the table have called in the past, sometimes more than once, before discussing certain issues with people who contacted us.

So, now, before we move into the discussion of identity testing, records and retention, let's recognize the folks that we have here to help us in our discussions. We've already introduced Mr. McGuffin and Dr. Bolar, who I'm sure is on his way, Dr. Croom and Dr. Wang.

On the other side of the table we have two people from FDA, and I would be grateful if you could find a microphone and introduce yourselves. They have both been extremely instrumental in developing these documents.

MS. STRAUSS: I am Karen Strauss, and I work for Office of Special Nutritionals, and I have been a facilitator of the working group, trying to help put things that I get into an order that sort of makes sense, I hope. And so this is sort of the culmination, I hope, of a lot of hard work, and it will be interesting to hear the discussion of the committee.

DR. OBERMEYER: I'm Bill Obermeyer. I had just a few minor comments that I had put in or helped put in here, but other than that, just Division of Natural Products, and I'm just here to answer a few questions.

DR. BENEDICT: Thank you both. So unfortunately, especially unfortunately for me, Dr. Chassy, who is the

Chair of this working group, is unable to be with us, and I seem to have been elected to give you the overview of our deliberations.

And the charge to this working group essentially asked us to consider what would constitute identity testing of dietary supplement ingredients, and what records would be necessary to demonstrate that product safety is maintained throughout the manufacturing and distribution process. The charge is summarized in the documents that you have.

The information that you find in this report was contributed by the working group members, by representatives of FDA, as well as some particularly exuberant members of the public who attended our Chicago meeting and didn't know what they were getting into at the time. We roped them into providing some information for us.

We have had that face-to-face public meeting in Chicago and several very lively conference calls dealing with various issues, and we had a few sub--I don't know whether you call it a sub-working group--a few sub-working groups were established to hash out particular issues. And in many cases, almost all cases, we achieved consensus on what we thought should be presented to the committee. There are, however, some minority report statements that I'm sure you found in your documents, and I'm going to ask us all to discuss those, probably first.

The issues are, this draft report takes a narrow definition of ingredient identity testing. That is, we were prescribed to establish the origin, the nature, the characteristics, the form, the taxonomic classification where that's applicable, of dietary supplements. We did not address microbial and chemical contamination testing. This is to be done at a different time. We acknowledge that there are limitations to the analytical methods currently available for a lot of the things that are going to be incorporated into this type of food supplement substance.

We included, we hope, the possibility that the whole procedure will evolve as testing evolves, and so that petitioners can take advantage of things that appear and incorporate that into what they wish to do. The draft report includes identity testing guidance for each supplement category as it was defined in DSHEA, but it notes that for a lot of these things there are no validated tests, and that some things you've got solid tests and some things you don't.

And so we hope we've provided the flexibility that everything can be accommodated based on what we have, without putting unnecessary strictures on industry up to which they cannot rise until we have something for them to rise to that. But we still, of course, expect testing as best it can be done and documentation as best it can be

done.

The testing procedures are limited, of course, for certain things, botanicals, dietary supplements, and they're easier for things like vitamins, and that's what I'm trying to say, not doing a very good job. You will have noticed that there's more information in the report for botanicals than there is for a lot of other things. The reason is, testing is straightforward for some things and really doesn't exist very well for others.

And of course the expertise of the working group members was sort of weighted in the direction of botanicals. We attempted to find individuals who could represent this category that has the terrible name that I can never remember, but it has something to do with a supplement that's designed for something else, and it really is supposed to mean animal products. I'm sorry I'm not being very explicit. The working group did, however, attempt to be fair and attempt to represent every category that was listed, inasmuch as we could.

With respect to recordkeeping, we included guidance to manufacturers to develop written procedures for their manufacturing practices, and to keep and review the records of the day-to-day use of the procedures in order to maintain the GMPs. We felt this was very important.

We've also included guidance to manufacturers

concerning distribution and post-distribution issues, and the question of consumer complaints has come up and should come up, and that's included for discussion as well.

So what you find in your document is a preface, an introduction, and a little discussion of the organization, of the outline; a glossary which we felt was very important; a general outline for principles for identity testing; a section on records and retention; and a series of appendices which in general the committee agreed on completely, with one exception that's expressed in the minority reports.

And I know you've all become familiar with this document, and I don't propose to give you a lot of detail. I would like for us just to begin to discuss it, if that's okay, and I'll of course ask for comments before we discuss from the FDA people.

Let me point out that, again, we have six people who are not members of the committee technically, who worked very hard on this document and argued very strenuously, and they are here to explain any controversies. They are here to help us with our discussions, and please don't hesitate to ask whatever it is you wish to know.

I think that's all I have to say. Dr. Larsen, would you like to address any issues?

DR. LARSEN: Yes, I always want to say something.

DR. BENEDICT: Quelle suprise.

DR. LARSEN: Let me have you back off just a bit on your statement about the members not being members of the committee. They are not standing members of the committee.

DR. BENEDICT: Thank you.

DR. LARSEN: Some are temporary--some are consultants to the committee and were made temporary voting members for the purpose of this activity. Others are industry liaisons to the committee, as opposed to industry representatives on the committee. The representatives are standing members; the liaisons are more or less temporary members.

DR. BENEDICT: Ah, ha.

DR. LARSEN: So they are not standing members of the committee but they do participate as temporary members of the committee for this purpose.

DR. BENEDICT: Thank you for that clarification. I stand heavily corrected.

Ms. Strauss, would you like to add anything?

MS. STRAUSS: Around the table I distributed one additional minority report statement that refers to the question of use of the terms "validity" and "validation," etcetera, and around the table we've distributed them but I haven't to the audience here, so for those that are interested I could also provide a copy.

DR. BENEDICT: So while those are being

distributed--do you have additional comments? I'm sorry.

MS. STRAUSS: No, that's it.

DR. BENEDICT: Okay. Let's find, if we could, the minority statements, and they are found in the briefing book just before "significant scientific agreement" occurs, and there is no way to give you a page number. It's the last two pages, which is probably not any more helpful than before the thing. It does begin with "draft minority report statements," which narrows it down just a little bit. It's about this far into the document from the back.

Okay, now that we're all there or here, we can take them in order, or why don't we look first at the auxiliary statement that Karen Strauss passed out to you.

There was considerable discussion on the use of the term "validate" or "validated" or "validation." It was thought by several members of the working group that this had implications certainly to chemists and to some individuals in industry that couldn't be supported for some of the tests that we're proposing that people do.

And it was suggested that we change the term from "validate" to "substantiate" or to "substantiation," and what you have before you on this one piece of paper that was passed out--everyone see it? Looks like that--is a suggestion to do that. And this paper shows every possible place in the document that this might occur.

And example is the one on page 13, line 42, reword to read the following: "Extracts should be manufactured with botanical ingredients identified as in paragraphs (a) through (c) above. A validated chemical assay"--oh, I'm reading the wrong thing. This is the place where "validated" is appropriate, I think. "A validated chemical assay, such as those of the AOAC, pharmacopoeias, and other internally validated or substantiated analytical methods are the only analytical methods relevant to identification of this form of the botanical ingredient."

Which I assume means if you've got a good test and it's validated, that's fine. If you don't have a validated test and there's an internally substantiated method, you can use that. And this has been done throughout the document.

If you would like to comment on that or ask questions about it--Dr. Hotchkiss?

DR. HOTCHKISS: Let me make sure I understand what you've said. You're not telling me that the words "validity", "validation", "validated," have been removed from the document or are being proposed to be removed from the document. Are you--I think what you're saying to me is that in those cases not involving a chemical analysis, microscopy, for example, that in those places the words "validated", "validation" or "validate" have been substituted. Is that what you're talking about?

DR. BENEDICT: That's essentially what we're saying. If there is no validated test, we'll use a substantiated method. Does that reflect what we've said?

MS. STRAUSS: It's probably more accurate to say that "substantiated" was put there in addition to "validated"--

DR. BENEDICT: Okay.

MS. STRAUSS: --in almost all of the cases.

MR. McGUFFIN: So in almost every case--

DR. BENEDICT: This is Mr. McGuffin.

MR. McGUFFIN: --"validation" was replaced with "substantiation or validation."

DR. HOTCHKISS: Well, I guess page 8, line 9, that's not the case; page 8, line 24, that's not the case; and page 17, line 2, that's not the case, according to this list, and I've just gone through quickly and jotted them down in my book. In some cases what you're telling me seems to be the case, but in other places it seems not to be the case.

MR. McGUFFIN: Right. I did say--this is Michael McGuffin, again--in most cases. And we ought to look at those specific ones and see. Can I read the first one, then, from the text?

DR. BENEDICT: Sure. Let's do that one.

MR. McGUFFIN: On page 8, line 9, "The general

principles to be considered in determining the appropriate ingredient tests are outlined. Included are characteristics of the dietary supplement ingredient, of the test techniques available, of the testing environment, and of the ingredient test method," and we put in the word "substantiation" rather than "validation."

And then you really have to look at our definition of "substantiation," which is very closely synonymous with our glossary definition of "validation." And our caution here had primarily to do with the generally used definition of "validation," which is something different than our glossary definition.

Our glossary definition is really a dictionary definition, but the concern arose out of the knowledge that the scientific community refers to a validated methodology as one that has been scrutinize by a specific procedure that includes multiple center testing and a number of very specified reviews. And what we were trying to do in this regard was to assure that method validation include internal validation or substantiation also; that a manufacturer often is the best source of the methodologies, and those had been excluded in earlier drafts.

DR. BENEDICT: Dr. Buchanan?

DR. BUCHANAN: Can I make somewhat of a recommendation here? The term that's usually used when

you're talking about a validated method is an official method as opposed to one which has not been collaboratively studied. The definition that is used for validation here is more consistent with the way "validated" is used in conjunction with evaluating a food process. It would be--that definition would be the definition of "validation" that we would use, for example, in HACCP, as opposed to an official collaborative or verified method or validated method, and in some cases there are not official methods.

DR. BENEDICT: So is it your suggestion--well, let me start again. One of the concerns was that "validation" as a term might strike fear into the hearts of people who see it in a different context, and is it your suggestion that using "official" would alleviate that discomfort?

DR. BUCHANAN: Certainly "official method" means to us that a method has been reviewed appropriately by either ourselves or a methods organization such as AOAC, etcetera.

DR. BENEDICT: Does anyone have a comment on that?

DR. BENEDICT: I would like to suggest, Bill, Dr. Obermeyer, you're much more involved in chemical methods validation in terms of its vocabulary.

DR. OBERMEYER: Yes, I agree with your understanding about "official" in there, but what we have at this time is really a lack of AOAC or published validated

methods. So, again, if they could be internally validated, and that could be the chromatographic and based on the International Congress for Harmonization, the parameters set up there, the rigor. It could be AOAC, kind of again parameters that would be used to again indicate that these methods were valid, not necessarily published in AOAC, that those would be acceptable.

So we didn't want to necessarily indicate that only official methods could be used, but as long as they went through a lot of parameters, and they could be done again internally, and it would be again very similar to AOAC but they're just not going to be published in there. And again, data to show the evidence of validation, you know, would be needed.

DR. BUCHANAN: The other factor that I would like to emphasize is that if an official method is available, there is a very strong preference for its use as opposed to an alternative method which may not have been validated. So in the presence of both, the official method will almost always have precedence.

DR. BENEDICT: I think that's an excellent point.

Dr. Hotchkiss?

DR. HOTCHKISS: I was going to make a similar comment. In another part of life where I deal with standards based on methodologies--not just chemical

methodologies, by the way. You can validate non-chemical microscopy and identification methods, as well, so I don't think that's an issue.

The way that this is normally handled is similar to what Bob Buchanan just said. You start out with a statement that says where--something to the effect of where official or validated methods exist, they will be preferred or used. Where they do not exist, where they do not exist, the methodology must be internally--or whatever words you wish to choose--validated and evidence given for their validity.

That's the way JECFA, FCC, and others handle this, rather than try to invent some new kind of word that--for which the nuance, the differences are, to me at least in my vocabulary, quite subtle between this definition of "substantiation" and "validation," and seem not really to address the issue.

The issue is that if you have a validated or official method, that's what you will be required to use. If you don't have that, you'll have to provide evidence that the method you are using is meeting the needs. That's what you want to do, and that's the language that I would suggest that you incorporate, and forget about this new kind of strange government words.

DR. BENEDICT: So, anyone else?

[No response.]

DR. BENEDICT: I'm not sure how to deal with this. Let's let that go on the record in very declarative sentences, as it did, and let's move to the next one for the moment, and that would be the FDA Fish and Fishery Products HACCP Regulations. We'll just discuss this, if we need to.

"Working group members request agency confirmation that the FDA Fish and Fishery Products HACCP Regulations apply to dietary supplements when the characterizing ingredient is derived from fish and fishery products--fish oils, fish cartilage. The report sections specific to written procedures and records for receiving materials"--etcetera, there--"guides manufactures to seek records that demonstrate compliance with FDA Fish and Fishery Products HACCP Regulations. However, members are uncertain as to the applicability and extent of applicability of these HACCP regulations to dietary supplements derived from fish or fishery products, in particular since this information is perhaps not generally available to a manufacturer."

Did we get a response from the FDA to this?

MS. STRAUSS: Yes, that that HACCP, as I understand it, they do apply to the fishery products, so substances such as fish oils and cartilage would be--would need to be covered by HACCP.

DR. BENEDICT: Okay. The next one is one that is

definitely a minority report, Reporting Serious Adverse Events to FDA.

"Some members believe that the written procedures and records for handling complaints should guide manufacturers to report serious adverse events to the FDA MEDWATCH system to ensure that the agency has information needed to protect public health."

"Because of existing concerns about the current usefulness of the system this guidance was not included in the report," after a vote of the working group, and this is an area where we would like guidance from the people around the table. Dr. Hotchkiss?

DR. HOTCHKISS: I'm trying to remember my regulations, but as I recall, there already are regulations within the CFR that require manufacturers to report such adverse outcomes, and I would assume that they would be applicable here as well. Could somebody perhaps address that?

DR. BENEDICT: Dr. Larsen?

DR. LARSEN: I hope I'm not stepping in a place in the wrong way here, but my understanding is that there are requirements for certain drug products, yes, but for the food products I don't believe we actually require that this be reported to FDA under MEDWATCH.

DR. BENEDICT: Dr. Wang?

DR. WANG: The discussion here is reporting to the FDA MEDWATCH, and there are some food products that require reporting of those adverse events, like if you have low acid canned foods, you have even under process, you have to report. For infant formula, that the company is supposed to review their complaints, and if there are complaints and if there's any serious illnesses, they are required to report to the FDA within 15 days.

And so this is the area that there were quite a bit of discussion back and forth, and it was one that why we put it in the minority report for the group to discuss.

DR. BENEDICT: Dr. Bolar?

MR. BOLAR: For the record, it's Mr. Bolar.

DR. BENEDICT: Oh, I beg your pardon.

MR. BOLAR: This is in error.

I just wanted to mention that some of us had concerns about a requirement to report adverse events to MEDWATCH, partially because we're not comfortable that MEDWATCH is the appropriate vehicle for reporting those kinds of complaints.

There are a number of discussions going on right now as to how industry might be able to assemble and communicate that information, and I think we generally view that as an important element for assuring safety of dietary supplements. But specifically MEDWATCH I think has some

issues that need to be discussed, and we didn't feel that it was appropriate to include that recommendation in a guidance document that would impact the GMP procedure that supplement companies would have to follow.

So in general concept I think there's industry support for something along this line, but we're not fully convinced that MEDWATCH is the appropriate vehicle.

DR. BENEDICT: Dr. Applebaum?

DR. APPLEBAUM: I'd just like to mention that there's also a working group that's looking at this as it relates to passive surveillance for the dietary supplement industry, and this is a project ongoing. So maybe we are-- so it is an issue. It is an issue of concern, and there is a working group established by FDA to address this, similar to what we have recently gone through with emerging science, significant scientific agreement.

So it's currently being looked at, so it may not be appropriate at this point in time to focus a lot of effort and attention. I think it should be noted that this was the recommendation of the advisory committee today, but it is being looked at and it is a collaborative effort, if I can call it that, between the government, between various segments of the food industry, as well as university.

DR. BENEDICT: So would it be everyone's opinion, then, that this is a moot question, if a working group that

involves FDA is dealing with it? Dr. Larsen?

DR. LARSEN: Just one point of clarification. The working group is a working group of the Food Advisory Committee. Okay?

DR. BENEDICT: It's one of those secret working groups.

DR. LARSEN: No, no. This is one of three that we started to institute a year and a half ago, one of which you are discussing right this moment, but in terms of being able to staff these working groups for you, we have had to step them, step through them. And we're trying to get through the GMP one, we've started the adverse event reporting one, and there's a third one.

In fact, I have an e-mail here about a person that's supposed to be on the third one, that's concerned about not having heard about where her papers are. But there's a third one on consumer research that, as soon as we are able to conclude the GMP one and have the AER one firmly on its way, we can then begin to start the third one. And so these are all working groups of the Food Advisory Committee.

DR. BENEDICT: So would then anyone have objections to just striking this part from the minority report and letting it be taken care of by the other working group? Is there an objection to that? Dr. Applebaum?

DR. APPLEBAUM: I don't think to strike it. You know, to have it remain and we just continue. You know, because we're spending a lot of time discussing this particular one--

DR. BENEDICT: Sure.

DR. APPLEBAUM: --but to strike it would not accurately reflect the particular individuals that were tasked with looking at this, so I think it should remain. It is a legitimate concern, and it's as noted, but at this point in time it's being dealt with as it relates to a work in progress.

DR. BENEDICT: Dr. Wang?

DR. WANG: I echo that, is that maybe we just amend it, that it's going to be looked at by another group, and not to strike it out.

DR. BENEDICT: Fine. The next item on our minority report, Performing Multiple Tests in Identifying Whole Plants and Whole Plant Parts.

"Some members are concerned that the principles outlined for performing multiple tests in identifying whole plants or whole plant parts might create a loophole that gives a means of escaping testing." We just wanted to make sure it was noted that "Creating a loophole is not the intention. The intent is to emphasize the need for multiple testing and that sufficient identity tests should be

performed to ensure that what is on the product label is true and accurate."

I would invite discussion of this, if there is any.

DR. CROOM: Stephen?

DR. BENEDICT: Dr. Croom.

DR. CROOM: I haven't kind of heard an overall. This strikes to some of the goal of the committee, because when I look at this, I want it realized that we were looking first at a performance standard, whether multiple or single, are sufficient. And I think it's very key for the full committee to realize, if they look at page 4 in the report where we start, because there are so many details here, and I'll go to line 36 on page 4.

It says "Performance standards must be sufficiently accurate to distinguish or separate the ingredient from other ingredients that could adulterate or be confused with it." That's the real goal. And we start off that paragraph, as you note, saying that the report is not prescriptive.

And why I want to point this out is that if you read this, realize as a guidance document, not a GMP, because it's not stated very clearly in what I see is sent to the Food Advisory Committee. But then we took a lot of time coming up with examples, and unless they were taken in

context, say, well, how could you meet a performance standard that would separate your ingredient from what it could be?

But if you can keep that goal in mind, and that it's the performance standards, because if you read all of this, there's a prescriptive. In many of our discussions we're dealing with those kind of details, that there was obviously rarely it was what to know what to do to be right or wrong that was economical and doable at the time.

Because I think it's important to realize that what the committee did here was to look at--and I think this should be spelled out very clearly, these are identity standards at this time; that the way the proposed GMPs are written pretty much apply to processors and manufacturers at that site, and to say how can you make those identity standards appropriate.

And there was, just as we've heard in the other groups, a great discussion of what's doable now, and the law, DSHEA even makes clear you cannot require any methods that are not available now. And so part of the dilemma is to say what do we develop that's available now, while trying to set a situation--and that's why I'm keying in on performance standards--that if in the future there were more economical, more accurate, more applicable standards, that this guidance is not frozen in concrete, right?

Because that would not serve our real mission here. Our mission is to say what's on the label. And therefore, let's face it, if we--because they are not AOAC nor USP nor any other officially sanctioned methods for most of these ingredients, we also ended up with more flexible terms to try to reward innovation in whatever format, so it could happen in a timely manner.

I do want to make one comment at this point, Stephen, that in the future another additional thing that I think must be done is that we have to expand this to the ingredients at the time of collection, and that is excluded in the proposed GMPs. And that exemption in my opinion creates a huge opportunity for misidentification that cannot be totally corrected later with large volumes of material, no matter what analytical test is applies.

So if we're serious, what we need in the future is a different edition of good plant practices that tell us more guidance on how to identify the varying collection and quality, whether from cultivated or not, and that will expand beyond identity into what crop protection agents and other quality issues.

But my point is that even for identity, identity is in many ways easiest and most accurately done at the time of collecting the whole plant, not later, if we want to assure the correct species and plant parts. So that is one

whole area that we did not address and needs to be addressed in the future.

DR. BENEDICT: Well, I agree with what you say, but I thought we have some provision for that in the document, in the first part of--I'm trying to find the page and I seem not to be able to find it. I thought it was in part four, where we addressed--

DR. CROOM: Well, we did, but what I'm referring to is, if you read a proposed--as published, the ANPR, you will see--and I'm not sure, because of printing this off the web, if it's page 5702 or 5703 because of which way it prints out, but there's an exclusion for the ANPR that says, "establishment engaged solely in the harvesting, storage or distribution of one or more raw agricultural commodities, as defined in Section 201(r) of the Act, which are ordinarily cleaned, prepared, treated and otherwise processed after being marketed to the consuming public."

So all that means is that you're right, we spent a lot of time discussing this, but if this exclusion stays present, then it would rule a lot of that null and void that we discussed, Stephen. That's what I just realized probably last Friday in reading back what we didn't go through.

And so I think it's worthwhile to point that out, that this is a consideration at the FDS to say, for example, if we go to the details now, and considered it prescriptive

and not performance, I would say a farmer who's raising 1,000 acres of a plant, it's stated right now in our guidance document that he would have to do microscopy, chemistry and morphology. Well, that would be an absurdity if the plants were properly identified.

On the other hand, there are certain problems of scale that, of mixed lots and things, you have to do every test you can because of the non-uniformity of the raw material. So I think everything we recommended has some basis in merit, but again I go back to I think there's only one question, and that is our performance identity test, to say, "Is it a system that you've developed that's tight enough to assure us, and if it's botanicals, that it's St. John's Wort, for example, and not another of the over 300 species of hypericum. Have you developed identity tests that what's on your label is what is there?"

And I'll emphasize that that is not typically done by chemistry, microscopy, or other methods to a definitive level, and so you have to start at an earlier point where you have whole plant materials, for products that are not generally in cultivation and are not generally well characterized. These are not cranberries or apples or anything that's been well characterized in cultivation, that you know your source, for many of these products.

DR. BENEDICT: Does anyone wish to respond to

these comments? Please.

MR. BOLAR: I just wanted to add that I think we need to keep in focus here that much of what is written in this document does pertain to the broad spectrum of cultivation and all the way through the manufacturing of the end product, whereas the ANPR is targeted toward the manufacturer and the processor of ingredients, and I think it's appropriately targeted there. But this document I think really does encompass a broader scope, and there may be other regulatory mechanisms that are more appropriate toward the grower and the cultivate of these crops, but these principles would still apply.

DR. BENEDICT: Dr. Applebaum?

DR. APPLEBAUM: I just have a question in regards to products sourced overseas. If Dr. Croom could just explain, would that be the responsibility of the purchaser to--because, you know, I like what he's saying, and I just want to know how in terms of practice that would be done for products sourced from overseas.

DR. CROOM: I think the way we look at this is, there are two things that happen on a company level. You have to audit your supplier, your raw materials supplier, whether domestic or overseas, and I would say just in that audit that you need to know how well are their specifications at the time of collection. In other words,

do they have them tight enough that they can give you exactly the ingredient that you've purchased?

So that ties in, when we see GMPs, it has to do with supplier audit as well as the specific ingredient. And I would say for that specific you would have the same question. If I'm buying--to me, in the food industry it would be, just like a long time ago, it might be is it a hard red winter wheat or a certain variety versus another? And I need a certain specific type for the product I'm going to manufacture. So you would expect that person to be able to demonstrate to you that it was that particular type of plant within even a species that you desire?

DR. BENEDICT: Do you have a follow-up?

DR. APPLEBAUM: Yes. Well, and then you would be recommending that the necessary records be kept on the part of the, for lack of a better term, the purchaser, the customer of the--

DR. CROOM: I'm not suggesting that--I don't know the total answer. I don't know that it's necessarily that the final manufacturer keep that. I'd leave that open. I would say it's certainly worth considering, just if you could audit your supplier and their ability to do that certain one, and I would turn it over to those of you in industry to say how do you handle this.

I don't particularly feel the knowledge to say

that, but I think if you had that knowledge base, that these ingredients would meet your specifications. I don't want to decide who keeps the record. I'm just--we're at the beginning to even say you should even ask those questions.

DR. APPLEBAUM: No, no, and I'm here playing devil's advocate because it's an issue we're dealing with right now as it relates to a term called "traceback," so we're dealing with it as well.

DR. CROOM: And that's where I'll admit my limits. You know, I'm just trying to be the technical expert to say to prove the identity of that ingredient, you need to get this information, and anything else logistically is not in my expertise.

DR. BENEDICT: Dr. Wang?

DR. WANG: I just have a question regarding, on page 14, line number 4 is that the waiver of this multiple testing if their--if the lot is in quantity of less than 500 pounds, and we did not get into further discussion there, as are we talking about whole plant in the wet weight form or are we talking about in a dry weight form. The reason I have this question is, if you translate the product into the finished consumer units, they are totally different, dry weight basis or the wet weight basis. So that's one, I throw it out as clarification.

DR. BENEDICT: And that was something Dr. Ertl

designed for us. Is anyone able to address that? Mr. McGuffin?

MR. McGUFFIN: I believe that the intention was on the weight basis in which the product was to be used, so if you were manufacturing with an undried product and using less than 500 pounds, at the point of manufacture it's still not dehydrated, then that would be the relevant weight basis. That's generally not the case. Almost all of the material in the marketplace is dehydrated, so generally it would be on a dried weight basis except in that specific instance.

DR. BENEDICT: Dr. Wang, do you have more?

DR. WANG: Well, I have a follow-up. Again, for a guidance document, the way I view it is that it's kind of hard when you start putting a number on it. And even though the intention is that you do have to conduct multiple testing, because of certain--but when you start putting certain exemption on a certain level, it could be misinterpret in the guidance document. Thank you.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: Can you just tell us where the 500 pound number came from, not 50 or 5,000?

MR. McGUFFIN: It primarily came from pragmatic issues. We developed the concept of multiple testing in work that Forouz Ertl and I undertook with some other people

in the industry in the middle of this process, when we realized that it may have value. We had started by simply trying to identify the tests that are relevant to the different forms, and then Dr. Ertl proposed that multiple testing is the best way to assure identity in the whole form.

We then tried to examine what actually goes on in the marketplace, and recognized that there are quite a few of the smaller manufacturers who are producing their own raw materials, people that are literally growing their own products, drying them, making their products. And to go back to Dr. Croom's example, in those cases they're identifying it at an agricultural point. We thought that it need not be subjected to multiple testing.

We made the number up out of whole cloth, but it had to do with representing what we believe to be the upper limit of companies of that size in their actual practices today. So although we made it up, it had a reference in practicality in actual use today.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: We're still dealing with the draft minority report, is that right?

DR. BENEDICT: We are. We're just trying to get through those, and then move to the--

DR. HOTCHKISS: Open up to broader issues?

DR. BENEDICT: --to the broader issues. And the good thing is, we're getting lots of nice things on the record for the FDA to mull over.

So the last issue--oh, sorry. Dr. Buchanan?

DR. BUCHANAN: I'd like to follow up a little bit further on Dr. Croom's commentary, which seems to be a minority report within the minority report. Your basic recommendation at this point, technically, is that starting the Good Manufacturing Practice at the plant, at least in terms of identity of the botanical in question, is inadequate; that it needs to go back to the source, the site of cultivation. Am I capturing--

DR. CROOM: That's correct.

DR. BUCHANAN: Thank you.

DR. BENEDICT: Okay. The final issue in the minority report series is Inclusion of Plantain/Digitalis Case Study, and some members of the committee are of the opinion that it would be instructive for individuals to see how this happened. Others are of the opinion that it might create obstacles in the context of being unnecessarily critical and giving the impression that misidentification is a widespread thing. And as you can see, it found its way to the minority report series because we were unable to resolve this. Would anyone like to question or comment? Dr. Kuzminski?

DR. KUZMINSKI: I can appreciate the concern expressed in the minority report about the inclusion of the case study. It's a negative case study. My question is a simple one: Is there a positive case study that could be included along with it?

DR. BENEDICT: Does anyone have a suggestion? It's probably sufficient that the record contains a request for a positive case study. Hearing--yes, Dr. Wang?

DR. WANG: Could you elaborate? What do you mean by a positive case study?

Before--can I make one comment about this?

DR. BENEDICT: Sure.

DR. WANG: Oftentimes--you know, I work for the State Health Department--and oftentimes when we get involved is when we hear there may be some problem, that it may trigger a traceback because of illness and it may trigger a recall. Again, expressing the reason for including this case study, the way I felt, these are not that common. And what I'm trying to say is that to include an example here to show you, there is a lot of--there are opportunities that could be misidentified; the herb could be misidentified.

And in this case this so true that--so it's just to call to the attention. Maybe a few years from now when people go through this guidance document, they have forgotten. You know, most of the time you don't have

problem, but there is history that there had been a problem.

And so that was the reason why that the minority was put in, because it was said that whether we should include something. When we have a problem, we learn from our problem, we correct from our problem, and that it will never happen again. Sometimes it does, so there's cases there to show you not to do it.

DR. KUZMINSKI: Thank you. I'm for the inclusion of this case study, but if there is a concern that it represents a negative viewpoint about the frequency of misidentification, perhaps, or lack of identification, then why not include an example where the industry has lots of evidence that the actives have been properly identified? And that's what I mean by a positive case study.

DR. BENEDICT: So would you be comfortable with some sort of enumeration that out of X number, only Y number were misidentified, but we provide you with that one for edification purposes? I would assume that greater than 99 percent of things that are on the market are properly identified and not adulterated. Would that raise your comfort level? I think just a positive case study would be almost anything, I would think, unless I'm missing the--

DR. KUZMINSKI: I think it would be up to the--I don't want to sidestep this really at all, but I think it would be up to the working group to recommend, if they agree

with the concept of inclusion of a positive situation. I guess my point is, I'm trying to--what's the spoonful of sugar here that's going to help the negative case study go down?

DR. BENEDICT: Dr. Obermeyer, did I see a glimmer of a response?

DR. OBERMEYER: Well, you made a statement that most of them may be--a very high percentage may not be adulterated. Adulteration takes a wide, I guess, berth here in this one, and we didn't address potency or anything like that there, and we're only looking at main identification, so I wouldn't want to go that far and say percentages of them are unadulterated.

DR. BENEDICT: Thank you.

Dr. Hotchkiss?

DR. HOTCHKISS: Generally, in my experience case studies, even if negative, can be very instructive and prevent future problems, and therefore I think it's a very useful thing to include.

DR. BENEDICT: Thank you. So if there are no more comments on the minority reports--did I skip one? I beg your pardon. Did I skip the Reliance on Authenticated Plant Reference Material? Well, then, let's deal with that.

"There is a concern that the recommended use throughout Sections IV and V and in Appendix E of

'authenticated plant reference material' as defined in the glossary is unnecessarily narrow. This position expresses a belief that the term 'authenticated or other accurately identified plant reference material' provides more practical guidance. An alternate approach is to delete the words 'by a qualified plant taxonomist' from the definition of an 'authenticated plant reference material' or to change these words to 'by a person qualified to make such determination.' This position believes that such deletion is consistent with the inclusion of experiences other than academic studies in the glossary definition of 'training or education,' and does not in any way lessen the recommendation that only plant material that has been positively identified be used as a reference."

Comments are welcome.

DR. CROOM: Stephen, since I was the one that brought this term to the committee, I think--I would welcome others that resolved it--as long as it's an alternative, what I wanted is a tight enough definition to say authenticated plant material is determined by a competent plant taxonomist. It did not become a single choice or anything, but a reference tool, and I think at that point this issue probably went away.

My concern was, I did not want the definition diluted to a point where it wasn't clear where that

particular tool was well defined, how it was done. And there could be other alternatives, as we have in here, of in-house reference materials and other options of technical guides that can be used. So I think we're okay on that.

DR. BENEDICT: Dr. Buchanan?

DR. BUCHANAN: Just for my own edification on the areas that were covered, typically when you have a series of methods that involve microscopy, at least in the areas that I'm familiar with, in microbiology and pathology, et cetera, what you test is the effectiveness of the operator through a series of consultations or a quality assurance program.

In association with this plant reference material, and also your section on validated methods, I did not see any discussion of QA programs for methods that by their very nature are subjective and typically would require this kind of consultation. I know it's a standard practice in pathology, that the pathologists periodically get known samples that are known to somebody else and they have to accurately identify them. Were these kind of processes considered in your deliberations?

DR. BENEDICT: Dr. Obermeyer?

DR. OBERMEYER: In the, I guess the art of botanical microscopy, since it's basically a dying art, we did not go back into looking at accreditation for this technique at this time because of the lack of reference

material, lack of experience. There are things that are coming up now to help positively identify, but it's not accreditation. There would be authenticated reference materials on a CD ROM for comparison. But no, we did not look at accreditation for the actual microscopist at this time.

DR. CROOM: And I would say that--

DR. BENEDICT: This is Dr. Croom.

DR. CROOM: Dr. Croom, yes. Thank you. We're just developing where even the materials to come to your thing to say, just like you have authenticated chemical reference materials that have run through your test, the point I'm trying to make here is just that very first step that's just to say, someone who's qualified for that particular plant, to even assure you that that plant reference material is the true species and plant part to use as your reference material is even accurate. We're just starting to develop the tool at that little baby step, and you're taking us to a wonderful direction, but you can imagine we don't even have that first step yet.

DR. BENEDICT: Dr. Applebaum?

DR. APPLEBAUM: Well, I guess I have a concern, and I appreciate that statement you made about this being a dying art. But you have a dying art involved with products that are very popular, so--and again, that's--that leaves me

troubled.

DR. OBERMEYER: Well, even with that dying art, we are trying to revive it. CPR is being done by FDA and through CFSAN to give training sessions. Stanley Chicowitz, who you met the last time, we have successfully given three or four of these week-long courses to again extend this experience back out into the industry, and there is only FDA and I think it's McCrone's Institute, and I think Ed Croom has a little bit of his university doing some microscopy training, but at this moment we're really giving CPR to this.

It's a very good, simplistic type of testing, and it can be done by a wide range of even economically burdened groups. So, I mean, we would like to have this come back, and there are some I guess fine points to overcome before it can be again widely used.

DR. BENEDICT: Mr. McGuffin?

MR. McGUFFIN: I'd like to also address your concerns. It's very much a dying art compared to what it was a century ago, but the body is much warmer today than it was a half a decade ago. There is significant activity being undertaken in England. There are some microscopists that are busily putting the references together, primarily. That's the tool that's needed. The American Herbal Pharmacopoeia will publish a document of something over 100

verified references within the next 12 months. So it is relatively a dying art but, again, it is--the resurgence is real. The industry has recognized the usefulness of this particular testing method for the materials that we use.

DR. BENEDICT: Dr. Harlander?

DR. HARLANDER: The document also includes a number of reference books, as well. As I recall, some of those were brought to the Chicago meeting, and so it's not like there's nothing out there. I mean, they're not books that might be familiar to those of us who are like in the food industry, but for those that are in this area, we had a pretty long list of other reference books.

DR. CROOM: Let me just add, there are references in the back of the report, to add this to your answer. The new tools we're talking about is both training people, and I would say because of the lack of trained people or people that were at formal courses longer than a week. Both in my group and others, as Bill has mentioned, we're trying to make more user-friendly--you know, start out with even "Here's this cell type to that, to this sort of thing," so you could have a lab technician not even trained in microscopy, be able to apply these tools to do the definitive identity.

DR. BENEDICT: Okay. Thank you.

Ms. Strauss, do you have something to add?

MS. STRAUSS: Yes, I just wanted to point out that even though in the document we haven't specified what would be the qualifications for a particular type of task, we have given some information on the identification environment that includes the personnel and the equipment and supplies, and it does address that personnel should be qualified to do the task that they have been assigned to do and gives a little bit more detail. But it hasn't been left unaddressed. It is there.

DR. BENEDICT: Okay. Let's now move if we can to general discussion of the document, the draft report that you were presented with. Any questions? Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Yes, and I hope I'm not opening up a can of worms here, but throughout the references to reporting and procedures, in a variety of places, but in particular the first one I found was on page 23, line 12, there's a reference to "Records should be retained for 1 year after the expiration of the shelf life of the dietary supplement," and I was wondering how that is determined. And I don't know if that relates to potency or other issues, but it's throughout the records section.

DR. BENEDICT: Would anyone like to comment? Mr. Bolar?

MR. BOLAR: Your question is how is the expiration date determined? Well, that will vary from product to

product. It will depend on the claims that are made for the constituents. If a specific one or more components with a potency claim is made, then the expiration date is generally keyed off of the level of that ingredient as it deteriorates over time.

And these are generally determined through real time studies. Many times, however, accelerated stability studies are used. Particularly in vitamin and mineral products, accelerated stability is used. It's a little more problematic to apply those methods to herbal and botanical products, however. Other factors are taken into account, as well: microbiological, taste, odor, etcetera.

DR. SIGMAN-GRANT: Might that not be addressed by including that in the definitions section, a little bit, a descriptor of what you've just said, as an addition to this document?

DR. BENEDICT: You're speaking of a definition of how expiration dates are arrived at?

DR. SIGMAN-GRANT: Because there's nowhere else mentioned in the previous part of the document, and then it just appears.

MR. BOLAR: The concept of stability studies is addressed in the ANPR, and it's somewhat, I think, beyond the scope of what we were addressing here. But if it would serve some purpose, I'm sure some sort of definition could

be included.

DR. SIGMAN-GRANT: It's just a suggestion.

DR. BENEDICT: Thank you. Anyone else? Oh, Dr. Hotchkiss, sorry.

DR. HOTCHKISS: One of the eight major issues addressed, as I read through this document, is identifying particular substances, different herbs and so forth, obviously a critical issue. Not a lot different than identifying other food ingredients, food ingredients of botanical origin or plant origin, for example, gum arabic, carrageenin. The list goes on and on and on.

The approach taken in those cases, both in terms of commerce, labeling and regulation, is to write a specification for what gum arabic is, and including methodology to confirm that, purity, safety issues, da da di da, rather long. I'm sensitive to this because I find myself in the unenviable position of doing this for life. JECFA, FCC, U.S. Pharmacopoeia, da da di da, on down the list. You've mentioned or a couple of people mentioned an Herbal Pharmacopoeia that's apparently in the works or available.

I was just--and maybe I missed it, maybe I over-read it, but when I was reading through here I kept expecting to find some place where it was going to say that committees of experts or whatever would define these things,

for example, would say what St. John's Wort is, and that would then become the standard for units of commerce, which is what happens with gum arabic. It eventually, usually, for things like gum arabic, gets translated into the CFR and so forth, and eventually becomes a world standard for these things, and seems to be a reasonable approach for other food ingredients. Did I just miss that in this document? Was it not considered? And if not, why?

DR. BENEDICT: Comments? Okay, I guess that was the comment. Dr. Obermeyer?

DR. OBERMEYER: Actually, we did consider that, and American Pharmacopoeia does develop monographs. USP is also in the process of defining a lot of these articles, and we have considered that. The actual identification of a lot of these materials had already been done in the older editions of the Dispensatory. And so microscopic identification, a lot of the chemical constituent extractions, things like that, have been defined, but they are being reinvestigated by AHP and USP to make a better, more modern determination of these constituents.

DR. CROOM: That's very true. There are a lot of--

DR. BENEDICT: This is Ed Croom.

DR. CROOM: Ed Croom. Sorry. There's a lot of initiatives. We mentioned some of these here. I'm in total

agreement with you, though, that a couple of years ago, when we take the broad spectrum, to me--we have CFRs, we have food chemical Codex--there's a need to be a compendium of dietary supplement ingredients with specification. I think there's a crying need for that to be done by an objective body.

I will append to that, though, because I am on the U.S. Pharmacopoeia, also, and when you come to me in my botanist hat instead of my pharmacognosist hat, I'll tell you that gum arabic, some of these gums and resins are not clear to me what species they're really coming from. So I would still add to that that we need a good plant practices in front of that ingredient kind of compendium to assure what's the range of the species giving us that ingredient specification for these, for these products.

DR. HOTCHKISS: Well, you may be right about U.S. Pharmacopoeia, but not in FCC and JECFA, because I wrote them in JECFA. I know what--

DR. CROOM: You know, all I'm--

DR. HOTCHKISS: FCC's is very carefully defined. It's a--

DR. BENEDICT: Get closer, please.

DR. CROOM: Right, and all I'm saying is, at this point for many of these botanicals we don't know what's actually being collected--you probably do, then, in what you

wrote--and which ones their sources are. And so I'm just saying we're going to need both to develop that ingredient specification.

DR. HOTCHKISS: Let me ask you, though, if you don't know what's being collected, as you indicated, then how does any of this apply to it? That seems to me to be incongruous. You're saying that we don't know what whatever wort is, but--

DR. CROOM: Okay. Let me qualify--

DR. HOTCHKISS: --but we're going to do these analyses on it.

DR. CROOM: Let me qualify that. Many times in commerce, just like when I'm talking about especially some of the gums and resins, you may start out with a number of species and it just be called one. It's a little bit, not just do we not know from anything, but I'm just saying the precision of exactly what all is being called that one species, to my standards may not be being met. Okay?

DR. HOTCHKISS: Yes. I'm sorry, you've confused me a little bit. Are you saying, for example, if I'm talking about carrageenin, that that is not carefully defined? I can tell you that they went clear to Bill Clinton to define what carrageenin is. That's the truth. I guess I'm a little--

DR. CROOM: I'm not trying to get into those

specifics. I'm just saying for many--realize that for many botanicals we have over 1,500 species, and I'm just suggesting to you that it's good to start that ingredient specification with also good plant practices as well as an ingredient specification.

DR. BENEDICT: Dr. Kuzminski, did you have a comment?

DR. KUZMINSKI: Yes, thank you. I've read through the document in a kind of detailed way, and it's quite a detailed document. It's just an observation I'd like to share.

If the intent--and I guess I'm a little torn in my feeling--if the intent is to provide guidance in Good Manufacturing Practices to the dietary supplement industry, and we've had discussion here and we've heard in the past elsewhere in our lives on perhaps the uneven playing field between food products and dietary supplements. Coupled with that, we've heard discussion earlier today that dietary supplements are a food.

So if we're to provide guidance here in this document on how to make a product, how to make a dietary supplement, how to analyze what to do for the active, how often, what records to maintain, etcetera, etcetera, I think that's a very valid objective of the document. But then as I read the document, I harken back to my experience in

pharmaceutical manufacture, and the tone of the document seems to resemble that more than it does in terms of providing Good Manufacturing Practice guidance for a food product.

Now, I don't necessarily feel that's wrong, because dietary supplements, in terms of what the manufacturer can say about them on their package, as the regulatory situation exists today, is guidance in terms of structure, function claims, et cetera. So I see a mixture of guidance, if you will, that's more from a practical viewpoint, formatted, required of a drug necessarily, a pharmaceutical, yet is applying to something that's classified as a food product.

I think there's a need for that little extra emphasis because of things that the manufacturers say about the dietary supplements. And I don't know if that's an issue or not for the FDA, but I think it will be an issue for the industry.

DR. BENEDICT: Thank you.

Dr. Wang?

DR. WANG: Just a point of clarification. We were discussing some of the gums. The purpose of using those things are actually to improve the functional properties of food products during manufacture, and CFR 21 has really clearly spelled out your graphs, you go through the

petition, generally recognized as safe.

In this dietary supplement, and we had a lot of discussion, a lot of these source materials are not from this country. They may be gathered from the wild in foreign countries and then brought in here, see. And so that's why the raw material testing was important, necessary. And we're seeing a lot of different types of herbs, and of course the functional properties of these things serves differently than when you have ingredients that's going to become a component of a food. This is the specifically targeted substances.

DR. HOTCHKISS: Excuse me. I'm Hotchkiss. I have to tell you gum arabic only comes from Senegal in Africa. Pterygium, by and large, only comes from a couple places in the world, as well. I mean, I guess I don't understand the difference. I understand that there are differences in the way they must be regulated and defined by the law, but the worldwide source is no different, actually, of these things. In terms of food ingredients, you're correct, they are added to food for a specific functional purpose.

DR. BENEDICT: Mr. Bolar?

MR. BOLAR: I wanted to respond to the earlier question. Mr. McGuffin and I were both party to an industry group that helped draft the original document that was used for the ANPR, and we recognize that under DSHEA, that it

provides that any dietary supplement GMP be based on food GMPs.

And many or some in industry feel that that is all that should be necessary, but I think the majority feel that because of the manner in which these products are manufactured--there are many similarities to the way drugs are manufactured--the types of claims, both in terms of claims about effectiveness as well as the quantitative claims that we make, make these products very similar to pharmaceuticals in many ways. And to the extent that GMPs for foods are designed to assure the safety of food products, we felt that many of these factors that apply to pharmaceuticals were also applicable to dietary supplements, in order to assure their safety as well.

So I think there will be some who are concerned about the pharmaceutical nature, perhaps, of this guidance as well as the ANPR, but I think the majority of industry recognizes that as necessary.

DR. BENEDICT: Dr. Kuzminski?

DR. KUZMINSKI: Thank you. Just to show you that I really did read it in detail here, on page 9--and I think there's just a little nip there on--under "Certificate of Analysis" on line 25 the word "written" is omitted, where as on page 21 on line 1 it's included. And I think the intention is to have it in there, so--

DR. BENEDICT: Thank you. Additional comments or questions? Dr. Applebaum?

DR. APPLEBAUM: This has been an education experience--

DR. BENEDICT: Microphone, please.

DR. APPLEBAUM: This is an education experience for me, so again my questions might appear naive, but this term "wildcrafted," these plants growing in the wild, I'd just like to ask Dr. Croom again in terms of--or representatives from the industry--in terms of what percentage of product coming into the United States or used in the manufacture of dietary supplements that are sold in the United States would come from "wildcrafted" sources?

DR. CROOM: I'll see if industry has some statistics, but let me say there are going to be two different questions here you ought to ask. One is the diversity and the other is the tonnage, and I think they're both important.

In other words, if we looked at diversity, I can answer that. Diversity, a huge majority is from wildcrafted, of the diversity of the species. I'd have to ask industry if we have numbers on the tonnage.

MR. McGUFFIN: This is Michael. We actually do not have good tonnage data that would organize what proportion of the total mass is from wild products.

DR. BENEDICT: Okay--

DR. APPLEBAUM: Just one point, then. Then it goes back to Dr. Croom's. It's going to be difficult, but again, I support your statement very much, for identity to be done at the time of collection. And again, I'm thinking about, you know, wild mushroom pickers, you know, from Wisconsin, you know, in terms of they go out and, you know, that type of, but I'm just thinking in terms of the complexity of this problem.

DR. CROOM: I can assure you, both as a plant taxonomist and actually someone who, not on a regular basis but even in my college days as well as recently, I go out with commercial collectors. I know the mistakes they make, even in the U.S. I know the standards versus a wildflower guide that you would even have to use to identify.

All this is easily and economically correctable--okay?--to improve our precision, and I can assure you that we have to start with the people saying more specifically that if you have a small, well known plant in a well defined area, you're not going to have much problem with well defined. This market has taken off, and like any market taking off, you don't keep the same people who have been doing it for years, that knew what they did. It's a huge economic opportunity, and at that point your standards for identity, starting in the field, have to be tighter or it

will be corrupted.

I'm sorry.

DR. BENEDICT: Yes, I think we've made that point very strongly for the record.

Let's welcome Mr. Levitt, who has just joined us. Welcome.

MR. LEVITT: Thank you. Continue.

DR. BENEDICT: Thank you.

So my feeling is that most everything that everyone wants to have said or to have asked, that pertains to whether we're going to accept this report or not, or whether you would like to have the FDA consider additional points or not, has been said. And under that assumption, I would rather not ask the opinion of the committee on every small point that we have discussed.

What I would like to do, with your permission--and feel free to object--is the same thing we did with the previous document, that is, vote or give your opinion to accept or reject it. If it's accepted to be transmitted to the FDA, it will be with the understanding that all of our comments that we have made will be considered strenuously for incorporation or for removal from the document.

In fact, if no one wishes to object, I will just declare that that's what we're going to do, without having to poll the group. If there are a few straggling comments

that you would like to incorporate into the record, why don't we do that now, or of course object to what I've just proposed? Dr. Hotchkiss.

DR. HOTCHKISS: Just a point of clarification. Are you putting in with that up or down vote the whole of the minority report?

DR. BENEDICT: Yes.

Dr. Buchanan, did you have a comment?

DR. BUCHANAN: Same exact question. Thank you.

DR. BENEDICT: All right. Hearing nothing else, let's move--I'm sorry, Dr. Applebaum. I missed your hand.

DR. APPLEBAUM: I'm so sorry. I just want to make sure, a clarification, that Dr. Croom's comments will be part of this document.

DR. BENEDICT: Oh, yes. Well, they'll be part--they'll be considered by the FDA for inclusion in the document.

DR. APPLEBAUM: Okay. All right.

DR. BENEDICT: Is that--am I accurately representing what we're going to do here?

DR. LARSEN: Yes.

DR. BENEDICT: Yes, the answer is yes?

DR. LARSEN: Yes.

DR. BENEDICT: The Executive Secretary has said yes. Be that noted.

DR. APPLEBAUM: I hate beating--

DR. BENEDICT: Dr. Applebaum, you're still here.

DR. APPLEBAUM: You know, I hate beating a dead horse on this one, but I just want to make sure in terms of--if I'm out of order, then I apologize--that perhaps Dr. Croom's comments in terms of the identifying being done at the time of collection--

DR. BENEDICT: Yes.

DR. APPLEBAUM: --is not part of this. Correct? Am I correct on that? Is that my understanding?

DR. BENEDICT: I think there are those of us who think it is, but it could be--

DR. APPLEBAUM: Then if it is, then this is--

DR. BENEDICT: --it could be emphasized perhaps a little more strenuously.

DR. APPLEBAUM: If it is part of this document, then I am--that's my last statement.

DR. CROOM: I have to qualify that.

DR. BENEDICT: We will flagellate this deceased equine.

DR. CROOM: I have to qualify that. The recommendations of how to implement that are there. What I'm pointing out is as you're saying, but in the ANPR there's an exclusion of harvesters and processors. So if it's in the document and if that exclusion stays, then it

wouldn't matter what we said here. So we have to address the issue of how we have good plant practices, starting with identity and quality, at the time of collection. Okay?

DR. BENEDICT: Yes. So we're all, as they say, squared away, or maybe the past tense is "squorn" away. All right, so we are pretty close to where we should be, according to the schedule, even though we thought we would be faster. And the schedule calls for pressing forward for another 30 minutes and initiating our discussion of Significant Scientific Agreement, and I think that's what we will do. Let me just collect my notes here.

We're joined at the table--oh, wait. Yes?

DR. LARSEN: Dr. Kuzminski was trying to raise this issue.

DR. BENEDICT: I'm terribly sorry.

DR. LARSEN: You didn't go through the final round of getting the committee's agreement on up or down.

DR. BENEDICT: I suppose I paused, and I thought you would object if you wished to. That's my error. Shall we go through the committee and seek acceptance or rejection of this document? Now, clarify for me who is able to exercise an opinion on this. Just the FAC as it stands?

Dr. Applebaum?

DR. APPLEBAUM: I was beginning to think maybe you didn't want me to give--

DR. BENEDICT: I thought about having you cut off.

DR. APPLEBAUM: But I endorse this going forward to FDA.

DR. BENEDICT: Thank you.

Dr. Brackett?

DR. BRACKETT: Accept.

DR. BENEDICT: Ms. Richardson?

MS. RICHARDSON: Accepted.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: Accept.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Accept.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: Accept.

DR. BENEDICT: Dr. Kuzminski?

DR. KUZMINSKI: Accept, the same.

DR. BENEDICT: Thank you. I appreciate the heads-up, as they say.

So we're joined at the table by Ms. Susan Pilch, whose name tag is being--oh, I'm sorry, I'm very sorry--Dr. Susan Pilch, whose name tag is being held up for us. She's the second person from FDA who's been involved with us. Dr. Chris Lewis began 50 years ago when we started this process. Are you not joining us at the table?

DR. LEWIS: I'll stay here.

DR. BENEDICT: Okay, she will stay in the audience, and Dr. Pilch will be our support person for this discussion.

I will begin, and it is our intent to do this similarly. I'll give you the briefest wisp of an introduction--most of us are pretty familiar with the issues--and try to establish points for discussion, and then we'll ask Dr. Pilch, perhaps Dr. Larsen, perhaps anyone from FDA who wants to comment, and then we will open it for general discussion.

So through NLEA, Congress required that the FDA use a scientific standard to authorize health claims. They wanted the claims to be of long-standing nature, such that changes would be rare, and the consumer could make long-term plans for his or her lifetime about increasing their general well-being. So the considerations that were designed to be included in this concept were the totality of the publicly available evidence, and that there should be significant scientific agreement that the evidence supports this claim.

And when we began this process, we arrived at the opinion--sort of--that this means that after all the available evidence has been considered, that a number of qualified experts must achieve significant scientific agreement. It was our early opinion that this does not mean that all studies have to reach the same conclusion, and it

does not mean that all experts are in total agreement, reaching total consensus.

It was further mandated that the studies should be well designed and well conducted. They should have scientific credibility. Because of the varied types of studies, and probably the varied number of studies that would be available, we concluded early on that a very specific definition would be practically impossible to obtain, and that some sort of generality had to be built into the document.

By this, I mean it would be not in the public's best interest nor in industry's best interest to say, "We require you to have this many clinical trials conducted in a certain way. This kind of information was not likely to be obtained.

And so to generate the report, the working group began with the results of the Keystone dialogue. We held a number of meetings, conference calls, passed around several reviews of drafts. Our major goal was to provide the FDA, and therefore provide to petitioners to the FDA, with a framework by which they could plan studies and by which they could evaluate studies that would lead to a health claim.

Our outline that we began to work with included that we should describe what a good study was, and that we should give an idea of which studies would have more weight

when presented to a group of qualified scientific experts.

We had hoped to provide suggestions about measurements and measurements of food substances during the studies. We wanted to provide guidance about how to evaluate the various studies that might exist, and of course incorporate a little bit of a suggestion about how statistics should be applied to this.

We wanted to make it clear how the totality of evidence could be elucidated and how quality could be judged within the bounds of what we were able to do, and of course to elucidate what was meant by "significant scientific agreement." Especially in light of recent things, this has become more important.

So in the final analysis for significant scientific agreement, does the evidence in support of the claim outweigh the evidence against the claim, as adjudged by a group of disinterested, highly qualified, scientifically qualified personnel?

And so we present to you the results of a lot of effort by a lot of people on the working group and within the FDA, and I will first ask Dr. Pilch if she has anything she would like to add, and then we'll open it for discussion.

DR. PILCH: No, I think you've done an excellent summary of what we were trying to do with our approach, to

give petitioners some idea of what it means to look at the totality of the evidence, what sort of evidence can be considered, how that has to be looked at in terms of individual studies of quality, and the overall evaluation of the body of evidence that has to be present to justify a health claim, and then how significant scientific agreement can be assessed from that.

DR. BENEDICT: Thank you. And you have before you the original charge to the working group which I'm sure you've all read, and the suggested product.

You will note that somewhere in here it asks for software. We'll just eliminate that from discussion now. We never got that far. The reason is, the FDA at the time didn't have a lot of software going on, but now, in the ensuing three or four years, most things end up as software with the FDA, and the working group just figured that's going to happen. So if you're looking for where that is, it isn't.

Are there questions? Dr. Applebaum, welcome.

DR. APPLEBAUM: I'm only asking this, Mr. Chairman, only because I know others want to ask questions but they always want someone to go first.

DR. BENEDICT: And we appreciate you being the initiator.

DR. APPLEBAUM: On page 17, if I could just ask

for what is meant by the term "disinterested."

"Significant scientific agreement can be supported based on an objective"--I understand that--"and disinterested review of"--

DR. BENEDICT: Could you get a little closer to the microphone?

DR. APPLEBAUM: I just have a question in terms of an expert reviewing the data is disinterested. I'm getting caught up in my terms, so if someone from the working group could explain that.

DR. BENEDICT: Would you like to go for that?

DR. PILCH: Yes, I would say--

DR. BENEDICT: This is Dr. Pilch.

DR. PILCH: --yes, that this would imply independence and no vested interest in the outcome of the review.

DR. BENEDICT: As opposed to not interested in what's going on.

DR. PILCH: Yes.

DR. APPLEBAUM: Because I understand the issues surrounding, for example, an industry expert, and let's use oats for an example. If you're an industry representative who is also an expert in oats and nutrition from oats, there is going to be definitely an issue surrounding conflict of interest. But if I'm a researcher and my whole career--and

I'm in academia--has been spent looking at oats, I'm not necessarily going to be disinterested.

So I'm just raising that, because sometimes there is--there does arise an issue. So I'm saying that I don't want those oat experts in academia to be eliminated because they have an interest based on their career research in this particular area.

DR. BENEDICT: Dr. Hotchkiss, did you have a comment on that?

DR. HOTCHKISS: I had exactly the same question, and I guess you probably have thought this through very carefully, but it is often impossible to find an expert, wherever they come from, who is disinterested. If they really are an expert, they may have an interest. Usually the words are framed somewhat differently in terms of "independent expert," "without apparent bias," and such as that.

But a "disinterested expert" is a little bit of an oxymoron, and can get in trouble, because again on some of the panel--other related panels I serve on, very often, for example--oats is a great example--maybe one of the world's experts, maybe the world's expert in oats in some aspect comes from an industry who makes oats, because somebody has tied them to that job for 35 years. It's just a very unusual word to have in there.

DR. BENEDICT: Dr. Buchanan, do you want to address this as well?

DR. BUCHANAN: Yes, I would just like to point out, if the grammar police ever chased us down on this, that the definition of "disinterested" is "objective." So basically your sentence reads, "based on an objective and objective review of...." While we tend to imply certain things with "disinterested," the exact definition is "objective."

DR. PILCH: And I don't think we certainly meant at all to imply that it would be people without subject matter expertise. That is a type of disinterested review that, say, happens with the NIH Consensus Development Conference, where the evaluators are removed from the subject matter.

Another way of getting a review with independence is also to be sure to get a balanced representation of different views from the experts, so that if there are pro and con sides, hearing from both is often a helpful way to deal with that and still have the expertise on the panel or on--

DR. BUCHANAN: The word "objective."

DR. HOTCHKISS: This is Dr. Hotchkiss. We did use "objective." We just followed it up with, apparently, a synonymous word.

DR. PILCH: If "disinterested" is a problem, I think--

DR. BENEDICT: We can certainly have that dealt with. Thank you.

Someone else? Dr. Kuzminski.

DR. KUZMINSKI: I would be interested in the working group's discussion, or was there discussion, about how the expert panel would be established on a particular--

DR. BENEDICT: As I recall, the early discussions are very similar to what you read in the Emerging Science document, and we talked about including that and then we left it out, figuring that the FDA would be best able to judge how that should be empaneled.

If anyone else would like to comment, please do. The working group, members of the working group are significantly absent today, so it's pretty much a one-horse operation.

DR. LARSEN: I was going to say, Dr. Benedict, with the departure of Dr. Harlander, Dr. Benedict is left swinging on his own for this one.

DR. BENEDICT: Yep, I am the working group. Yes. That did not elude the Chair.

Additional comments? This could be quick. Dr. Buchanan.

DR. BUCHANAN: I was going to say I wouldn't worry

a whole lot about the selection of the panels. That would, since most of these would be advisory committees of some sort or another, and we have very strict rules for advisory committees, this is really moot in terms of the discussions here.

DR. BENEDICT: Thank you. Okay. Well, I guess one more shot.

Seeing no additional comments, I invite you to respond when polled, whether you think this is an appropriate document to be remanded into the custody of the FDA. Dr. Applebaum?

DR. APPLEBAUM: Yes, I do.

DR. BENEDICT: Thank you.

Dr. Brackett?

DR. BRACKETT: Accept.

DR. BENEDICT: Ms. Richardson?

MS. RICHARDSON: Yes.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: Accept.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Accept.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: Accept.

DR. BENEDICT: Dr. Kuzminski?

DR. KUZMINSKI: Accept.

DR. BENEDICT: Wow. Well, thank you all for your attention and diligence to this. We have--Mr. Levitt would like to--has issues that he would like to deal with.

MR. LEVITT: Only pleasant ones. I know it's Friday afternoon and I'll be very brief.

Let me first of all, Dr. Benedict, thank you for chairing yesterday's and today's session in the absence of Dr. Brandt. I appreciate your willingness to do that. And thank all the new members as well as continuing members. I see some familiar faces from last year's, what was it, three days on Olestra that we spent? As well as some new members.

In keeping with the changing of the guard and time moving on, we also have two members who are--this is their final meeting, although as you know, we move you into postgraduate status. You never quite really escape.

But I have the pleasure to present both Rhona Applebaum and Donna Richardson certificates of appreciation on behalf of Dr. Haney and myself, and want to recognize your significant contributions over several years to the work of the Food Advisory Committee. We thank you for the time not only you take out of your schedule, but the lending of your expertise and thoughtfulness to discussions. The work of this committee is very important to us carrying out our mission. So I thank you both. I will save you the trouble. I'll walk over.

[Applause.]

DR. BENEDICT: And in my capacity as Chair, I'd like to add, while this is being done, that Ms. Richardson and Dr. Applebaum have become good friends.

And it was, as you can observe, of course, they provided sparks of inspiration and wonderful questions, and Ms. Richardson represented the consumer to the hilt. The consumer was never wanting while she was around the table. She always brought up the issues that needed to be discussed. And Dr. Applebaum was always very inquisitive, very pleasant, very nicely aggressive on the issues, and it was a pleasure to have served with both of you during the time that I was able to serve with you.

I know Dr. Brandt would say many more and many better things than I'm saying, but you've got to live with this. And so I would like to offer, on behalf of the committee, our personal gratitude for your years of service, and I can also attest to the fact, you're never going to get away. I stand as testimony to that.

Mr. Levitt, would you like to add anything else? Okay, thank you.

Insofar as I am able to tell, we have completed our business. Would the Executive Secretary like to add anything? I will pass the microphone along for the dreaded administrative announcements.

MS. DeROEVER: Lynn, would you like to take a shot?

Very briefly, you do have your voucher information. If you have any questions or you want to talk about that, we'll be here for a while, if you get those in to us.

To remind you, comments, written comments you have on the working group documents, we'd like to have them by Friday, the 23rd of July.

And I'm not certain if we've received everyone's calendar for planning future meetings, so after you get back to your office and check, if you could also drop that in the mail, that would be very helpful.

That's all I have, except to thank you for coming.

DR. BENEDICT: I have one other thing that I'd like to address, and I realize that this event occurred some time ago, but I don't think before this committee we've actually addressed it.

And that is to express our similar intents and high level of gratitude to Dr. Lynn Larsen, who served as Executive Secretary for so many years in such a wonderful capacity, and although we are amply helped, we will miss you greatly, and we wish you the best in all of the new things that you're doing. Thank you very much.

[Applause.]

DR. BENEDICT: And Dr. Buchanan would like to make a couple of statements.

DR. BUCHANAN: Yes, just real quick, because I know you all want to get out of town before you hit National Airport on Friday.

I want to thank you all for coming. For you new members, I look forward to working with you for the next several years on what will promise to be a whole range of issues.

I would also like to remind you that if you have any recommendations--and this is for new members and outgoing members, etcetera--how we can make the committee run more effectively, how we can make it easier for you to participate, please do not hesitate to give me a call. We're really interested in your comments.

Thank you all for being here.

DR. BENEDICT: Thank you, Dr. Buchanan. Unless there are further comments--Dr. Applebaum?--we stand adjourned.

[Whereupon, at 2:45 p.m., the committee was adjourned.]

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CERTIFICATE

I, **ELIZABETH L. WASSERMAN,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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ELIZABETH L. WASSERMAN