when we figure out how we want to review them.

Just one closing thought. In terms of how to provide guidance, I would ask that if this reported is accepted and that recommendation is left there, that you allow us the flexibility to not be too specific about how that guidance should be; or word it in a way so that it can be used in a variety of models for doing peer review; and it doesn't limit the flexibility and the future of how the peer review would be structured.

DR. LANGER: There were several comments. All four of you. Go ahead.

DR. NESTLE: I was going to say that I absolutely second, after going through this process, the need for instructions on how to do it. So that it's very clear that the chair of the committee and the agency know what the objectives of the review are before the process starts, so that people don't come in and talk about the details of their research when the review really wasn't of the details of their research. And most of the time spent in the

review was having people talk about their research and equipment, when that really wasn't what this was about.

So I don't think it needs to be spelled out in that kind of detail; but the objective should be clear. And the review process should be designed to meet those objectives. Is that fair?

DR. FENNEMA: Oh, that is absolutely fair, yes. And I think the element of self-analysis is something missing that is absolutely essential; that the group being reviewed needs to sit down probably for a day or two, and decide in their own minds "Hey, how can we do things better?" And to present those proposals in written form to the review committee.

The outcome of that is going to be much, much better than what we were able to do this time. A very beneficial process.

DR. LANGER: I'm going to get those other comments in a second, but I'm just wondering whether Bern, it sounds to me like

we're talking about minor wording changes, and whether you and Owen could just maybe during the lunch break or a break work on what that wording should be.

DR. SCHWETZ: I'm not so worried about wording as I am the concept of how extensive that guidance would be.

DR. FENNEMA: Well, this certainly, I think -- put it this way. There is a role, a very clear role for the group that's being reviewed and the management of that group to have a voice in the emphasis of what's going to be looked at during that review process. And in essence, some of the details of that.

This group I think has a distinct role in setting general guidelines for how these are to be done. This self-analysis, for one thing; the agency had no awareness of the need to do this sort of thing. The point that Marion had just mentioned, the fact that we spend probably 40 percent of our time listening to the details of various research programs within the agency, and that's not what we wanted to hear.

What are our problems? What are your suggestions for overcoming these problems?

DR. NESTLE: How can we help you?

DR. FENNEMA: Yes, how can we help? That's what the focus should have been, and that's the sort of thing that needs to get into these review guidelines we're talking about.

DR. LANGER: Of course one thing could be done -- this is just another thought that I've seen in some cases -- that you almost have a pre-meeting, you know with the committee chair and maybe yourself and maybe you, and you try to figure out an agenda and a program.

DR. FENNEMA: That's excellent, and that's part of thing you can put into this little guideline.

DR. BUCHANAN: Certainly based on the experience we acquired as a result of this process, if I might have gone through it, I wouldn't do it necessarily the same way again. I think that there were some differences and expectations that you had versus what we had. And certainly I think having been through that

now, how do we know how to avoid those differences?

We also had some expectation in terms, and I have to say that they were articulated -- at least the instructions that we got that were articulated -- that even though the focus of the risk assessment was on research planning, et cetera, we had some expectations that there would be at least some discussion of the programs in providing an overview of what we actually do in some of the areas that we have active research programs in.

So it was again a balance of, our interests were in the management of our higher program, but there was certainly some expressed interest in providing you with some details about actually what that program encompassed, and that huge breadth of activities that we're involved in on a day-by-day basis.

DR. FENNEMA: But there were some very clear misunderstandings in terms of what the expectations were in the process.

DR. BUCHANAN: Everybody tried to make

the best of it; I'm not being critical of anybody. But it would have been so helpful, if these guidelines set down well in advance so that everybody knows "Well, here's what's expected of us."

DR. LANGER: Are there some other comments?

DR. DAVIS: It sounds like -- or two comments. One, not having been on this particular review board -- in the past I've served on quite a few, especially for these governmental reviews -- it's dangerous if one gets too much in the details of the science as opposed to the direction and policies of the institute.

Because what you will have is people sitting on this side of the board who often won't understand the science -- I mean, you're the experts in what you're doing in your lab, and so you stand there and you tell us all this great and wonderful stuff that you're doing in terms of the details of your science. We're sitting there, they were probably sitting there

not knowing where that was. Rather, we're probably best helpful in terms of your vision, your direction, your policy, et cetera.

The second point I would make, somewhat echoing Marion's comments to sort of merge Dr. Scolnick's comments -- I spent 20 years in the Air Force doing research, and if you look at publications, we often rarely published anything because they went into military kinds of journals or they went into tech reports. So if you ask for a list of the things that have been published, a person could be very active in his or her field, doing excellent work, and yet have very few publications.

I think this summary that you mentioned --

DR. NESTLE: Federal Register notices count.

(Laughter)

DR. DAVIS: Yes, but I think this summary that you also mentioned in terms of -- what is this person doing and how is this

impacting the science? The list of publications might be small, but --

DR. SCOLNICK: That's just a small part of --.

(Simultaneous discussion)

DR. DAVIS: We're not going to shortchange -- if it turns out there's only one publication of three, but what's the impact?

DR. COLWELL: I'd like to bring another perspective. I feel very strongly that research does belong in the FDA.

Obviously you can't do all that you need to do when the source is out there, but there is the partnering with other agencies that can be done more effectively. For example, the genetics of drug resistance. The NSF funds research on this; not that we would direct the research specifically to meet your needs, but certainly much of the research that we do could meet your needs; and it would be very helpful, I think, for some of your key scientists to talk to some of our staff so that they know what these needs are, and that when

proposals come in that do get funded, that there could be some interaction between those investigators and your investigators. So that there could be a synergy that could be very effective for the FDA in getting the basic research knowledge that you need and to apply it to the problems that are very real and very relevant to some of the directions that we have.

Secondly I would suggest that you might want to take the model, Bob, of the National Science Board. You raised the issue of the science of regulatory decisions, and having to do science and that. Perhaps at this point the Science Board for FDA could develop for you a position paper with maybe two or three meetings of folks who are expert and to provide them the kind of guidance which gives a strong justification for the direction in which you go and then you can couple that with the internal review of the sort that has been described, and which I concur, namely self-study and identifying problems; and then the

Science Board would then have a position paper. Between the two efforts you have a very strong justification either for arguing, not only successfully but try, arguing for new resources. You would have a very strong underpinning for that request.

So it seems to me that a board, this board, could truly be a very strong and powerful science board for the FDA in some additional ways than we think pursuing the cost.

DR. LANGER: We're running a little late, but why don't we take a couple more comments. Ed?

DR. SCOLNICK: I think I'd really like to applaud your direction to review the science of the majority of what FDA does, which is the scientific review of product applications, issues that affect the general health of the public.

I think that's a really important part of what you're undertaking to do. I'll make a couple of comments; one, just picking up on

what Dr. Colwell said.

In today's world, with the technologies that exist to share information globally, the agency doesn't do everything itself; it really needs a system to be able to access globally what everyone in that field is doing. And the redundancy and waste, frankly, in the global regulatory process that today is not taking advantage of that in a global sense, is staggering, if you were to stand back and look at it.

I think if the FDA took a leadership position and tried to change that entire process by virtue of what it does in getting information that it needs, it could really improve itself into the whole process globally.

Secondly, I think you can have, you have a very effective mechanism in place in FDA, which has worked really quite well over the years; and that is, you have these external review boards which you bring in to review the company, and they're made up of academic scientists from, in theory anywhere in the

world. I don't know what your regulatory guidelines are and who you can populate those boards with, but there's no real reason you can't do that in yet an additional level to review with permanent, rotating, temporary rotating periods of length that give some substance to it. Really senior scientists from around the world who could come in and help you review the science of your regulatory process, who are therefore not tainted, because for those periods of time they are not consulting with anyone and are not part of any other company.

If you use that concept, which has been extremely effective, extremely effective, you can review your regulatory processes -- something like that.

DR. COLWELL: Can I make another addition. Because together, fit with a position paper that can be part of your Science Board.

Let me just take the area of biotech, for example. There's an interagency movement

toward developing a microbial genome program, interagency for the government. Looking through reports and data, it would be extraordinarily helpful to have the full sequence of Listeria, for example, and a few of the other number one pathogens you've got.

It may not be something that you could get funded by the FDA alone; but if it's known that this is a top priority bacterium and if you're at the table discussing the priorities, we could get these done and in that way enhance your capacity to do the kind of work you need to do.

DR. BUCHANAN: I feel I need to jump in and make some comments, and what is not actively reflected in the report -- largely because we probably didn't actively focus on it during the review process is that our scientists are heavily networked and rely on the basic science that takes place through your organization, through NIH and the Department of Agriculture, we have very formal and very informal ties to all of those activities.

So for example your suggestion about the Listeria genomics, this is a project that's actively being done by Jacqueline LoHorr in France currently at the Pasteur Institute. She is already doing this.

We have, and one of the reasons why the President's Food Safety Council tried to develop this, this Joint Institute for Food Safety Research, is to make sure that we're not having a great deal of redundancy across federal agencies, but that it is a coordinated activity.

So for example, we have a need for more information in order to contemplate standards for microbacteria-impaired tuberculosis. We have gone to NIH and we continue to sit and are aware of all of the research in that area that NIH is doing. At the same time we have formally requested of the Department of Agriculture because they have certain -- they have farms; we don't. That they conduct certain types of research in microbacterium tuberculosis and its thermal

resistance.

By actively seeking all of these opportunities for leveraging, we know fully well that there's no way in the world we would ever get the kind of research budget that we would need to address all of that myriad of questions that were faced.

So we focus our activities into working with each of those groups to get the basis sciences, taking up the basic science where there's a gap that we need to address. And then being able to take the resource from all of that, do the applied science that we need to do in order to get our regulatory mission addressed in a timely manner.

DR. COLWELL: I think that's laudable and I'm glad to hear it. What I'm saying is that I think there could be even greater communication to your benefit, then you probably deserve a seat at the table where these discussions are going on, rather than just a pipeline to it.

MR. LEVITT: And any way you can help

us get that seat at the table, instead of a pipeline going in, you know, we ought to take advantage of.

DR. BUCHANAN: Right.

DR. COLWELL: That's why I stay on the Science Board.

DR. LANGER: Why don't we take two fast points. Go ahead.

DR. DOYLE: I was also on the committee, the review committee, and I think we found an awful lot of areas where there are opportunities for improvement. But I personally want to commend both Mr. Levitt and Dr. Buchanan for what I think is an incredible they have done in just two years in advancing the agency as far as it has.

They're the leaders, and when Bob Buchanan said FDA, CFSAN is the leader in the area of quantitative microbial risk assessment they are, they're leading the world in that area. They brought that concept to the agency, and I think this is an approach that's truly needed to specifically address what needs to be

done to enhance food safety. It's not just being a cop anymore, but it's actually taking a scientific approach to this.

I commend them both, and I think we really need to recognize, they have made a lot of contributions in just two years. They're looking for more ideas on how they can do it better.

DR. LANGER: Harold?

DR. DAVIS: Just a quick point. Better than mentioned the, how do you structure the review panel for regulatory issues? I don't speak for all of industry, but clearly we would not, at Amgen, want to see someone from Merck looking at our package, et cetera. But when it comes to the consultants, I think most of us recognize, when we get leading consultants, that you're consulting for a whole host of groups; and so that's just a given in the industry.

But if you use top name people, that they are already looking at SmithKline and Merck and whatever. We have confidentiality

agreements with them. In fact, one of the reasons we go after the top people is because at least they have a background in what's going on in the industry already, and what is going on at the agencies around the world. So that's a given with us as it relates to consultants.

DR. LANGER: Let me, just two quick points, because I wanted to see if I could get a motion to accept this report with the caveat, though, that Bern and Owen might just work on that, exactly the wording of the issue of peer review. I think the spirit of this is -- is there anybody who would make such a motion?

[Moved and seconded]

DR. LANGER: Motion to approve?

[Show of hands]

DR. LANGER: A second just before a break, you wanted to introduce --?

DR. SCHWETZ: Just to introduce people who came in since everybody was introduced earlier. Dr. Colwell, welcome, glad to have you here. And Dr. David Feigel, the Director of the Center for Devices and Radiological

Health.

DR. LANGER: So with that, I'd like to take a ten minute break and be back say about 5 of 11.

[Recess.]

CFSAN's Dietary Supplements Strategic Plan

DR. LANGER: We're going to get started. So Joe, are you ready?

MR. LEVITT: I'm ready.

DR. LANGER: Be seated, please. Joe Levitt's going to talk about CFSAN's Dietary Supplements Strategic Plan.

[Slide]

MR. LEVITT: I'm going to take a couple minutes before I start going on dietary supplements, and give you a little background of how we got there, and tie in some of the comments that were made in the previous discussion.

When I became the center director a couple years ago, I had the same reaction Marion Nestle had, which is "Oh, my gosh, how are you going to do all this stuff?" And one

of the first things we did was we developed what we called our 1999 Program Priorities document. We provided this to the review committee.

Since at the end of the year we actually put out what we call our report card on the document -- I'll get copies over lunchtime and bring it to folks if you're interested -- which shows that we accomplished nearly 90 percent of the objectives that we had laid out during the year. And we felt quite good about that, good enough that we had the courage to go the year 2000 priorities, which is patterned after the 1999, even more ambitious.

So we feel at least we've got the program in a direction. One of many items, one line of this entire book was to do a dietary supplements strategic plan, and I want to talk about that.

But I am going to do one other quick prelude, if you'll go on to the next slide.

[Slide]

Which is, as we have been working through the center, we have joined on our senior staff and decided that our overall mission, the specific priorities are good and important, we did a page back and say our overall mission is we want to be building a world-class organization, and that there's three principle components.

The first is that -- the first is backwards [slide]. But I know it well enough that I will tell you what it says; that we need to have a strong science based-program for our decision making. Unlike all decision-making. I know that this Board will agree with that; that we need to have a strong science-based process for informed decision-making, and that has to underlie.

So as you look at our priorities document, know that there is a strong science foundation under every one of those. We'll see if the next one is like that.

[Slide]

Number two, we have the operational

capacity to implement the decisions we make in a timely way. I think historically CFSAN has done actually very well on science base. We've heard some of that, yours leading to strength, and also this is an area we, as well as a lot of FDA, have a lot of work to do in terms of being able to follow through on the decisions we make in a timely way, and the priorities document is one way of helping us do that.

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The third is to develop what we call a culture of accountability, cooperation and respect. We want to be sure that we are accountable and are held accountable for what we try to do. But we also realize that we can do that in a way that reaches out to people, both externally and internally, and shows respect for others, for ourselves, and for the law in which we operate.

So you take those three things together, take the strong scientific foundation for decision-making and operational capacity to follow through, and a culture of

accountability, cooperation and respect, and we feel that is going to help us build a truly world-class organization at CFSAN; and we have dubbed that what we call our new day. And a new day simply means what's past is nice; what's future is what is important; it's a new day and we will do whatever it takes in order to accomplish our mission.

[Slide]

So that's kind of general background surrounding all of our programs. Let me take that now and go into the Dietary Supplements Strategic Plan, and we'll see if it fits.

[Slide]

What I want to do here is cover four main points; (1) why we set about doing this in the first place; (2) talk about the public outreach process that we had; (3) a summary of the plan; and (4) the next steps, where we're going to go from here.

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Okay, why develop this plan?

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About a year ago, a little more than a year ago, Dr. Henney had the good opportunity, as we say, to testify before Congress on the subject of dietary supplements. We all kind of hustled together to figure out, "My gosh, the law was passed five years ago." The theme was that FDA hadn't done very much, that was kind of the image around it. And went back and said, "Oh, I guess we haven't done much, we only published 25 Federal Register notices during that time." And that juxtaposition was kind of odd because that would have been viewed as a lot having been done. But against what was needed, it was clear we still had to do much more.

What we actually lacked was a clear road map of how we were going to approach this law. The law had been very controversial; the law is a different kind of law than our law was that FDA has to operate, and that is mostly a postmarket law not a premarket law; and we dedicated ourselves -- in the course of this year, one of our items was, we would develop a

strategic plan with public outreach, how are we going to approach dietary supplements, can we do that in a collaborative way with outreach?

Now Dr. Henney had three statements I'll just read to you quickly that came out at that hearing. Number one, FDA is aware that Americans place great faith in dietary supplements to help maintain and improve their health, and that the scientific evidence documenting the benefits of a number of supplements is increasing.

So number one, the law is that dietary supplements is here -- there's a lot of interest and there's increasing science evidence behind them, so let's move forward.

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Quotation number two is the challenge to FDA is to strike the right balance between preserving consumer's access to products information while at the same time assuring the safety and proper labeling of all these products. So not only do we have to maintain access but assure safety and proper labeling.

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And the third is it is clear, therefore, with the benefit of hindsight, we still have a way to go in achieving full implementation of the Dietary Supplement, Health and Education Act, what we call DSHEA, and of developing a workable regulatory framework.

We started with public outreach, and let me tell you what we heard.

[Slide]

We had actually two meetings; one was in Washington, one was in California last summer. I chaired both meetings myself. We also got written comments, and there were a lot of themes in terms of what we heard.

Number one, at the first meeting, frequently mentioned, almost everybody said "deal with safety first." That's quickly followed by, as part of that, "Get your adverse event reporting system in shape." We have a system that is earlier in its development, I'll call it, than what you have in drugs or

biologics or in medical devices. Get good manufacturing practices in place, strengthen your enforcement.

And actually the one thing that was a surprise to us, certainly not -- but a surprise, is increasingly a number of calls for enhancing the science base under these products. And that was music to our ears, but I'll tell you, it was a bit of a surprise. There were a lot of different ideas how to do that, but there was a clear theme; you've got to enhance the science base under these products if they're going to have credibility in the marketplace.

[Slide]

There were an additional number of things that also emphasized you need to clarify what you -- how you have to substantiate claims, a lot of call for increased consumer research on how consumers read labels, special emphasis on botanicals and again need for collaboration, and both need for sources, but also for leveraging resources, much of what

we've heard earlier this morning.

So that was kind of the first meeting. We then went to the second meeting out in California. And we had actually a different kind of meeting, significantly. What happened I think was that the health professional community, particularly the medical community, realized they were not represented at the first meeting. You know, we put out our notice, "people come." The outreach wasn't very good in that area, but they heard that they weren't there, and they came by in droves to the second meeting. And we heard a very different message from them.

We heard concern after concern after concern. "We don't believe in the safety of these products. We don't believe the claims are valid. We don't know what's in them, and what FDA's job ought to be ought to be to tell the public that these products are lousy, and it is a buyer-beware world." That was the message we got for about three or four hours.

[Slide]

We also had a number of consumer panels that included a parent of a victim, of a college age young man who had just died, and that had its own imagery around it as you can understand; there was a strong message of buyer-beware; a call for what they called a Consumer MedWatch for adverse event reporting, reflecting -- we had not adequately conveyed that consumers can submit adverse events to the existing MedWatch. So there is an existing consumer medwatch, but people clearly were not aware about that. And especially concerns about marketing to elderly, to women, to children, to populations that are perceived as vulnerable or willing to take these products with greater risks, and with women, particularly pregnant women, was emphasized.

[Slide]

So you kind of had really two different meetings. There was also out there a number of things that were the same, and once you got by that, there were the same themes; food safety first, adverse events, enforcement,

science-based claims and substantiation. And again GMPs and on down the line.

So you had a residual common theme, but I really felt you had to take these two meetings and kind of put them together. What we did was we tried to put them together and first develop five --

[Slide]

-- internal strategy teams around these simple categories; safety, labeling, boundaries, enforcement and research, and that ended up being the framework for our dietary supplements plan.

[Slide]

As we went through the meetings -- and this is actually a slide I used about last September for meetings in the summer and a plan that wasn't yet out. But it was number one clear that this was going to be a long-term implementation process, that we have a growing now multibillion dollar industry that is all over the place, and a lot that needs to be done to try to get that under proper control.

Number two, that science needs to be much more central to this whole area. A lot of what happened in the earlier days of dietary supplements is to me what I just call product sales. You know, you can buy the product, and you sell it. And you rely on whoever sold it to you to worry about the science behind the product.

There is a growing recognition that that's not going to work over the long haul, that there needs to be a much stronger scientific basis to this entire area.

Number three clearly will require resources, a substantial amount.

But four, a blueprint development is fully achievable. This is something we vowed coming out of those meetings we could do.

[Slide]

And this is what we came up with. We came up with a plan to cover your books that looks like this -- you notice, I like different colors for my covers.

[Slide]

We came up with four program objectives. Number one, that we wanted to, needed to fully implement this law, and there was a lot of noise around whether FDA likes the law or doesn't like the law, and I say "You know what? It doesn't matter, it's the law. It's a new day everybody. Wake up, realize we've got a law we've got to implement, let's figure out how to do it. We've got to fully implement the law."

Number two, the goal needs to be to provide consumer confidence in the safety, composition and labeling of these products. And that's what I call by putting -- that was the message, really, out in California. We don't have confidence in the products; people express it in different ways.

Well, consumers ought to have confidence in these products, as they have in all other products.

Third, we need to have a strong science-based regulatory approach. That is what has made FDA successful in every other

area we've been successful; we need to take those lessons and apply them here; and Fourth, we have to recognize this is going to be a long-term effort.

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Now, interestingly when I put this out, you never know the things that you do that kind of come back at you very quickly. On the cover of the plan -- some people never get past the cover, you know? The cover of the plan says Dietary Supplement Strategy, 10-Year Plan. And the first question I got was: Why is it going to take you ten years?

Well, I made the mistake, the first person I talked to I knew well, and I was a little too flip and I said "Well, we really said ten because we didn't think twenty would make it past" --

(Laughter)

Their reaction was, why not a two year plan, why not a three year plan? Why is it going to take you forever? That unfortunately has been interpreted that "we're not going to

do anything for ten years," which is not the point. But the point is number one, we have to be in this for the long haul. This is not something like the food label where I was also very involved with years ago, an important new law, massive effort. But once you get that new food label done and on, you kind of go on to a lot of other things.

This is a program that is going to be with us, more like the OTC review program, or like medical device amendments; this is a whole product area that is just going to grow and grow and grow. So one thing I wanted to signal, and didn't do it effectively enough, is we have to be there for the long haul.

Number two, we are going to have to find a way to get the resources; they have dedicated staff. When I say that, it's not that the staff that work there were not dedicated; both of them are, but we need a full staff -- we need a full staff just like any other program you have that's effective. You need a real staff that's dedicated to this.

And third, and I think this was a mistake that was made at the time, the fact that DSHEA is a postmarket law, meaning you can largely market products without FDA premarket review. That does not mean it's a low-maintenance law. Everybody wants to compare this to the drug law, which is a premarket deal. But if you compare it to the food program, food goes onto the market -- except for food additives, food goes onto the market without FDA review; and we're the whole center and have our field resources devoted to regulating that as a postmarket program. So we have experience here.

But the perception was, because it's not free market, meaning you don't need any resources to do this; it's low maintenance. Really, there's a lot that FDA needs to do to get the framework in place. I think it's one thing, if we accomplish nothing else with this ten year plan, it's to articulate what really needs to be done to implement DSHEA in a proper way.

[Slide]

So we took that and we developed our program goal, which I'll just recite here; we put it right at the beginning. By the year 2010 -- that's that ten year goal -- having a science-based regulatory program -- the emphasis on science -- that fully implements the Dietary Supplement, Health and Education Act of 1994, fully implements DSHEA, thereby providing consumers with a high level of confidence in the safety, composition and labeling of dietary supplement products.

In that last line, the high level of confidence in the safety, composition and labeling of dietary supplements products is the mantra that I learned to recite again and again and again, because I think that's really what we're trying to achieve.

[Slide]

Okay, so you heard that I had five groups put in together. We just took those five groups, we added them to outreach, and that became how we developed the overall plan.

[Slide]

What I am going to do is I am not going to go through every item in here; I'm going to just give some illustrative highlights of what we have in each of the sections.

Under safety, number one is adverse event reporting. We really have to get our system at a level of performance comparable to the other systems within FDA. There is a lot of knowledge in FDA of how to do this right. And we are making good progress there.

One thing that is different is that all of our reporting is voluntary. Interestingly, very few come from manufacturers. Almost everything comes from health professionals or more even from consumers.

So we have essentially raw data that comes in to us. There is nobody else behind us doing the follow-up, but most drug reports will come in, you know, from Merck -- Merck has an army of people to go back and follow-up adverse event reports that they receive on every one of

their products, I'm sure. But we don't have that army behind these that come in; they're just raw data that come in from consumers.

Like, "I had a problem with this, and here are my medical records." So we have to kind of sort through that, so we have both a, kind of a more sophisticated kind of analysis we have to do, a more complicated. Happily, we got many fewer reports than we get in drugs than in medical devices, but it's a growing number. We need to have a system that just has all the basics. The reports come in, they're logged in, they are redacted, they are reviewed, they are triaged, and follow-up goes accordingly.

We know how to do the system, we need the bank to resource it. We have had our request in at Congress last year; it passed the House side, it did not pass the Senate side, did not pass the committee; so we've renewed that request this year. We feel that's absolutely essential if we're going to get that program running.

Good manufacturing practices. Probably the one thing that everybody agrees on is we need to have GMPs, and we have on priority goals to publish our proposed reg this year. And third, just a notation of new dietary ingredients. The law does have a provision that new ingredients -- and new is defined as after 1994 -- they do have to go through a premarket notification process with FDA.

As time goes on, as we get more away from '94, there is going to be more interest in that provision. So there we have to handle like we do, FDA does other premarket provisions. We have to have the guidance in place, what are the standards, what is the level of evidence that's needed, and that's going to be a bigger issue as time goes on. There are a lot of other things in the book you see on safety, but those are the three most important.

[Slide]

No. 2 under Labeling. Somebody

earlier referenced Pearson v Shalala. This is a court case that FDA lost in the Court of Appeals that deals with health claims on dietary supplements. And basically what FDA had tried to do was to set out a standard of evidence that has to be achieved, much like we have in all the other areas you're familiar with, for that claim to be made.

What the court said was, "Well, wait a minute, why do you need all that evidence? Why can't you have less evidence and just say 'all the evidence isn't in'?"

It's a different approach, of putting a qualified claim with a disclaimer. We had a public meeting on this just a couple weeks ago. It is of enormous interest in the dietary supplement industry as it is in the food industry as a whole, for potential application in their mind in there. This is a very challenging area, and this is something you didn't even have a year ago to deal with.

So this is in DSHEA, but this is in dietary supplements that is a new area that we

need to deal with I think very directly and thoughtfully, and where we have a lot of energy devoted to that.

Number two, we have ongoing health claim petitions; we need to be sure we're able to review those. And three, we have to start dealing with the issue of substantiation of claims; what is needed to make the claims. That of course plays off into number one in terms of whether a disclaimer is involved.

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From labeling we go to boundaries. One thing that DSHEA did not do very well was articulate clearly where the boundary between drug stops and supplements begins, or foods or even cosmetics. There was a lot of publicity about a year ago; many remember a product called Benecol, which is now being sold as a spread.

We took a very strong position that that was a food, that it was not a dietary supplement, that it was represented as a food, and the law says it is represented as a food,

then it's a food and it has to meet the food safety standards and all the other food standards. And we succeeded, and the company has cooperated with us.

That is an example of the boundaries. We recently put out our final regulation on structured function claims, quite controversial in part because once you clarify the lines everybody goes, "Oh, my gosh, you clarified the lines!" Of course when you don't clarify the lines, they complain "You know what? It's all foggy out there. I don't know where the lines are."

So we're working hard at drawing the lines. We also recently, as part of the Pearson meeting, we had a panel on: Should health claims include claims for mitigation and treatment of disease? We have a petition for treatment of EPH with sol palmetto. Then the question again is, where is the drug line? Where is the supplement line? You know, what is the distinction.

And a whole host of issues;

botanicals, or some would want a whole different class and category for botanical products. That is something that's well down the road.

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Fourth is in terms of enforcement. Everybody agreed, and of course until it's their product. But by and large, everybody agrees with the principle that FDA needs to have a stronger capacity and presence in order to establish a level playing field. We are developing both an overall strategy and a lot of effort toward capacity building.

One partner who was not mentioned this morning, among many, is the Federal Trade Commission; in this area a very important and a strong partner for us.

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And finally, of greatest interest to this group is our work on strengthening the science base. We need to number one be sure that we're enhancing our internal expertise. Unfortunately we began that process by losing

our two pharmacognizsts, which was clearly not by design; and so here we have a -- if your group came back this year, instead of the c.v.s coming in, I would have to give you the c.v. going out.

Everybody has their own reasons for moving on. Actually, CFSAN has a lower attrition rate than most; but we have to establish a critical mass in this program. And we do not have that yet, and that's I think probably our first goal internally, is to establish a credible cadre of internal experts that can effectively deal with this area.

We then have to strengthen research efforts, and I'm going to talk more about that in a minute, so I won't do that now. And third, we have to talk about oversight of clinical trials. As we're trying to encourage more research, you have to look and see, are there special needs that dietary supplements have that are not appropriate for the IME process but that we should have perhaps a separate investigational supplement process or

something, the same that was done years ago for medical devices, when they reach the same kinds of issues.

So those are the kinds of things we have to look at.

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In the science base of the research, we need to be working with NIH, with the Office of Dietary Supplements and Center for Alternative Medicine, with U.S.D.A. and others, on developing a long research agenda.

One thing, and it was kind of related to one of the comments Rita Colwell had about getting others to do the research for you. One thing we had done in the food safety area; one of the first things Bob Buchanan did when he came to FDA was develop a long set of research needs.

What we found was that by making a list of research needs and making that public that other funding agencies would use those in part as the yardstick on what to fund -- you know, the system can actually work that way.

And we want to apply that same here. There's a whole host of needs for research agenda. Research capabilities, again that's part of our internal science cadre of expertise. We need to have at least a critical mass within the Center so that we have the expertise to do the science, to have the broad policy and planning.

Third, we have to look at whether or not we have a retrospective dietary supplement ingredient review. This was done in all the other areas when FDA inherited a whole product line. It was done with OTC drugs, it was done with medical devices, it was done with the GRAS review in the foods area. When the food additive law was passed, and I think that again that will take time, that will take money, but if we're going to do it right, it ought to be done.

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Finally, probably no area is more important than dietary supplements for the importance of leveraging.

Bob already mentioned the work we're

starting to do with the University of Mississippi as an expert center that exists down there. We want to take advantage of that. We've already talked again, NIH, Office of Dietary Supplements, Center for Alternative Medicine, in terms of how we can leverage our different work. In fact, when I went over to NIH, I was surprised but intrigued when their reaction was they feel as overwhelmed as we do.

You know, we look at NIH and see this huge funding structure and they go "My gosh, our funding structure for our world is tiny." Just like your infrastructure for your world is tiny. So we're developing a camaraderie among the different government folks.

We're looking at NTP through NCTR, what studies, what product ingredients ought to be suggested for review under the NTP program; and so we are -- again, leveraging is going to be vital to our success in this area.

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Outreach. Bob mentioned that we are going to be establishing, as part of a

restructuring of the Food Advisory Committee, a separate panel that is devoted to dietary supplements; this is badly needed. We need to continue our stakeholder outreach and continue very much with open and continuous communication.

There are a number of groups here that are not our traditional groups we're working with, and we need to therefore make extra attempts to reach out to them, include them, and be sure there's clarity back and forth.

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Next steps. Where to from here? Well, what we said is that number one -- when I said it was a ten year plan I also said that we would articulate each year what we can do that year within our available resources.

So in the 2000 priorities document, the R pages, which are dedicated to this year's goal on dietary supplements. The A list - B list means that A list is the top priorities.

Within our 2001 budget now before Congress, we have renewed our request for

funding for a dietary supplement adverse event reporting system, and we are actively engaged with the developing community buying an involvement to this entire process. We began about a month ago with a meeting hosted by the National Consumers League, which involved again many of the affected players, who are trying to get people together or do some of the duplication, increase some of the synergy and say again, if we're going to develop the kind of consumer confidence in the safety and composition labeling of these products, how are we going to do that in a way that's efficient and effective? And that's our goal.

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In conclusion, this has been I think in many ways a very intriguing process for me. I've been very involved with this. I'll kiddingly say that when I first came two years ago and the Food Safety Initiative was so very, very visible, all my first speeches said my top priorities were food safety, food safety and food safety. And I didn't say it, but probably

my last goal was to work on dietary supplements. At the time the food safety issue seemed so dramatic and huge and compelling.

Well, even just a year later it quickly became clear that the cost of not paying attention was exceeding the cost of paying attention. And that it actually would be easier for us if we kind of jumped in and said "Wait a minute, let's grab the bull by the horns and figure, how are going to do this right?"

So we developed, as I said, a sizeable effort last year with a lot of outreach to say, "How are we going to do this right?" How are we going to develop consumer confidence. And then we will take this through our budget process and use it as a basis for building the resource base that we need both inside and outside in order to make the American public proud of this program as with other programs.

Thank you very much, and I'll be happy to take questions.

DR. LANGER: Questions or comments

from people on the Board or otherwise?

MR. LEVITT: It's interesting because of -- things that hit the media. This is one of the ones that is just a constant theme. I tried to be on vacation this week, and Tuesday night there was a Dateline NBC show on dietary supplements, Thursday morning, page 2 of the Post had a big follow-up story on it.

So it is a continuing theme. Also, one other thing and I didn't mention this but I should, that we're also calling on all my other colleagues around the table to the left as full partners in this effort. And everybody within FDA recognizes that dietary supplements is an area of enormous need. In last year's internal budget process, we've gone to a corporate-wide budget planning process in FDA with different areas like surveillance and research and premarket review and so forth. And every area recommended dietary supplements as the area of greatest need for this year within FDA.

So everybody, whether they're part of the program or not part of the program,

realizes that this is important. That didn't make it all the way through the process because of the various things that affect budgets as they go through, but internally everybody is saying yes, this is an area that we want to help. And so we will be taking advantage of that, too. But fundamentally, we're going to have to convince the Congress to fund the proper program.

DR. LANGER: Yes, Owen?

DR. FENNEMA: I would like to applaud your efforts to develop cooperation with the University of Mississippi. As you're well aware, the whole matter of dietary supplements is a troublesome one in terms of regulation, but the area of botanicals is an ultra-troublesome one, and there's some good expertise that lie there.

I think that's a good example of the kinds of cooperative relationships that FDA ought to enter into. This is going to be very helpful, and I applaud your efforts.

MR. LEVITT: Thank you.

DR. LANGER: Yes.

DR. NEREM: How well do you feel that you are aligned with the priorities of NIH? Is it a pretty good alignment or is it still early days, or?

MR. LEVITT: I think it's too early. I think there is -- when talking with them, a great interest of them in being aligned. And it kind of comes to the same point that Rita Colwell made before, "having a seat at the table."

I think what we're developing is a seat at the table and how to be sure that those funding priorities are meeting our priorities as well. So I say there's openness to achieving it, but there's not yet achievement.

DR. NEREM: This is specifically with the Center for Alternative Medicine?

MR. LEVITT: Right, specifically. And dietary supplements, both. But you're right; the first one has the money.

DR. LANGER: Harold and then --.

DR. DAVIS: You mentioned it, but I'm

not sure I still understand it, the issue with the Pearson/Shalala ruling. Would you restate?

MR. LEVITT: Yes, I'll restate that.

As a quick background, FDA has -- and this is really under the food labeling law from about 1990, a provision for what's called a health claim on a food or a dietary supplement -- and a health claim is viewed as a disease claim -- they have been used so far, mostly for risk reduction of chronic disease in healthy people.

So you see the fiber helps prevent -- whatever. That's that.

When NLA was passed there ten areas, ten specific dye-disease relationships that FDA was to review, for meeting the standard of significant scientific agreement. When FDA reviewed those, six it said yes to -- actually seven; I think one was added; and four we said no to.

The four we said no to were the subject of this lawsuit. And we said no because they did not meet what we felt was the

standard of reliability. We actually won in the district court but we lost in the court of appeals, which in the hierarchy of things is the only one that matters.

What the court said was that it built on a whole series of First Amendment cases in the advertising area primarily. They said "Well, wait a minute. What's important to consumers is information that's truthful and not misleading."

"We are going to remand these to the FDA to re-review these and say, 'Is there not a way to allow these claims to consumers with certain caveats? If the caveat is the data are inconclusive, say they're inconclusive. If the caveat is that these data are only preliminary and more research is needed, write, on the label: Data are preliminary. More research is needed following the claim.'"

With the general direction that under the First Amendment the goal ought to be disclosure first, not what they viewed as suppression. And that's different from the way

we've always done things. We've always said there is a standard of evidence, and below that you get to do more study.

But you don't get -- in fact, we had a meeting of our Foods Advisory Committee last June or so, and in that setting this is called emerging science. That when somebody says emerging science, I'm told that what they mean is science that's developing but hasn't quite reached the standard of reproducibility and reliability in the scientific community.

So what this court said was "Well here, can't you take" as I said "the data that are there and qualify them in a way so the consumers have truthful but are not misled to think that they have more than they have?

So that's what that case is about. At our public meeting, must have been two weeks ago because I was off this week, we had as I think one would expect, fairly polarizing views on that subject. You have the side that says "This is my constitutional right to make these claims, and the FDA, every day you're dragging

your feet." The other size says "Wait a minute, consumers are inherently misled if they're led to believe this thing is likely to work when the evidence is really so inconclusive that it really doesn't mean anything clinically. All it really means is, 'Interesting finding; we need more research.'"

And those are the two, if you will, polls of view that we have to somehow bring together. We are in court again on the subject; we've made a pledge to the court to reach conclusions on those four claims within about six months from now; so by next fall we will have reached our conclusion on what to do with the four particular claims. Meanwhile, there are more petitions that come in that ask for the same --

DR. NEREM: Back to the appeals court with these conclusions, or going to a higher court?

MR. LEVITT: It actually will go to the lower court.

DR. NEREM: Go back to the lower

court.

MR. LEVITT: Yes. You have to start again, at the beginning. The plaintiffs in the suit have already charged unreasonable delay, that it's taken us this long; and want the court to, if you will, hold our feet to the fire.

DR. COLWELL: What are the four that you were asking me?

MR. LEVITT: Can anybody recite those for me?

DR. NESTLE: Antioxidants is one of them.

MR. LEVITT: In back? Anybody here.

DR. BUCHANAN: I don't --

MR. LEVITT: My many legions of loyal followers?

(Laughter)

DR. NESTLE: One of them is antioxidants.

AUDIENCE: Both of them are not here.

(Laughter)

DR. DAVIS: Both of them. They're

dedicated, though.

MR. LEVITT: Very dedicated.

I don't want to hear them imprecisely argued, but why don't I after lunch bring it back.

DR. DOYLE: Along that line, Joe, remembering the results of the CFSAN review, you are incredibly short a step in this area. And what are you doing with RSAT (ph) to fill a gap?

MR. LEVITT: Well, the first thing we do is -- I made a big budget request which a little bit made through the administration, and we're fighting in Congress for that, devoted to adverse event reporting, and we'll come back again this year.

There's another thing about FDA staffing in general just for your education, which I have to tell you is bizarre. And everybody I explain this to says "My gosh, this is bizarre," but it's true. In that starting about 1992 or '93 when Congress passed the budget balance amendment to the financial laws,

FDA got a quote "level budget." So whatever our budget was, we'll say FDA's budget was a billion dollars. The next year it was a billion dollars.

The problem is before that we always got our inflationary increases, what's called "current services" in our financial world. So we can get current services, which meant FDA had to absorb all the inflationary costs.

Now in that year, that was the year the Department of Commerce was proposed for extinction. So we kind of thought "Mm, level budget, proposed for extinction." I know which one I'd pick.

So we actually thought at the time we didn't get a bad deal. We didn't realize until some years later that that became the new rule. And therefore what happens each year in FDA now is that the programs that have earmarked funding by prescription drug user fees were now Food Safety Initiative, those get if you will protected, and everything else, what's left gets to absorb -- just a new favorite word; we

absorb now -- we absorb our inflationary cuts.

What that means is, my program has about $100 million in my budget. I lose $5 million every year. Every year I have to find $5 million to cut, which means I need more people but I need people to leave to pay the people that are there.

When I explain this to industry folks they say "I could never run a business that way." I say "Well, it's just one of the joys of working in the government. But in Dennis Baker's world, in the field, his cut for the foods program is $7 million. So every year -- last year we were very fortunate; we got a $40 million increase, but we also had a $12 million cut. And somehow we're going to have to find -- us, FDA, we're going to have to find a way to make the needs of that case better.

I mean, what happens in U.S.D.A. in their inspection service, is they get their increases every year because under their law, if they don't have an inspector in a plant at every minute, the place has to shut down. So

there is a force that is sure that that funding is happening.

What happens at FDA, a little less happens, a little less happens, a little less happens, and you get nibbled away to death. And a lot of our programs are being nibbled away to death.

The good news is with this earmarked funding, it's been sizable, it's been substantial, and used well. But the silent part of that is these other areas are just less and less and less and less; and so our first role is to try to find a way to broaden funding so we can use new funds more broadly across the board with more flexibility, but also to find some way to deal with this constant erosion of current services and inflationary costs.

It's a real struggle that all my colleagues around that side of the table share equally. We finally find something we all agree on, you know.

DR. LANGER: One last question. Well, we'll take two. Go ahead.

DR. SCOLNICK: Are there implications of this case for how you deal with safety issues?

MR. LEVITT: The case presumes safety. If we thought there were safety issues, then that could be an effective reason for us saying no. The presumption on dietary supplements is that they're safe. There's a quote "history of safe use"; that was kind of a congressional declaration. One thing you see with all the publicity you hear around Ephedryl is what the government has to do in order to make the safety case in terms of taking adverse event reports, not having a prior body of clinical trials, and kind of filling it from scratch.

But if there was a safety issue, that would override the issue of claims. That is an issue of efficacy with presumed safety.

DR. SCOLNICK: It seems to me in the future as you articulate it, a bigger problem I think is really potential safety issues; because there isn't the body of clinical data. The safety issues, it seems to me in the longer

run, the bigger issue is the safety expanse. And trying to figure out a way that you could partner with departments of epidemiology and public health and --

MR. LEVITT: Or poison control centers is another one.

DR. SCOLNICK: Poison and et cetera, because to me that's the much bigger issue.

MR. LEVITT: Yes, safety first.

DR. COLWELL: But even basic research can be helpful here, because understanding the actual components, the molecular structure and so forth can be valuable.

MR. LEVITT: It's hard to imagine anything that we did that would not be helpful.

DR. COLWELL: Yes, that's true.

DR. LANGER: One last question.

DR. NESTLE: I'm teaching a course in dietary supplements this semester, so this is a subject of great interest, and I don't think it's possible to be too cynical about what's happening in the marketplace, in Congress, in the courts and everywhere else in this field.

And this is not something, given the number of products that are out there, this is not something that anybody is going to get a handle on very easily.

I have one question for you; and that is, what can the Science Board do that would be helpful in this situation?

MR. LEVITT: I would say help us identify areas of leveraging, universities, the seat at the table at other agencies; because for the scientific underpinning, the best thing we can do is to leverage what's going on anyway, and not wait for Congress to see what they will fund. I think that's the number one thing you can do to help us. Places like the University of Mississippi that we should be developing partnerships with and collaborate.

DR. SCOLNICK: Do you want a statement from the Board or something --?

DR. LANGER: What would you like from the Board?

MR. LEVITT: Uhmmm.

DR. NESTLE: He's not allowed to say.

(Laughter)

MR. LEVITT: "I'm here from the Science Board. I'm here to help you."

(Laughter)

DR. DAVIS: I think it seems to us that when those kinds of decisions were being made, and FDA is standing there with its own bias, obviously it's viewed by the public or the consumers or these companies that a note from the Science Board saying that, from a scientific standpoint, you know we are concerned, if we are, about these kinds of decisions that are being made. That comes from hopefully recognized scientists, a variety of areas, disciplines, et cetera.

DR. SCOLNICK: Or that we support X and Y initiatives. And try to make them specific enough that it doesn't --

DR. SCHWETZ: Give an example of something that might be helpful. One of the fears I have with dietary supplements is that because the rate of attention, the change in attention to this is going so rapidly that

we're going to jump right over what homework should have been done, and jump right in to trying to solve questions for which there is no background. And it's very tempting to do that as opposed to saying "Those questions are real, we'll get to them when we have a database to be able to handle them."

What we ought to be focusing on now has to do with all the questions -- what are the active ingredients? What are the components? What is the reliability from one product to another? There's a whole bunch of homework that needs to be done before we begin to say "This is safe and that's not safe" because we can't effectively do that yet.

And one of the recommendations could be to reinforce that the agency would work on the science underpinnings of decisions that need to be made about dietary supplements, so that it provides long-term guidance in this area. This isn't going to go away in the next two or three years.

DR. LANGER: So is that something that

would be useful to be able to say today? I mean, we could certainly, you know, make a simple statement like that, or would you like to come back to us next time with some other things that you'd like us to do?

MR. LEVITT: The two are not mutually exclusive.

DR. LANGER: No, they're not, at all.

MR. LEVITT: I would say certainly in terms of today, and I feel uncomfortable putting words in your mouth. I'd rather --

DR. LANGER: Well, you make a statement; we'll change if it we like to.

(Laughter)

MR. LEVITT: But, you know, any statement from a board of this stature reinforcing the importance of scientific decision-making in all these areas of dietary supplements is critical, and that FDA needs to have access to the kind of scientists and the kind of expertise that is going to allow us to make the decision the law charges us to make.

That is what is most at its core of

what we're trying to achieve here. And any other practical suggestions you have.

DR. DAVIS: I guess I'm a little uncomfortable with the discussion. In the past, serving at the NTP, NCTR, et cetera, one of the things we always identified were potential reporters in the audience, et cetera.

So I guess I appreciate your dilemma, standing there when we're talking back and forth about -- to do. I think personally any comments ought to come from the Board --

DR. LANGER: Oh, absolutely. I just wanted to sort of see, I think the motivation of asking the question was to understand what would be helpful to you and then we would move from there.

DR. SCOLNICK: I think again, just coming back to the safety issue -- to me, trying to define the components, as Rita said, the actual components that people are putting into things, and trying in the shorter run to ensure, based on whatever elementary science you can bring to bear in the short run, that

what's being done is safe and is not going to have a long-term negative consequence for literally thousands or larger numbers or smaller numbers of people is in my view even more important than validation and the scientific evidence that's doing good.

Because as long as it's not doing harm and there's some sense in a consumer of what they're doing or not doing, that's important, I think. Working out the scientific evidence to prove that these things are effective in the long run is an enormous undertaking. We're trying to ensure the safety, that some ingredients are not being put in as dietary supplements that are actually harmful to lots of people I think really should be --.

DR. LANGER: I think these are very important. I want to close the session up because we're running a little behind.

Let me make this suggestion: how about if Bern and you and Marion could maybe have a conference call at some point in the next few months and get back to us with sort of

a broader set of statements about what the Science Board could do. And from that we'll try to formulate some statements and some other things.

Would that be okay?

DR. SCHWETZ: Fine.

DR. LANGER: All right. Would you like to be on it, too?

DR. DAVIS: I think --

DR. LANGER: Terrific. That's wonderful. I've already got her down for something else for -- Rita, that would be terrific. Okay, so we're set on that. So we have a committee of four to report back to us on exactly what we could say. I think that would be terrific. Thank you.

DR. LANGER: Next, Bern wants to make a few comments as we move into the next section.

DR. SCHWETZ: Despite the fact that it's just before lunch, we're going to end the discussion on food safety, and we're going to move into two other examples, one before lunch

and one after lunch. But some other activities within the agency to strengthen or enhance the science base of the agency.

The first one is a competitive intramural granting program that I wanted you to look at, and get your reaction to whether this is something that you see as operationally beneficial within the agency.

Peggy?

Overview of the Office of Women's Health (OWH) Scientific Research Program

DR. MILLER: Hi. I'm on the program as Dr. Margaret Miller, but I go by Peggy, so don't get confused by that.

I appreciate Bern's putting us on the agenda and providing us with an opportunity to explain our program, our research program. But really want I want is your feedback on how we can work towards improving the program.

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What I'd like to do is just provide a very short overview of what our research program does, and then really open it up to

some questions that we've developed to try and receive your advice on the future direction of the program so that we can modify it to ensure that we're having a maximum impact on women's health.

And then if there's time, I would like to identify additional issues in women's health that we could bring before the Board and get your input on in the future.

Now, the Office of Women's Health research program was established in 1994, and we had three goals at that time; and the first one was to address gaps in current knowledge.

I want to at this point explain that when we're talking about a scientific research program, I want you to think very broadly about that. I'm a toxicologist, and it's not 20 rats in 4 groups, 5 doses; you know, it's --.

We look at where basic knowledge leaves off and where the regulatory decision needs to be made. And there's usually a gap there; sometimes it's small, sometimes it's -- I'm stealing this from Steve Sundlof. You can

see, I paid attention all those years.

DR. SUNDLOF: That's very good, Peggy.

DR. MILLER: So what our research program really does is it tries to fill that gap. What scientific questions can we answer, so that when we're making a regulatory decision the gap is not as broad as it is without the science.

We also do some basic research, some traditional studies, encouraging new directions in the area of women's health research. And finally, we strive to set a new standard of excellence in women's health research within FDA's regulatory mission.

Let me just briefly run through the current funding process. Every year representatives from the Office of Women's Health meet with the centers to identify high priority issues within the area of women's health. We then go back and we try to focus a bit; the office takes a leadership role in eliminating some of the high priority issues and trying to focus the program a bit.

We then send a notice out throughout the whole agency and ask for ideas or concept papers, and these would be soliciting from throughout the agency how we could design a research study that would help us address the high priority issue.

The office and the centers review those concept papers, we select usually between 25 and 30 percent of the concept papers to be developed into full research proposals.

Those research proposals are signed off through the center's management and then we send them out for a peer review, both internally and externally. As a result of the comments of the peer reviewers and our own internal review, we fund about half of those projects every year.

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Now, the program to date is in its seventh year of funding; we've funded 86 projects, we've spent about $8 million. In general the projects are of short duration. We usually fund projects for one to two years, and

the funding level is generally capped at about $200,000.

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When you look at the program, you will see that we've just funded a wide range of topics; and that is in part because of two reasons. One, the program is geared to fill in gaps, and there are gaps everywhere, when you look at womens health issues. Also if you look at the impact of the agency on womens health, the agency assures the safety and efficacy of products that are used primarily or traditionally in women, and so we have funded projects on what I call traditional womens health issues. And again these projects might be scientific research projects or they may be focus group testing, to see if people understand our labels.

[Slide]

But in addition to those traditional womens health issues, the agency also regulates a number of products which might affect women differently from men. There are diseases that

are more prevalent in women than they are in men. Or the manifestation of that disease is different in women than they are in men.

So we've also broadened the scope of the research project to cover what I'm calling these additional womens health issues. And besides that, the agency is committed now to eliminating inequity or gender bias in studies that are designed to show safety and efficacies of clinical trials, so we have geared a lot of studies to look at gender differences and drug effects, or using postmarketing surveillance to mine adverse drug reactions to see if women are responding differently than men, doing some of the things that you can't do preclinically in the small trials.

[Slide]

To monitor the success of the program, we use a number of quantifiable impact measures; we look at the completion rate and our completion rate is about, of the ones that are due to be completed, we're at about 90 percent, which indicates that the program has a

lot of dedication from our researchers. We look at publications in peer reviewed journals and federal registers, other things.

We look at outgrowths, whether the seed money that the Office of Womens Health has put into the project, has led to other projects in other areas or other activities, or whether the centers are carrying on that research in their own research programs, whether it's been integrated into their research programs.

We have also looked to see how the program is helping to improve the science base of regulatory decisions. So we will look at guidance documents for changes in labeling, or whether or not we've come up with a standardized analytical procedure for a laboratory for the field. As a quantifiable measure of the impact of our program.

However, the program also has what I call these non-quantifiable benefits, in that it raises awareness of womens health throughout the agency. When we send out this notice throughout the agency and people see that we

have grants coming and funding, it causes a lot of, "What is this? What are you doing? What does the office do?" And it provides a vehicle for us to discuss womens health and the issues of womens health throughout the agency.

It also helps to build FDA's infrastructure research. We do do some traditional basic research funding, and that helps these laboratories supplement projects that they had ongoing by piggybacking onto an existing project. Or we might fund a teratology study on Vitamin A just with OWH funding.

It ensures that the regulatory perspective and the goals of the agency are integrated into the research program so that we don't go off asking questions that really are not going to be impacting FDA's regulatory decision-making. Because we relied on the centers, with their personnel, their laboratories, their FTEs, we are able to leverage OWH funds quite effectively. We don't have to pay overhead, we don't have to buy

equipment, we can use the research dollars to get results.

And finally, it provides for employee development. The researcher who is sitting at the bench doing reviews day in and day out comes up with a research question. It affords them an opportunity to do that research and get credit for it and to be enlightened by the process.

[Slide]

While the program has many strengths, and we certainly are very pleased with the results we have so far, we're always looking for ways to improve the program. And one of the things we've noticed with the existing program -- the way we currently do it, where every year we go to the center and we say "What's your high priority topic in womens health?" The program has tended to focus on urgent and important issues. When we go to the center on a given week, on a given day, we get what issue is before them that week, that day, or last week at the most.

So the projects that we tended to fund have been focused on the here and now, and we really haven't set aside any way of saying "Okay, this is something we want to build for the future. This is not at our doorstep right today, but we see this as an issue out there on the horizon that's going to be coming forward for womens health, and how do we set aside some of our resources, our program to address those types of issues?"

One idea might be to have a science advisory board much like this group, and ask them to provide what's on the horizon of womens health. But I guess one of our first questions that we would have: Is there a need to balance or is there a need to do more of the longer-term research out there rather than just the, what I call hot topics or the topic of the day?

And if you felt that there was, how would you suggest that we go about figuring out what is, what should we be building for in the future?

So that's my question to the Board.

So do I turn it over to you?

DR. LANGER: That's fine. Okay, why don't we get some feedback? Thank you.

Yes, Owen.

DR. FENNEMA: Well, you touched on something I was going to ask a question about before you mentioned it; and that is that many of these research topics that you listed up there strike me as ones that if you're going to make progress on them of a significant nature, that you need in-depth research for many years, and yet you're talking about funding now for one to two years.

And it seems to me that you need to pick out some areas where it will really be desirable, the issues of longer-term projects than what you're doing now. And that may be where you have an advisory board to help you with this, I don't know; but I think that's going to be necessary to make the best use of your dollars.

DR. LANGER: Other suggestions or comments?

DR. DAVIS: If you look at the long list of areas you had up there, you're talking $200,000 at a pop, one of the things that Marion had mentioned when they looked at the CFSAN program was all the things they were involved in. And I think it would be too easy to dilute one's efforts by trying to solve everything.

There's quite a litany of areas that you put up there that the group could be involved in. I think you'd probably get more bang for the buck if you chose a few areas to look at in depth over time than trying to go after every issue that might affect women.

DR. MILLER: And then if we were going to chose -- well, we'll get to that in the next slide, I think. But there might be a role for a science advisory board to help us choose what areas are on the horizon out there in the future?

DR. LANGER: Ed wanted to make a comment, but I also wanted to check. Are you not done with your presentation?

DR. MILLER: No; I have two more questions for you.

DR. LANGER: Oh, okay. Why don't --

DR. SCOLNICK: The only comment, I have a hard time figuring out from what I've heard so far where what you do as part of FDA is different from NIH should be doing in womens health.

And I think the questions you were just asked about focus and divisions of funding, because the presentation is pretty global in itself, as opposed to FDA-related.

DR. MILLER: One of the things, and maybe I didn't express it strongly enough, is that we only fund grants that are within FDA's regulatory mission. So if we can get -- we have funded, cofunded research projects with NIH, so NIH is interested in it, then we will cofund with that.

But generally what we're looking at is filling the knowledge base. NIH will do lots of basic knowledge. But we're looking to fund research projects that will fill that gap

between where the basic research leaves off and where a regulatory decision needs to be made.

Or we'll look at specific adverse events with drugs that are specifically within FDA's purview, are there gender differences in how women react with pharmacokinetics, can we make categories of drugs that really need enough women in a clinical trial so that we can study them.

So these types of issues that are specifically related to FDA -- I call it practical scientific research. They're not the basic scientific underpinning of the mechanism, necessarily; but when do we need to ask the question, how can we be smarter in asking the questions that we need to ask as regulatory people to have the sponsors address?

DR. LANGER: What I want to do is, maybe if you will go over the other two questions, and then we'll just get the rest of the feedback.

[Slide]

DR. MILLER: Again, this gets to how

do we get to how do we identify high priority issues? The landscape, I heard them talk about CFSAN having a wide scope of agenda. If you look across the agency, between foods and devices and drugs and biologics, there's just a whole panel of products that FDA regulates that are used by women, and if we look at establishing high priority issues, even within the scope of FDA, narrowing it down to FDA, do we look at the safety of products for women? Do we look at efficacy? Should we be taking a step back from just looking at it from an FDA perspective and saying, "Okay, what do women get diagnosed with? And what's likely to be coming into the agency for us to deal with as regulators, as reviewers? Or do you look at diseases of women as a way of setting priorities?"

Because if a woman has a disease, we're likely to see products that are designed to prevent that disease or to treat that disease. And if we have the underpinnings of the research program in place, will be able to

make more intelligent, science-based regulatory decisions?

[Slide]

The last question we had is: How shall we be looking at modifying our current process to help with leverages to address these high priority issues?

We have in recent years allowing an FDA investigator to contract with an academic institution so the academic institution is actually doing the study; but the researcher is an FDA-generated research question, that an FDA reviewer has identified as being needed in order for them to do their job.

We've also done some cofunding with NIH, if FDA's regulatory mission overlaps with NIH, that we've cofunded some studies on pharmacokinetics and pharmacodynamic differences between men and women in drugs.

So we've done a little bit of that, but I was just interested in some other ideas of how we could use these mechanisms more broadly in the future.

DR. LANGER: Why don't we get comments?

DR. DOYLE: Joe Levitt had brought up the major need in the area of dietary supplements; I think I heard that that was kind of across-the-board, the centers, and certainly there's a lot of dietary supplements that would be focused in the area of womens use, and maybe there's a good match there since that's a real high priority in the agency.

DR. BUCHANAN: Actually, the womens' program has been very helpful to augmenting our program in dietary supplements, and we appreciate their vote of confidence and past activity with our program, and look forward to getting a big chunk of their resources --

(Laughter)

DR. ROSENBERG: In a way, you already have narrowed -- to me, there is already a narrowing. And that is, is the definition of where you fund, and that provides a pretty narrow window. You don't want to fund things that NIH is going to fund, and you want to kind

of really focus on these gap areas.

If you kind of do that, and then you allow investigator-initiated ideas to run its course, which is the way it should be driven, as the quality of the idea as it fits that position. It seems to me those are the two things you need in combination to make this work; it's to make sure you are defining yourself as an area of funding that's different from others, and then let the investigators decide through the right peer review committee as to what's good science to fund in that area.

I'd keep it pretty open as long as it -- I don't have a problem with all these topics, because you've narrowed it by where your --

DR. MILLER: Right.

DR. NEREM: You may have said something and I just may have missed it; a person can get a one to two year grant. Can they get a renewal of that grant?

DR. MILLER: They can submit another grant, and we will compete it with our funding,

yes --

DR. NEREM: Does that happen, or is there a prejudice against that in the review system?

DR. MILLER: No, there's not a prejudice against it and it does happen. Generally what we like to see is for our money to provide seed money and for them to be able to get other resources to carry on their projects.

DR. NEREM: Where would they get those other resources?

DR. MILLER: Either from the center itself; NCTR has other mechanisms like CRADAs. So there's other vehicles that we can -- we like to try and -- especially in the new directions area, we like to provide seed money; and if it is a viable program, we'd like to see other groups pick it up and then use that.

DR. NEREM: I'm very much in tune to the seed money idea, but when there are other resources to carry on after you've been seeded; but I very much have the impression that this

is a resource-limited organization.

DR. MILLER: Right.

DR. NEREM: So are there really those resources to carry a project?

DR. MILLER: Well, we look at them as our outcome measures, if it's likely to lead to a labeling change, if it's likely to lead to another guidance, if it's likely to lead to some outcome measure, that's a regulatory decision-making. And the way we've structured it thus far, those have tended to be short-term payoffs, more or less.

And one of my questions is, should we be looking at the longer-term investment so maybe we wouldn't get a guidance out of this this year, but we build the infrastructure to help with the decision five or ten years out. That's kind of the balance we're trying to weigh at this point.

DR. NEREM: I haven't looked at your program, and I don't have the knowledge to really evaluate most of the things you're doing; but it just it seems to me a one to two

year timeline is just too short.

DR. MILLER: Too short.

DR. LANGER: We have lots of comments. Marion?

DR. NESTLE: In answer to the question, do you need an advisory committee? Yes, everybody needs an advisory committee.

(Laughter)

What I just heard here, though, really caught me up short because it reminded me of the same issue that we dealt with in the CFSAN review, which was, "How do the priorities get established in the agency?" And it was the question that we asked over and over and over again. I've just heard that you're competing with priorities, that there is some tension between how the funding -- I mean, Bob is happy to work with you because that means he gets to take resources for his initiatives, but that doesn't say what the entire agency is doing as a whole to establish priorities and how your priorities fit into the priorities of the agency.

That's hard for us to deal with; at least it's hard for me to deal with. I can't speak for anybody else. So that's the same issue that comes up over and over and over again, how do you establish yours? How do they establish theirs and how does all this get worked out in a competitive environment in which lots of other people are doing research in areas the FDA is involved in doing research.

DR. MILLER: When we establish ours, we meet with the centers, and we say "What are your priority issues in womens health that you're dealing with this year, in this fiscal year?" Usually we just do it on an annual basis.

So if they're working on dietary supplements and dietary supplements is a big issue for them, then we'll say "Okay, what dietary supplements are used in women, where is the overlap between dietary supplements and womens health?" that the agency can impact.

That's the other piece. Where if I do this research, it's going to result in

something the agency can use --

DR. NESTLE: And nobody else is doing.

DR. MILLER: And nobody else is doing.

So that's how our program integrates it to the centers, under the current process. And I said, the only downside to that that I see is that we tend to deal with issues that are urgent; this is the high priority, you know; we don't deal with long-term chronic illnesses because those are knocking on our door today.

DR. LANGER: Bob, did you want to--?

DR. BUCHANAN: I just wanted to offer one point of clarification for you, Marion.

While they help fund some of our research supplement it so that we get in areas we don't normally go in or wouldn't have the resources, they do not pay the salaries of our PIs in conjunction with these; these are supplemental funds.

So we have a great deal of interest if they're going in to proposing areas that are

not within our priorities, that we're involved in that priority-setting process. And it does take place, we sit down, we talk about what our priorities are in terms of our programs, they talk about what their priorities are, we sort of come to an agreement on what are the areas that match the priorities of both programs. And those are the ones that wind up surfacing, and we request additional ideas from the scientist on the staff.

But it's not totally bottom-up driven. There is a decision because we are -- it's the resources coming from our research program that actually pays a big chunk of this program.

DR. LANGER: Dr. Anders.

DR. ANDERS: I have had some familiarity with this program in my relationship with NCTR, and have always viewed it as something of a pilot project program. And I think Joell James' work on folate and Down's syndrome is a classic example of how OWH funding allowed her to get preliminary data by reaching to an NIH grant.

My question is, one way to judge on the success of a pilot project program is how many of these pilot projects went on to funding by NIH or the agency or whatever. Do you have any information about that?

DR. MILLER: We capture that under outgrowths. I have statistics; I didn't bring them today, of how many projects have gotten picked up by other people that have spawned other research. We fund that under the outgrowth. We do monitor that as a quantifiable.

A little bit, we have a little problem with boundaries, like the dietary supplements. If I funded one piece of a small project five years ago, do I still claim credit? I think the folate example is a good example of where we had outgrowth. The effective drugs on cardiovascular disease is one where we've had a lot of outgrowth as a result of a little bit of seed money that was put in.

So we monitor those as outgrowth of projects. But as I said, I'm not sure how long

we can keep on claiming credit for some very good work that she keeps doing in other areas.

DR. DAVIS: I guess what I'm wrestling with is, what do you all perceive as your mission. Because I'm hearing where you think we ought to be going, and as I look at the brochure in our booklet, one of the sentences that jump out, it says that:

> It utilizes a competitive peer review process for selection of the highest quality project with an emphasis on projects with the greatest potential for significantly contributing to knowledge of womens health in a brief period of time.

So to me if you start looking for, where is this going to lead downstream or what's the outgrowth, it sounded like when you first started that you have a defined problem that has specific interest to FDA, and so how do you solve that problem? What's the answer to that in terms of labeling or regulatory decision-making?

It is so easy I think to drift off

into basic science if you're not careful when you start putting up this long litany. And you say "Well, NIH does basic science." But I think all of us who know anything about NIH know they're doing all kinds of stuff; clinical stuff, basic science; that they don't limit themselves to just basic science, because it becomes nebulous how you define basic science versus clinical science a lot of times.

So I think you're going to use up your funding and your resources if you don't have a mission that is clear and then stick to it, especially in the short term. I personally like the avenue of, how is this going to provide FDA something they can specifically use to make regulatory calls? And I think that's the work of FDA. Anything other than that, trying to understand diseases or, if you ask yourself what diseases are out there, they'll likely come to us, to me that starts to smack of not regulating issues but trying to get ready for something that might come that may or may not come.

DR. MILLER: So I guess if I -- what I hear you saying is, whether it's long-term or short-term, as long as we keep that goal is, how is the FDA going to be able to use this information to improve womens health, which is what our goal is, then we'll be fine; that that focus, as long as we keep that shining.

DR. SCOLNICK: Is it to improve womens health or is it to improve your ability to make regulatory decisions?

DR. MILLER: That impact on womens health.

DR. NESTLE: Exactly.

DR. SCOLNICK: Yes. I mean, to improve womens health is an NIH function, not an FDA function.

What is your peer review process? I would just echo what Harold said. I really have a distinct sense from listening to you that the lines are really blurred.

What is your peer review process for these grants?

DR. MILLER: We have internal peer

reviewers as well as, we ask the principal investigator to identify three external reviewers that are knowledgeable in the field; and then we contact them, ask them conflict of interest questions, ask them if they would agree to review the project. Then the office staff sits down with the internal reviews and the external reviews to put together the final portfolio.

DR. NEREM: Sort of like asking the president to give three names of people to write letters of recommendation for --

(Laughter)

DR. MILLER: Well, unfortunately with the diversity of projects that we have before us, we also asked internal reviewers; and if we feel that there's other people in the area. So we have a database now of reviewers much like NIH does, that we can tap into on certain projects that have been good objectives.

DR. LANGER: Any other questions?

Yes.

DR. NEREM: Just one thing since you