SCIENCE BOARD TO THE

FOOD AND DRUG ADMINISTRATION

TUESDAY, SEPTEMBER 30, 1997

WASHINGTON PLAZA HOTEL

MEMBERS PRESENT:

Robert S. Langer, ScD., Acting Chair

Elkan Blout, Ph.D.

Michael A. Friedman, M.D.

B.A. Schwetz, D.V.M., Ph.D.

Leslie Z. Benet, Ph.D.

Gilbert A. Leveille, Ph.D.

Richard B. Setlow, Ph.D.

Pedro Cuatrecasas, M.D.

Rita Colwell, Ph.D.

Frank L. Douglas, Ph.D., M.D.

Susan K. Meadows, M.S.

INVITED GUESTS

Bernard Liebler, M.S.

(PARTICIPANTS CONTINUED):

FOOD AND DRUG ADMINISTRATION

Charles Grieshaber, Ph.D.

Neil D. Goldman, Ph.D.

Samuel Page, Ph.D.

Beatrice Droke, M.S.

Steven H. Chasin

Neil Wilcox, D.V.M.

Susan Homire, D.V.M.

Anita O'Connor, Ph.D.

Donna Mentch

Melissa Busch

I N D E X

P R O C E E D I N G S

(9:36 a.m.)

DR. LANGER: If people could be seated, please.

I'd like to welcome everybody, the participants and observers, to the Science Board of the Food and Drug Administration today.

My name is Bob Langer and I'm going to be acting chair today. Dr. Kipnis, who is the Scientific Advisory Board Chair is unable to attend. Since I have to leave at around 3:00 to go to the National Institutes of Health, Dr. Les Benet has agreed to chair the final hours of the meeting.

I'd like to introduce Dr. Elkan Blout, to my left, who is the Senior Advisor for Science to Commissioner of Food and Drugs, and he'll introduce the Science Board members, and then we can introduce the remaining people.

DR. BLOUT: It's hardly necessary for me to introduce the Science Board members, but I'll start on my left with Dr. Leslie Benet,

UCSF.

Do people want to say anything?

Dr. Gilbert Leveille, formerly of Nabisco;

Dr. Richard Setlow, from Brookhaven National Laboratory;

Dr. Frank Douglas from Ruselle Herse. Is that correct? (Unintelligible). The names keep changing. And we're delighted that you're here. I don't know if you're based in Frankfort now.

DR. DOUGLAS: I'm based in Frankfort now.

DR. BLOUT: Thank you for coming.

DR. DOUGLAS: I commute between Frankfort and New Jersey.

(Laughter)

DR. BLOUT: And Dr. Pedro Cuatrecasas. And tell me, what current affiliation, Pedro, do you want to use?

DR. CUATRECASAS: Independent.

(Laughter)

DR. BLOUT: All right.

DR. CUATRECASAS: Quasi-retired, or semi, or whatever. But very busy.

DR. BLOUT: With experience at NIH in a large pharmaceutical industry and most of all in science. Thank you all for coming.

I should say that Ruby Hearn called this morning. Didn't get me but got Dick Setlow, and told us that she is ill and, unfortunately, will not be able to join us.

DR. LANGER: Maybe I'll just introduce Bern Schwetz, who is the FDA's Interim Chief Scientist, to our left;

Susan Meadows, who's the Executive Secretary for the FDA Science Board.

And then we have a number of people on the right-hand table -- Anita O'Connor from the Office of Science;

Charles Grieshaber from the Center for Drug Evaluation and Research;

Neil Goldman from the Center of Biologics;

Neil Wilcox and Bernie Liebler.

What's going to happen is that at 3:00

there's going to be a public comment session, where anybody in the audience can comment.

I'd also like to introduce Ms. Susan Meadows, who I mentioned earlier, and she's going to make a few housekeeping announcements.

MS. MEADOWS: Thank you.

The first order of business, I think, is to explain the microphone system that you have in front of you. It's a little different than ones we've had in the past.

You have one single button that's an on/off button, and obviously the red light comes on when you are speaking.

I understand the system allows perhaps only three microphones to be on at once, so if you're not speaking, please turn off your microphone so others can get into the system.

The chair does have the ability to interrupt anyone who is talking, so has great powers this morning.

A couple of other things. We do have a couple of breaks scheduled, one in the morning, one in the afternoon. Our lunch break

at noon, the Science Board members will have a section within the restaurant, which is across the lobby, for lunch.

The telephones and restrooms are located in the lobby outside of this room, going toward the main lobby of the hotel.

One other thing, we've provided some notebooks for you. If you would like, in the back of the notebook is an envelope. We will be happy to take the contents and mail the contents to you following the meeting. If you would like for us to do that, please put the contents in the envelope and we'll take care of it.

As well, one other note, and that is, we still are accepting nominations for the Science Board and would ask that if you have some candidates to please pass those names on to me anytime.

Thank you.

DR. LANGER: Let me just see if Dr. Blout would like to make any opening remarks.

DR. BLOUT: I just want to say that I consider the session we're having at 10:15, which Dr. Schwetz will chair, to be one of the most important sessions this Board has had.

It will attempt to define a personnel review process within the Agency and a program review process within the Agency, both of which, external people feel and some internal people are badly needed.

So please give it your attention and please give us -- nothing is frozen at this point, but any suggestions you can make about what's planned would be most welcome.

DR. LANGER: I just wanted to mention that Dr. Michael Friedman, the Lead Deputy Commissioner at the FDA, is expected to arrive at 10:15.

With that, let me introduce Bern Schwetz, the FDA Interim Chief Scientist for a report on the Science Board recommendations on FDA research and Dr. Anita O'Connor for an update on the expertise, database, and the FDA Information Retrieval System. Anita is the

Senior Science Policy Analyst in FDA's Office of Science and the project officer for the first initiative.

Bern.

SCIENCE BOARD RECOMMENDATION ON FDA RESEARCH

DR. SCHWETZ: Thank you, Bob. And good morning to all of you. We appreciate your being here today to help us with some of these items that are up for discussion today.

What I want to introduce and what the subject of a lot of the meeting today is about is our efforts to begin to implement the recommendations that were in the report of the Science Board Subcommittee on FDA Research. This was the topic of discussion at the last Science Board meeting, and we, I think, have made a lot of progress in moving toward identifying what we can do and to begin to implement those recommendations.

I will just briefly summarize some of that this morning, but then through the day we'll be commenting on what some of those implementation steps are. As Elkan has already

said, some of these are of considerable importance as we proceed forward, and I think some big steps within the FDA in terms of research and the implications for science in general.

One of the things that was implemented that affected me personally was Mike Friedman's request for me to serve as the Interim Chief Scientist. The recommendation in the report was that we would have a chief scientist, and Mike's response was that, until we have a Commissioner, there wouldn't be a decision to hire a chief scientist because that should be the choice of a new Commissioner.

Not knowing when that new Commissioner would be identified, we decided it was not in our best interest to wait months to begin to do this, so the decision was made that I would serve as the chief scientist.

That involved me moving from the Arkansas location, where I was head of NCTR, National Center for Toxicological Research, and working in the Office of Science up here, I've

reversed that so that I now live here and run NCTR from here.

But it means that I'm able to spend about twice as much time working on Office of Science issues as I had before. So it has allowed me to get involved in a lot of the issues and to be available to people locally, which makes a considerable difference in being involved in the science issues within Centers and the Office of Regulatory Affairs.

It wasn't happening to near that extent while I was located in Arkansas. The other thing that this has done, it has permitted me to meet with the FDA Executive Committee. That's all of the Deputy Commissioners and the Commissioner, as they deal with the day-to-day issues of the agency.

So it does give the chief scientist that presence in the FDA Executive Committee, which is part of what the recommendation was from the report.

So that's where we stand with the chief scientist situation today, and I'm real

pleased to be representing that position.

Another one that we had talked about within the Agency and was recommended firmly in the report was to develop an expertise data base to enhance communication within the Agency.

We have found a way to do that using the FDA information retrieval system that we've talked to you about over the last couple of years, which came about because of one of the recommendations of the Science Board.

It's nice to be able to see that we can now implement things that need to be done in the Agency and use that resource that we've already developed in that computer system first without having to regenerate and rebuild that every time. So now we've got several modules that we're adding to first, as these other recommendations and needs some up.

So Anita will be talking about where we are in the expertise data base in just a few minutes.

We have had a working group chaired by

Dr. Grieshaber, looking at the peer review process within the Agency, and it consists of representatives, as Chuck will describe, from all of the Centers in ORA in trying to define how we should deal with the peer review of programmatic work, peer review of individuals, individuals from a laboratory setting, and scientists who are reviewers, or from the non-laboratory setting.

So that becomes a major thrust within the Center to get that job done, and it certainly has significant implications for changing the culture of science within the Agency in the future.

So this is one that we really do want your input on.

Another one that we've been working on is to develop an FDA research plan. The importance of that is that this begins to draw us closer to the virtual science center that was recommended in the report, and we are looking at how it is that we can better connect the research planning and the research

capabilities within the Agency than we have in the past because of the partitioning between Centers that has built up through the years.

So I'll come back and talk about that a little bit more, but we are making progress on developing an FDA research plan, which also implies that we're getting closer to a system that will permit us to identify FDA research priorities as opposed to just individual Center priorities.

So that's kind of the range of things that we have been working on and, one by one, we'll talk about these in more detail through the day.

So to start this process, I would ask Anita -- Elkan?

DR. BLOUT: I just want to say a word about Bern's position.

I think it is significant and important that Mike Friedman agreed with the recommendation that we not wait until we have a Commissioner -- official Commissioner in place -- to put a chief scientist in place.

Bern is the Interim Chief Scientist and certainly will be a candidate for the Chief Scientist's position when a Commissioner is in place. But he's doing a marvelous job, and he's the ideal person to get this position started.

One of the recommendations of your Subcommittee was that the Chief Scientist sit with the Deputy Commissioner for Operations and be in the office when any science decisions were made and to participate in the financial aspects of science decisions, and all of you who have been in other organizations know how important that is.

That aspect of your work is not yet fully integrated, but it is part of the charge. So I am delighted that we've come this far, and a further step will occur, I hope, within the next year.

Congratulations.

DR. SCHWETZ: Thanks.

DR. BLOUT: Thanks.

DR. SCHWETZ: Anita, will you update

us on the expertise database?

EXPERTISE DATABASE & FIRSt INITIATIVE UPDATE

DR. O'CONNOR: Sure. I have an overhead. We've also put the same overhead in front of everyone.

Let me just say that, first, it's really going well. We have an increasing number of users every month. Next time we meet, I'll show you the statistics.

One of the things we're doing, we're starting to develop data bases. And, as Dr. Schwetz mentioned, we're developing an expertise data base, which was recommended by the Science Board Subcommittee on Research.

This is a data base which is accessed through the FIRSt system. It's a web interface. It's actually a relational data base, and the information for the user is entered by the user so it's self-populated.

The user enters the database with a password that we give them so that only the user can enter or modify information about him or herself.

On the overhead in front of you is a listing of the information we ask people to enter. You don't have to enter every field. It's a form, it's a web form, that you go into and actually enter. And as you enter the information, it gets downloaded automatically into a relational database.

Clearly, the database is in the pilot form. We got it up in August and it's in a pilot phase, and we expect to complete the pilot by November 1st.

There are about 100 to 200 in each of the Centers that will participate in the pilot. You have to go through a pilot phase so that you can iron out what are the essential key words and other glitches that one normally encounters when you're developing a computer system.

So we're asking people to, for example, describe their past positions, their education, to describe themselves by using key words that they select.

We're asking for the five key

scientific publications, the most important, any patents held, and then to describe themselves using key words for whether their expertise is a regulatory position in FDA or scientific expertise if they're in a laboratory position, or perhaps both.

We're also asking them to list major laboratory equipment, expensive laboratory equipment, and also unusual laboratory equipment so that we can start to share these resources.

We expect to finish the pilot by November 1st, and the schedule is to complete the final database within two months after that, so our goal is to complete the Agency database by January 1st.

Another database that we are putting on line is another equipment database, which we'll be developing this fall, and in addition to the laboratory equipment that members will enter into this database, we have another database which facilities group in FDA maintains, so we're going to develop that for

the web, so that we've got another equipment database, so that we can start to share those resources also.

Any comments or questions on what we're doing?

DR. LANGER: Any comments from the audience or anybody else?

(No response.)

DR. LANGER: I guess it's pretty clear.

Okay. Well, I guess that will probably give us even a little bit more time for the area which Dr. Blout mentioned is really one of the major things we want to cover today, which is the FDA research peer review process.

FDA RESEARCH PEER REVIEW PROCESS

DR. LANGER: So what I'd like to do, again, is introduce Dr. Bern Schwetz, Dr. Charles Grieshaber, and Dr. Neil Goldman to discuss the FDA research peer review process.

DR. SCHWETZ: Under this heading of the peer review, there are two distinct things we want to do, one of which it is asking you for approval of one request, and that has to do with the approval to form a Subcommittee of the Science Board to do a specific review. But before we come to that, we want to talk about the peer review process in general.

As we started to look at the peer review process, it confirmed what we knew, but it put in front of us what part of the initial hurdle was to get to this process of developing a consistent peer review process that could be used across the Agency.

And that was that all the Centers had in place systems for doing peer review, and if there hadn't been anything, it might have been easier to develop one than it is to go through

the stage of evaluating what you have and, on doing it, and replacing it with something different, because that creates a large amount of resistance and feelings that what I have is what we should adopt and let's get on with it.

So there was an initial stage of reviewing what we have in trying to figure out why it wasn't meeting the expectations, and then a process of a large number of meetings that Chuck has had with his work group to begin to move forward with a broad range of questions.

For example, the extent to which the peer review process should truly be external as opposed to a combination of internal and external;

How do we deal with the programmatic versus the individual peer reviews; are they done together or are they done separately?

Do we centralize this process in, for example, the Office of Science, and it would all be done from a central location, or do we disburse it and have it be -- Chuck, am I

giving your talk yet?

DR. GRIESHABER: Keep going.

DR. SCHWETZ: Whether it would be disbursed and handled in all of the Centers and then the information flows for central review; all of those kinds of considerations, part of what this group has been working on, with the bottom line being that we would come up with a process that, as a minimum, would assure consistent review if not actually be one review process, but considering the diversity of the Agency and the diversity of the research and the laboratory, parts of the Agency that are not necessarily research in the minds of a lot of people but laboratory activities for which the investigator is not permitted the option of designing his or her own research program.

All of that makes it more complicated because you have the question of researchers versus support people, even at all GS levels within the government.

So against that range of questions that this group has been discussing, they have

come up with the recommendations that have been distributed to you at this point, which are still recommendations by what we want to solicit.

We want to inform you of some more of the activities as Chuck will give you but then to prompt the discussion of where this should go and whether or not for sure we're on the right track and what the track should be from here.

Chuck.

EXTERNAL PEER REVIEW

DR. GRIESHABER: If you don't mind, I'm going to stand up here (inaudible).

Good morning, ladies and gentlemen. It actually is a real pleasure to be here and to talk about peer review, a project that a lot of us have been working on for the last three months.

Actually, I have, I don't know if it's a distinction or a dubious distinction; we've heard now that there are three areas of implementation of the Subcommittee's report

from last spring, the appointment of an interim scientist, chief scientist, which is an absolutely, universally well accepted move;

The creation of a database that you just heard on expertises, which allows us to freely communicate across the agency and will allow us to find individuals who have like interests and expertises, and so forth, and discuss research.

The distinction that I have is to chair a panel that is dealing with peer review, and that's met with accolades in some quarters with a nodding and in other quarters it's meet with a lot of concern and some beads of sweat on foreheads, because people really aren't used to how an outside total look at peer review of the FDA might evolve.

So what I'd like to do this morning is briefly describe to you where we are and have discussion, because we really want your advice and counsel, comments, suggestions. How do we go beyond a standard that is set for peer review in general?

How does the FDA, as it's constituted, look beyond a standard set of peer review criteria, of peer reviewed process, and so forth?

But before we do that, let me just tell you where we are today.

As Dr. Schwetz indicated, we do have a Committee, and I acknowledge them both for their effort and their concern with peer review, and these are working scientists within each one of the scientists.

I'm not going to read them to you, but actually I wanted you to know that there are a lot of hard-working people that are contributing both their thought and their effort to this peer review issue, the institution of a process, and the criteria associated with it.

Let me just tell you what we're doing, why we're doing it, and how we're doing it.

I notice that Dr. Friedman just stepped in, and he was the one who issued this charge to draft a process for peer review, at

first, of laboratory-based research programs and research scientists.

No strings attached, free thinking, design a peer review process.

Now, parenthetically, he told me that the process and criteria for peer review should be transferable to all science-based programs and individuals in the FDA, meaning non-lab based scientists, regulatory scientists, and so forth.

I'm actually discussing here with you, so if you feel compelled to stop me or ask a question, please feel free. I would be delighted to do so.

That also goes for you, Dr. Friedman. You can make your points at any particular time.

DR. FRIEDMAN: Chuck, thank you. I'm known to be such a shy person about that, I fear I would sit here quietly.

DR. GRIESHABER: The strategy that we followed -- and we implemented this about three months ago; we had our first group meeting in

July; was to establish a working group consisting of the representatives that I indicated early on here, and we wanted to do a couple of things.

We wanted to review what we already had at the FDA. Dr. Schwetz has indicated that every center had peer review, both of individuals and their research programs, and so forth.

We wanted to see what was available on the outside at other places, well known, like the NIH, the CDC, the EPA, Department of Energy, USDA, and major academic institutions.

We looked at criteria for tenure and so forth.

What we did was we then crafted a strategy, based on this information, and what we felt might work here within the FDA, and came up with what you'll see here in a moment.

The one principle that we established, though, was that the peer review would be conducted by experts who are external to the review unit.

We had discussions on whether it should be external to the FDA and came to the conclusion that there are a lot of experts within the FDA in Centers, in other Centers, that perhaps we can utilize their strengths and so forth, so we didn't want to shut ourselves out from that.

What I would like now to do is walk you through the process that we've actually outlined in the handout that you have.

The first thing that I should do is familiarize you with the structure of the FDA. This is the Science Board, you all. This is Dr. Bledsoe, the Science Advisor, and then the rest is the structure, generically speaking, of the FDA, from the Commissioner through the Deputy Commission for Operations and on down through the Centers and to the individual research units.

This is my depiction. I'll try to hang on all of the review groups as we go along.

Now, in your handout, I gave you an

overhead that actually showed that we have made the recommendation or coming up with three types of Committees beyond the Science Board that would help us do this peer review, particularly of programs.

They are a Board of Scientific Counselors, which is described on the first page of your handout;

A specific scientific review panel. There would be one for each Center and the Office of Regulatory Affairs;

And then the nuts and bolts of the program review groups who actually would go in and physically and intellectually review the research that is going on.

Now -- and, again, I'm emphasizing -- this is a proposed.

We felt that the Science Board is a key element here, a key element in advising the Commissioner and through the Commissioner all of the individuals associated with the research chain of command in the Agency.

A Board of Scientific Counselors, as a

subgroup of this, we felt would be a key element here who could look at the top agency level, the decisions that go on in terms of resource allocation for research, strategic planning, what's important, what's not, how to get something done, across the whole agency; in other words, the blurring, so to speak, of center lines.

This Board, as conceived of, would actually be composed of a chair and a vice chair who are members of the Science Board, and then two members that would represent a Committee that I will discuss in the next step that are aligned with the individual centers.

So that this Board actually gives us an overview, a total review of the decision-making process, how resource is allocated, and so forth. Can't emphasize that enough.

The next Committee, outlined here in red --

DR. BLOUT: Chuck, do you want to be interrupted?

DR. GRIESHABER: Please.

DR. BLOUT: I encourage the Science Board members to interrupt as we go along.

DR. GRIESHABER: I will say, before I'm interrupted, that what we've designed so far is almost like the superstructure here. We haven't really put as much thought into the implementation of how are you going to do this and so forth but who might be the kinds of people that might be on the boards and what kinds of decisions that they would render and so forth.

I'm sorry.

DR. CUATRECASAS: It seems to me that the functions that you describe for the Board of Scientific Counselors, that those functions are primarily, or should be primarily, those of the Office of the Chief Scientist and those are the things that that office, Chief Scientist, given all the input that he or she receives from all of the other Committees, other groups, and from the Deputy Commissioner and from everyone else, I'm just concerned that you're getting into another level, a very hierarchal

level.

Certainly the other review panels, the Centers of Scientific Review Panel, will be a critical one, and that panel will have the interaction with the Centers directly, as I think you show here.

This diagram doesn't show it so well. There should be a dotted line, I should think, as well as the Research Program Review Panel should have probably more dotted lines.

But whether a separate Board or scientific counselors is necessary, I can see the need for some communication between the Centers, the scientific review panels, for the Centers.

But whether they need to form a large Board of Scientific Counselors, or two from each of the review panels would sit on that, creating a group of 16 people, I just wonder if that's a little bit burdensome.

DR. GRIESHABER: Well, I'm delighted that you brought this up because we've had long discussions. Actually, there are two types of

discussions.

I agree with you. The group that is reviewing the Center is a particularly important group. We feel that the Science Board is an important group as well, and there was a question whether the Board of Scientific Counselors is listed up here at the top, actually does need to exist, you're right.

Could the Science Board perform that function, receive the reports from the Center review panels?

The other thing is, the Chief Scientists -- I thought the Board of Scientific Counselors, and we believe this could be an Advisory Committee to the Chief Scientist, the Deputy Commissioner for Operations, on things. Are we doing things appropriately to the scientific community in general?

As I said, you can envision the Science Board doing that as well.

DR. CUATRECASAS: Yes. Actually, I do see a function for it, but perhaps such an important entity made with half the people,

half individuals, perhaps have seven; that is, the chairmen of each of the Center Review Boards or Panels, plus the chief scientists. And then maybe that Advisory Board should be more of an Advisory Board, should be chaired by the chief scientist.

And, principally, the chief scientist is getting the input from all of these reviews of the Centers. In a way it may be flapping it out a little bit and diminishing it.

DR. GRIESHABER: That is a nice consideration. I worry a little bit about the chairmanship because we're trying to do this on an external review basis.

Bern, would you want to comment, or Mike?

DR. FRIEDMAN: I want to listen right now.

DR. SCHWETZ: I think that's an insightful recommendation and one that I think would be workable for sure. This group should be advisory to the chief scientist and to the Deputy Commissioner for Operations. That's

where we need the input. Whether or not that person chairs it or receives -- there is a chairman and he receives or she receives the information, I think that's less important than just recognizing that that is where the input is needed, and that particular group of representatives can pull together all of the input from the next level of the reviews. Your comments are good.

DR. CUATRECASAS: Yes. I just have a sense that having three panels is a bit burdensome, a bit bureaucratic. You think about the numbers of people. You have 16 people meeting on that panel, you have to get all those people together, two from each of the Center Boards, and then all those people who have also to come from the Science Board, two people from the Science Board on each of those just seems a little bit too cumbersome.

I can see the value for it, but I wonder how practical it is.

DR. BENET: I disagree with Pedro for a couple of reasons.

One: The whole purpose of doing this is to get buy in from the scientists in the Agency. This Science Board has no expertise in selecting -- the duty of this Board of Scientific Counselors is to select the review committees and to receive the reports of the Review Committees, and I want expertise from the Agency who feel that this is their Agency and looking at their review of science within the Agency and selecting the people.

We don't have that expertise, and I think you do need to have a visible group representing all of the Centers in an organization that's going to run this review process and not have the Science Board run this review process. I think it's important for the morale of this process.

DR. CUATRECASAS: That's exactly what I'm saying. In fact, I'm saying, don't place the Science Board in such a critical position, much more of an overview. Push everything lower.

DR. BENET: But you were saying that

you don't want the Board of Scientific Counselors, and I'm saying you do need an overview group.

DR. CUATRECASAS: I think this should be at the level of the Center Review Board, so pushing it down at that level, you need to communicate. I mean, that's where everything's going to happen. Every Center is different. In my view, every Center will have its own review panel.

Those panels have to come together in some way, but I'm saying, let them come together only with the chairmen plus the chief scientists.

DR. BENET: That's exactly what the Board of Scientific Counselors is, the chairmen and the chief scientists.

DR. CUATRECASAS: No, it's two members. I'm saying just have one member. The chief scientist does not appear on this.

DR. BENET: Okay. I can go with one number if that's what your comment is.

DR. CUATRECASAS: Only it's

diminishing its role, making it less burdensome.

DR. LANGER: Okay. But we're really down to only disagreeing about the number of people from this group that should be on that group. Is that a fair statement or not? I'm just trying to -- and the size of the group. Yes. Okay.

DR. CUATRECASAS: The proposal is that two members of each of the Center panels be that group. There will be 16 people.

DR. LANGER: Right.

DR. CUATRECASAS: I'm saying there's no need to have more than seven, and I would suggest eight.

DR. LANGER: Okay. So let me hear Les' comments on that. I mean, it doesn't sound to me like there's major disagreement. We're down to issues of size and number of people from this group.

DR. BLOUT: I don't disagree with that. I mean, you can see, looking at this Board, why you have double the membership of

the people that you need to participate so you have representatives of each Center.

So if you want to have one person from each Center, plus an alternate, you accomplish the same thing because maybe alternates would show up anyway.

DR. CUATRECASAS: Well, the other person is important, also, in that proposal because that is an alternate.

Again, the major work is going to go at a level of Centers, and that's where the science is being done and that's where the major review is going to be done. So it's a bottoms up approach.

What we're saying is we're really going to get into the Centers, they're going to review them, they're going to involve the individuals in the management of each of the Centers. The Center director will have a key role.

The results of the reviews of the Centers, of the individual Centers, the results of those panels, will be then described and

will be somehow interfaced with the activities of the Center.

But, in addition, we want all those reviews to come together into some kind of -- you know, some overall view.

And it's the role of this other Board of Counselors, or whatever we call it, to kind of bring all these together. But it's going to be for a much different purpose.

So at that level, I would think, is in communicating with the management, the high management of FDA. That's why I'm suggesting that the chairmen of each of the Center panels, plus the chief scientists, the chief scientists being the chairman, because then that person then would be responsible to communicate with the Deputy Commissioner and whoever else, and the Science Board.

DR. LANGER: I don't see any fundamental -- fundamental, I'm underlining that word -- disagreement.

What do you feel, Les?

Why don't we continue. Yes, go ahead.

DR. DOUGLAS: I want to make a comment, or probably a few comments.

I also had problems with the three tiers which seemed somewhat bureaucratic, but I probably was going to go in a slightly different direction, and that was to collapse the two reviews, because -- the CRSB and the other review.

The reason being is that I think there are two things that are needed.

There is one which deals with the expert quality and another which deals with policy.

And for me, and I agree with Pedro, the Board of Scientific Counselors ought to be that group that is really dealing more with policy type issues that bubble out from all of these reviews across Centers and should be chaired by the Chief Scientists.

And what should happen is that that group with the Chief Scientists should come to the Science Board with the implications from policy perspective that have come out of these

reviews.

Then there should be, at the level of the Centers, these review panels with the external experts, and its chief scientist should play a role in ensuring the consistency of the quality of the review, the consistency of the expertise, productivity, and on and on.

So that what comes out makes sense for the Board of Scientific Counselors to review.

But I would make it the responsibility of the Centers to do those reviews with external experts down at the level of the science.

So, for me, there are two levels: the Board of Scientific Counselors, chaired by the Chief Scientists, that really deal with policy issues that bubble out of the reviews of these different Centers, and that comes to the Science Board;

And then there is a panel in each of those Centers that deal with the scientific issues, the technical competence, scientific competence, the scientific leadership,

et cetera, of each of the Centers that have everything to do with quality and scientific rigor.

DR. LANGER: Rita.

DR. COLWELL: I'm afraid I have a sense of deja vu here, or vuja de. And that is that what you're setting up is very, very similar to the nostalgic reviews that go on every 10 years at the National Association of Land Grant Colleges and Universities.

Having had to run one of those for the university system and having been involved in others, the plan of action is really very, very similar; and that is, you have the individual who's, put it in this case, groups being departments of the divisions, in this case, which would be equivalent of campuses, reviewing what they are carrying out their mission; is it appropriate, the achievements, et cetera.

And then having sort of a system review which is Board of Scientific Counselors.

So I don't think the structure is

terribly novel. I think it has been shown to work.

You may wish, I think, to look at the nostalgic reviews because somehow some of the experiences in the last 50 years could be taken to heart; that is, you don't need to rediscover the same mistakes, and you might want to benefit quickly from the successes. So that's a suggestion.

DR. LANGER: Other comments at this point?

DR. SETLOW: I think there's a distinction between the Center Review panels and the Research Program panel. The research Program Panels are in-depth reviews of particular research endeavors, whereas the Center is not going to go in depth for the individual research programs, whether you make the Research Program Reviews a subsection of the Center reviews and actually that's the way they operate. They're more or less a subsection.

But that's in-depth, individual

research programs, and it's essential for those programs. You couldn't have such an in-depth review go on Center-wise. It would occupy the Center with so much time, they would never get any other work done. You really have to fragment that in various ways.

DR. DOUGLAS: And that was my suggestion, you make the Centers responsible for the program reviews also. And out of those program reviews, you begin to look at the mission of the Centers, and that's what comes to the Board of Scientific Counselors, because then that has everything to do about policy and the Centers and are they on target.

But the Centers have got to be the ones who are responsible, in my view, for the real program, scientific rigor, et cetera, and not a Board of Scientific Counselors. It's too far away.

DR. CUATRECASAS: I agree. And I think that portion is exactly what is proposed here. This portion, I think, is very good and that what he proposes the Center Review panels

do is exactly that, and I agree with that.

I think, again, the bread and butter, the substance, is going to occur right there.

DR. LANGER: Elkan, do you have a comment?

DR. BLOUT: Chuck, you might mention why you don't have ORA up there.

DR. GRIESHABER: I didn't know how to control my software to put a seventh block --

(Laughter)

DR. GRIESHABER: -- and I asked for the -- or I apologize to ORA for that, but actually it would fall in the same category.

I put this up there because it gives an indication, really, where the importance lies and the discussion that we've heard here, the discussions that we have in our own Committees indicate that it's at the Center level where the real important decisions, real important discussions go.

The Board of Scientific Counselors, we have had very similar discussions, and I appreciate your input and so forth. I think

that it is clear if you go read and green on this chart, that's the elements that are the most critical and the areas where we wanted to focus on.

And those are where you bring in, as Dr. Benet indicated, the real experts in the particular area that you're focusing on, because that's what you want.

If you want to understand the quality, the impact, the innovation of a particular program, they have to be world class experts coming in, and that was our intent all along.

That's one of the reasons, as I said early on, we wanted this to be almost exclusively external, external review, so it's advisory to us.

You're doing a job that is equal to that in the scientific community in the world.

I think that the blue -- and that's the you, the Science Board and the Board of Scientific Counselors, we intended to have almost as an external review of our strategic planning, the quality of our thought, how we

bring the Centers together. So that's the kind of advice.

You're doing it right, you're not doing it right, you might consider this way and that way, and so forth. So that's the essence there.

But the real truth is down at the level of the Centers where the functional decisions are made, where the money is spent, the programs designed, and so forth.

Actually, you'll hear a little bit about how CBER is planning on doing that when Neil Goldman has the opportunity to stand here before you.

DR. DOUGLAS: That discussion really crystallized it for me, and it seems even clearer to me now from your summary, that the Board of Scientific Counselors ought to be an advisory group to the chief scientists and not in this -- you know, that's where the action is, red and green, and chief scientists need an advisory group. He pulls in to review that and then come to the Science Board with

implications policy wise and cut down the bureaucracy.

DR. LANGER: Mike.

DR. FRIEDMAN: I think this is a very useful discussion, and I am very complimentary of how the Agency has begun to look at itself.

I would ask this Board, though, to challenge us, and to -- I think the comments about the familiarity of this sort of a structure are very well made, and I think there's strength in a system that has been well tested.

On the other hand, I really would like you all to challenge us and say, but is this the right structure from the next century, because as good a system as this has been, I would like us to be free thinking and creative.

We need a system that is disciplined and formal. We have not had that. But we don't want a system that is rigid. I, frankly, have that concern.

The other point that's been made is we want a sense of enfranchisement where people

feel a part of this, but we don't want bureaucracy, and I think that's a comment that several of you have made that I'm very appreciative of.

We need, really, timely action here but we don't want to proceed precipitously.

This is a system which really -- this is a representation of the Agency as it has existed for decades, and I wouldn't mind you all challenging us and saying, but why are you thinking about science like this?

For example, the retrovirologists in CBER and the retrovirologists in CDER, aren't there Agency issues for retrovirology, rather than CBER and CDER issues?

CBER has some extraordinary strengths in immunology, but don't those also exist in CDRH for in vitro testing?

I guess I don't want to give away my prejudice here, but it's not that one system won't work and one system will work. I think there are several systems that will work, and we're proceeding towards something that will be

substantially better.

But this is an opportunity for you all to help us think more creatively and more innovatively about how we want to have science organized for the next -- in order to deal with the products that we're going to be asked to deal with.

DR. COLWELL: Again, I wish I could say that you are wrestling with a unique problem, but you're not.

Universities, with which I'm most familiar, are wrestling this right now. The most rigid form of structure is the Departmental structure. Trying to bridge it is like trying to attack a castle with a mote around it. It's very, very difficult, especially at a time when interdisciplinary research is so critical.

The interaction, the interface is where, as the kids say, the action is, so that biophysics, bioengineering, et cetera, are really critical.

So I think what would help in these

reviews and what has been useful is to have the counselors be charged with looking at how the structure and the view that's in the reports of the review panels, how they can provide information, that will allow linkages, but I think what you will find is that you may want to have an Agency Retrovirus Task Force so that each of the retrovirologists in each of the sub-units do meet, maybe once or twice a year or quarterly or whatever, because you don't have that much talent, in the sense of numbers.

DR. FRIEDMAN: I think you're exactly right. But as you review science programs and as you make decisions about the quality of the research and ultimately questions of resources, I suggest that you want to look over the whole Agency and not in the microcosm.

You're absolutely right. This is so reminiscent of medical schools or the bureaucracy that I'm familiar with in that sense.

You're exactly right about these are really very traditional issues that are hard.

DR. COLWELL: What you have to balance is the accountability factor; that is, having a structure to which each of the individuals in the component unit do have a reporting responsibility, but to have the flexibility so that they can go outside the box and work collaboratively without feeling restricted or, in some way, bureaucratically denied to speak and work with collaboratively folks in the other units.

I think this has to be done because there's just no other way of dealing with it.

And, again, I would say that the nostalgic review is not perfect but it certainly itself has been reviewed, the process has been reviewed. It's been going on for a long time.

It would be well worth having a discussion with the folks at Dupont Circle as to how they conduct their reviews and what are some of the problems, because you will eventually rediscover them and you might as well do it before you do the review.

DR. DOUGLAS: Let me suggest the following. We have a chief scientist now, interim chief scientist, but I'm talking about a program talking out of the recommendations.

We have a database of expertise and we have a review panel, a review system.

We can take those three components and start talking about how we use those three components to get to what you like to get to, Mike, and namely, how do we re-engineer.

And the issues that you're addressing are what I call the policy issues that have everything to do with how do I re-engineer. And you can re-engineer one of two ways: You can get a task force and take them off to the mountain top and say, okay, come back after viewpoint and re-engineer the whole place, or you can do it out of these types of reviews, getting the information you need around expertise, around programs, the quality, et cetera, moving those into your Board of Scientific Counselor with a chief scientist, who then begins, together, to look at what are

the implications for the Agency.

And after you have done a few of these reviews, probably two or three of these, and they will be done in part, they're not going to be done sequentially, because the Centers are relatively distinct, after you've done a few of those reviews, some themes are going to start falling out and the chief scientist and Board of Scientific Counselors are going to start, I think, naturally developing some themes that could then come to the Science Board which says, here are some of the themes we see which may need to looking at the Agency, researching the Agency differently.

And I think this actually is an excellent system you put together. It's just that I'd like to see the bureaucracy sort of moved out of it a bit and we separate the red and green as where the action is with respect to quality, innovation, productivity, et cetera; hence, for programmatic implications, and the chief scientist and Board of Scientific Counselors who take that and put them into

policy. They're looking across the Centers and then come to the Science Board.

I think you have the pieces in place to do that.

DR. SETLOW: I agree, but I think all of our problems come from looking at organization charts in two dimensions, and they're not two-dimensional, they're three-dimensional things.

You need some interacting structure over the all the red ones to look for the themes, as you've said, and that's the Board of Scientific Counselors.

There has to be someone there to point to three of the Centers and say, you have common themes, and see that and use that, ultimately, in some new form several years in the future. Well, you can't do it all at once.

I mean, my job at Brookhaven National Lab is to look for common themes between what we call different departments. Normally, there's a big wall between one department and another, but if you can convince several review

groups or several experimental groups that if they collaborate, they have an absolutely magnificent synergistic interaction.

And if you can do that, then lo and behold the synergism appears and so that's the job for the Board of Scientific Counselors.

DR. CUATRECASAS: I think, Mike, you've raised an extremely important issue, but I think it is largely separate from what we're discussing right now.

I mean, they are interrelated like many things are. But, understandably, you know, you're concerned, extremely concerned in a lot of sense with the likelihood that the Agency is not organized properly.

Administratively, organizationally, there are incongruities, and I hear you. What is the best way to get to that? I mean, it's going to be your job, ultimately, in the management, and you're looking for some help.

I think as Frank has said -- and I agree with Frank -- it's basically what we're doing here and what will happen out of these

reviews may help you. It won't dictate that, but it may provide some help in being able to align or visualize an Agency that scientifically is more sensible than what it is, and there are other elements as well that will come together in terms of review processes, in terms of responsibility to constituencies, to the public, and so on.

But I think that to a priori do something now that dictates the structure for the next 100 years, as you say, it is impossible. Because, at the same time, there has to be, as you also said, has to be flexible.

So what we should do is do something that will visualize and anticipate flexibility and change, so we begin something and we will be continually reviewing, so hopefully this panel and the Agency will be adopting what it's doing, according to the (unintelligible).

And then, eventually, you know, hopefully, we're optimists, we'll all get there.

DR. LANGER: Yes, Gil.

DR. LEVEILLE: I'm listening to this with interest, and I think we've all been exposed at one point or another to academic models and a whole array of reviews.

The problem with all of them, and I think the inherent difficulty here is one not of process but of structure.

The problem with academic institutions, as Rita has pointed out, is that the focus of reviews and the structures put in place focus on the preservation of the base unit, which is the academic department.

In this case, you're setting up a structure which, if becomes etched in stone, does the same thing. It preserves and protects the basic Center, and you have made it extremely difficult at any time in the future to ever change that structure.

So it strikes me that the process of scientific review is very critical, but that's a responsibility that has to lie at the top of the Agency, and whether that's at the

Commissioner or the Chief Scientist or the Science Board level to do those reviews on an ad hoc basis, you may want to initially do a review in this way.

But then it goes away, and any future reviews may or may not be the same way, but the important thing is to preserve the ability to change the institution, to restructure in a way that allows some flexibility over time, which right now you don't have.

And this system, this structure, not the review process but the structure, once put in place, would make it extremely difficult to do that in the future.

So I would encourage you to really look for a way to do these sorts of reviews on much more of an ad hoc basis than this would propose.

DR. DOUGLAS: May I suggest the following: The review processes don't necessarily have to solidify a structure but, rather, if Mike, you and your team came forward and said, we are interested as part of a

strategy in changing the way we do science at the Agency, we're interested, we don't know how to do that, we will be having lots of discussions and looking at lots of things because there are lots of constituencies.

As Pedro was talking about, we have to deal with the public, et cetera. It's not just the science.

But one place where we are going to get information is in the Centers, the programs, how they operate, and this is why we'll be doing the reviews.

Those reviews then get used differently because then the Board of Scientific Counselors have a clear mandate. They're looking for the synergies, they're looking for opportunities for change. They're looking for the programs that make sense.

They're looking at it in a larger context than any particular Center looks at it. They're looking at it strategically.

And so that the review process, although it focuses primarily on the quality of

the science done in the Centers and the reasonableness or the appropriateness of the programs, they nonetheless generate information that is used in a strategic way by the chief scientist and the scientific counselors who then capture that and bring it to the Scientific Board.

And I'd like to offer that as a novel way of looking at this rather than it solidifying.

DR. FRIEDMAN: I think those are awfully good points. I really value what you're saying. I think it's very important for us to recognize the incredible strength that exists within the Centers and not to diminish that but to actually enhance that by being open to new ideas and new ways of combining things.

I very much want to have the chief scientists have real power, have real authority to do things. I think that's a message that has clearly come from all the reviews that we've had and that I personally subscribe to.

And so I see his or her role being

critically important here.

The idea of testing out these ideas, learning to walk before we run, I think is a sensible one. And I think part of the reason Bern wanted me to be here at this meeting is because he knows how impatient I am, and he thought you all could talk some sense into me and, as usual, Bern is right.

You're doing a good job. I don't want to wait a decade for this. I feel like we're decades behind and we have opportunities that we're missing.

We're trying to do at least three things, and we're using different parts of this, and maybe the next iteration, Chuck, actually, the color coding will be for activities not for descriptions.

And the activities are to identify areas of emphasis and to reevaluate those regularly. And that's critical because it gets to mission relevance.

So you want, as was said, a strategic view of where should we be going, where do we

need to position ourselves so that two and three and five years hence we're in a good place? That's a very important and difficult task, very exciting task, but it's got to be done planning across the whole Agency.

That's one kind of activity. This Board has an incredibly important role in that but we need to think of new mechanisms as well, which I will regale you with at some subsequent meeting.

A second activity, though, is what we've been focusing on, which is quality assurance, peer review, judgments.

Okay, granted, that is within our mission. Is it being done well? Is it being done as well as it can be? Can it be reproduced somewhere else, or is it unique to the Agency?

That's the peer review that we haven't had in sufficient discipline, and that's very important, and that is a traditional academic NIH University model.

But then we need a third thing, which

is implementation in memory, which is to say, once we make these judgments, do we actually then enforce them, and you need some sort of a structure to be able to do that.

You don't want to bother, necessarily, a group of strategists with that. That's really a technical issue. It's a tactical issue, but it's critically important because if we don't discipline ourselves, if we don't then act upon our judgments, then the system is a phony one.

You can probably tell me that there are other elements that are necessary, but as we define these characteristics of what do we want from the system, we maybe can decide -- you know, I see the chief scientist, actually, washing through all of these. That's asking a lot, but that's what I expect the chief scientist to do.

But I can see this Board doing some of those things and not other of those things and specific research review groups might do some of those things and not others; that they might

be looking more at the specifics rather than the general.

DR. LANGER: Okay. We're scheduled for a break, but I think we're a little behind, so maybe we'll continue. If people need to get coffee or anything please do.

Why don't we continue.

DR. SCHWETZ: Bob, may I just make a comment --

DR. LANGER: Of course.

DR. SCHWETZ: -- in capturing some of the ideas here before we go to the other topic.

It's important that we move forward and not that we spend years trying to find a process, so that's one thing we need to do.

But how to preserve the flexibility so that this doesn't reinforce a structure that we may not way to live with, I think there are a couple of things that we can do.

Chuck just took his transparency down, but even though you're limited in your computer to six, maybe in addition to one for ORA there should be another one there for interface

activities.

That would be a way of emphasizing that we want to also peer review the interface the activities that don't follow a center structure and we either need to build that into the Center reviews or we need to have another mechanism that separately would review those major interface activities, and that can be the ad hoc process.

The Board of Scientific Counselors, but probably more importantly the chief scientist has to identify what those interface activities are and be sure that they get reviewed.

That will have to be done pretty quickly in many cases because the things that are often worth reviewing is how we deal with situations as they're building an importance, not an historic review of how we dealt with certain kinds of emergencies and give advice in retrospect.

Another thing is to consider that whatever plan we have will probably define one

cycle of review, a four or five-year process, whereby remove through and review. Whether you do it by discipline or whether you do it by Center, it'll take one cycle of that kind of time to get through the whole organization.

We shouldn't be looking, necessarily, for how to go beyond that. We ought to define a process to get us through one cycle of review of the whole Agency and then evaluate it.

This becomes an experiment of how to do the best job of evaluating the research.

If, in fact, at the end of this process we look at it and say that it's certainly missed in this case but it really hit this one, we would learn from this experiment, we've not had that five-year cycle before. It's been a random process or a structured process, but we haven't looked at it across the whole Agency.

So I think these are a couple of things that we can do that can preserve some flexibility.

DR. LANGER: Elkan.

DR. BLOUT: I know you mean to say this, Bern, but you didn't say it explicitly.

It's not only the interface activities that exist, it's those you wish would exist that don't exist in the Agency. I think that's a very important point.

DR. SCHWETZ: You have a letter in your packet that is signed by Neil and Dr. Kathy Zoon, the Director of Center for Biologics that outlines why it is that we want to initiate a review of the whole Center for Biologics.

And Neil and I have been working together, looking at the actual list of reviewers and making contacts to find out what outside experts could perform this review, and Neil's been working on the outside structure of how it would actually happen with the prospect of having this happen at the end of this calendar year or at the very beginning of the next calendar year, but it's in there.

What we need from you today is your recommendation that this review would be done

as a Subcommittee of the Science Board, so this now will be the development of another Subcommittee, together with the one on Toxicology, the one that Dr. Setlow chairs now on Toxicology, the one that we had with Dr. Korn.

So this would be another Subcommittee to accomplish a very specific function rather than form another Advisory Committee within the FDA.

Neil.

REVIEW OF CBER RESEARCH

DR. GOLDMAN: Thank you, Bert.

I want to thank you all for allowing me to come before this Board today and take this opportunity to ask you to consider our request for an external review of CBER's research.

I'd like to actually break this talk down to three parts.

The first part is just to give you some background of CBER, just to make you a little familiar.

The second part is to address the purpose of this review; and

The third part: A potential process for how we see this review taking place.

So just sort of as background, you have these handouts already in front of you.

This is a chart of the organizational structure of CBER under the Office of the Director.

That is, Dr. Katherine Zoom, we have seven offices. They include three product offices, two regulatory process review offices, and two administrative offices.

Now, fortunately, it came out darker than I thought, but the lab base research occurs actually within four of those offices:

The Office of Establishment License,

The Office of Blood,

The Office of Vaccine, and

The Office of Therapeutics.

As you can tell, the offices are, in fact, broken down by product responsibility.

The offices themselves are subdivided

into divisions, and the divisions also have product responsibility, but more specific product responsibility for that particular office.

Now, as you can see, I've outlined here -- or you probably could hardly see -- that there are, in fact, 12 offices that carry out lab base research.

Within each office, they are again subdivided into laboratories or branches, and we have 38 laboratory or branches within the 12 offices.

Now, just for some information purposes, at CBER we have 853 government employees and 103 that we consider contract employees.

They are composed of a number of categories of personnel and it's quite a diverse and wide category of carious personnel, but not surprising for Biologics. You'll notice that the major job series are the biologists, consumer safety officers, microbiologists, and the like, but we also have

veterinarians, toxicologists, pharmacologists, and physiologists.

DR. CUATRECASAS: Excuse me. On those numbers, how many would you say are PI, principal investigators?

DR. GOLDMAN: Next slide.

[Overhead]

In research of CBER, we have what we call full time equivalent investigators. We have 177. They're both NV and Ph.D. Half of those are permanent, the other half are temporary.

Now, all of our CBER research staff are, in fact, involved in the research or review of model at CBER. In this model, researchers are fully integrated into regulatory process.

That means that they, in addition to research, spend up to 50 percent, if not more, of their time doing regulatory work. Those regulatory responsibilities include review of INDs, PLAs, and BLAs. These are license applications;

Development of policy and guidance documents. They meet with sponsors and advisory committees.

They also participate in pre-license and annual inspections, and they evaluate adverse drug reactions and risk assessment.

Now, these researcher reviewers are instrumental in carrying out the mission of CBER, which is to protect and enhance the public health through regulation of biological and related products, including blood, vaccines, and biological therapeutics, according to statutory authority.

The regulation of these products is founded on science and law to ensure the purity, potency, safety efficacy and availability.

In fulfilling our mission, we conduct research as an essential element of science-based decision-making.

Now, historically, CBER dates back, back in the early 1950s, to what was then the Division of Biologic Standards, and in 1955, we

were mandated by a PHS order that we shall conduct research on problems related to the development manufacture, testing and use of vaccines, serums, antitoxins, analogous products, including blood and its derivatives.

It shall conduct other studies to assure safety, purity and potency of biologic products, to improve existing products, and develop new products.

In fact, it's this last portion of improving existing products and developing new products that CBER is taking quite seriously and has over lifetime, in fact, been responsible for many new products, such as the Rubella vaccine, and of late the hemophilus influenza vaccine.

And two of our former CBER employees, in fact, just last year, received an award, the highest award in clinical research. This is a Marian Albert Lasker award for clinical medicine. This was awarded to Rahall Schnerson and John Robbins who had done the work at CBER on inventing the hemophilus influenza conjugate

vaccine.

So what, then, is a biological product?

Well, according to the Code of Federal Regulations and the states for about 40 years, it's any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to be prevention, treatment, or cure of diseases, or injuries of man.

This definition has been quite a bit expanded over the last 40 years to include recombinant DNA derived proteins, monoclonal antibodies, as well as cellular and gene therapies, so it's quite a bit broader than the original definition.

Some examples of the major products that we handle include whole blood and blood components, like platelets; plasma and derivatives like our various factors -- Factor A, Factor 9, test kits to test blood supply for contaminants such as viruses.

In the therapeutics areas, of course, we handle the interferons, interleukins, up to

Interleukin 18, where we are now.

A myriad of growth factors, as well as hematologic and thrombolytics and, of course, monoclonal antibodies.

In the vaccines area, we handle all the childhood viral vaccines -- measles, mumps, Rubella, the new Hepatitis A vaccine that was just licensed -- as well as new bacterial vaccines. I say "new." Pertussis has now an acellular vaccine which is a new vaccine, the new hemophilus vaccine, but as well the old faithful, the tetanus, the diphtheria, and cholera vaccines.

So what do we then consider at CBER the function of research? And this would be mission relevant research.

It facilitates the approval of safe and effective products;

It supports decisions to withdraw products that are found to be unsafe.

We use research to anticipate public health needs and support informed decision-making in the prevention of an response to

public health crises.

Research encourages industry-wide adoption of new technologies and facilitates development of industry-wide standards and methods.

Research also contributes to improvement of existing products and development of new ones.

And, lastly, aids in recruitment and retention of excellent scientists. This was actually pointed out in the Korn Committee report.

Types of mission relevance research that goes on at CBER includes research on specific products, which includes, but is not limited to, mechanisms of action, potential toxicity, and surrogate measures of efficacy.

In this case, we're referring to research on products that we're either seeing in house as INDs or as license applications.

This also includes research on specific policy issues related to product class, disease area, or therapeutic modality to

provide the foundation for evaluating current and future biological INDs and license applications.

We do research in anticipation of things that we know are coming down the line.

We also do research associated with the development of methods and standards to which products can be compared.

Now, I've provided you in your little handout a list of what we consider at CBER the core research activities. These are the areas where research is absolutely necessary to support regulatory decisions.

You'll see some, for example, in the office of blood. We have research in the areas of blood cells and cell-derived proteins, coagulant proteins and their analogs, as well as on various contaminants, such as retroviruses and Hepatitis viruses.

You also have, for example, the Office of Vaccine. For example, the adventitious agents in vaccines, like the stealth virus, characterization of allergens, including those

that are now becoming standardized, and correlates of immunity and how these play a role in combination vaccines.

In the Office of Therapeutics, some of the research that we consider necessary includes the immuno response to biological therapeutics, healing and cell growth factor, and differentiation factors.

We also look at, as Dr. Friedman had pointed out, infectious agents, such as those that may be detected in xenoses in xenotransplants, such as our porcine retroviruses, which do well in humans.

And, lastly, the Office of Establishment License. We're looking at new techniques for testing noraviones of the polio virus vaccine, as well as developing new techniques for the detections of transmissible spongiform encephalopathies.

So why am I here? What are we requesting?

What CBER is requesting is an upper level center-wide review of research, so it

would be an evaluation of a Center's entire research program down to the division level.

This is, therefore, not intended to be an in-depth review of individual independent investigators and their targeted research, which occurs at the laboratory level.

Why are we requesting this review?

Our first objective is to obtain recommendations which will provide us assistance in making decisions or reduction of research personnel which is now mandated by our loss of Prescription Drug User Fee Act financial support and, to a lesser extent, by shrinkage of the Agency's operating budget.

At this moment, we have been told we must downsize our research group by 80 FTEs. If I can put this in perspective, we have now 240 FTEs. That means that we have to lose about one-third of our research group, and we have to do this, as I was told, over the next two years.

DR. CUATRECASAS: I'm not quite clear. I thought you had a total of 853, and that

would have been a 10 percent reduction. Why --

DR. GOLDMAN: In addition to people who are doing research, we have people who do full-time review. That really covered administrative people. Those people are not the people that we need to reduce in terms of PDUFA. Because this money went specifically for research, we have to lose these people out of the research part of CBER.

DR. CUATRECASAS: I see. And that's fixed? I mean, there are two reasons here: It's the loss of PDUFA, as well as the overall shrink in the --

DR. GOLDMAN: Yes. We are shrinking. We have to lose, I think it's about 3 percent a year over the next five years, so that is there, and that's as well going to happen, but that can be anywhere within our Center.

This, specifically, is a loss within research program area.

DR. CUATRECASAS: So the review that you're requesting is for research programs not the review of all of CBER activity?

DR. GOLDMAN: Correct. That is correct.

We look at this as a global review, which would provide us a more expeditious way to acquire the advice necessary for us to make those decisions about reduction, and we believe that this kind of review can be accomplished in four days versus waiting, as Bern had mentioned, four to five years for the completion of a typical in-depth review.

We also feel that this initial review of research may also be valuable not just for CBER but for other Centers in the field. And this may, in fact, what we're doing, may be a pilot program, maybe as you just mentioned this morning, a means to look at flexibility and get an overall view at the beginning, so that you can start to put these overall views together, send it to the BSC, and look at research across the Agency and see, as Dr. Friedman had mentioned, how you can integrate this information.

Our second objective is to provide

validation and participation in the implementation of a proposed model for coordinated research at CBER.

This actually was part of our strategic plan for the year 2000 and we derived a process by which we would evaluate and prioritize our research. That has been formulated in principles in a White Paper.

Part of that process was to have an outside group come in and evaluate the way we consider doing our prioritization, and this would give us an opportunity to actually validate our model.

DR. CUATRECASAS: Just a question.

DR. GOLDMAN: Sure.

DR. CUATRECASAS: Then the loss of PDUFA, does that affect all Centers or just CBER?

DR. GOLDMAN: It also will affect CBER, although not to a great extent, since the amount of research going on there is not as much.

CBER, probably of the two Centers, has

the most research, so it was probably using its money for that purpose.

I think there were some monies going into research at CDER level, at the drugs level, Center for Drugs level.

DR. CUATRECASAS: Of course, I think you know what my question really is; and that is, if there are a lot of Centers affected by the loss of PDUFA, then we need to be looking at a similar type of review of all of those affected Centers because we may end up taking people out of CBER, and it turns out it may have been better to take 100 people out of somewhere else and only 30 out of CBER.

I'm just making up numbers.

DR. FRIEDMAN: No, no, it's a very valued point. As Neil has pointed out, there really is no other laboratory research being supported anywhere else in the Agency on PDUFA dollars.

There is regulatory activity in ORA.

There is a considerable review activity in CDER.

There is a small, central component in management systems.

Certainly, there's CBER staff who do reviews, who have been supported by this, and that's going to be maintained.

Ts is really an industry proposal for not using the dollars -- not having the dollars be permissibly used for laboratory investigation, and that, unfortunately, falls most heavily, almost entirely, on CBER.

DR. GOLDMAN: Almost entirely on CBER. Yes.

Okay. I'm going to go on.

Who will actually carry out this review? We have in mind a peer review committee composed of scientists with high professional stature in their field.

They should be members who have a thorough understanding of the mission and needs of CBER, and the composition of this Committee could include a chair and vice chair from you, the FDA Science Board, supplemented with ad hoc members, from academia, other government

agencies, and industry.

By the way, other government agencies, in fact, could be outside the realms of our shores; for example, an IBSC and United Kingdom.

The makeup of the Committee should reflect the core disciplines in CBER. That includes immunology, bacteriology, virology, sub-biology and its components, as you see listed, chemistry, and clinical design, which would include epidemiology and statistics.

Now, you have in your handout, as Dr. Schwetz mentioned, he had already requested that we started giving him lists of potential candidates, members of this external review Committee.

You have this list and, in fact, we've broken them out by discipline and provided this information to Dr. Schwetz.

Now, I did this, this is sort of editorial. I happened to want to put a couple of cochairs. I put Dr. Bennett and Dr. Korn. That was just to fill space --

(Laughter)

-- although I would not --

DR. BENET: Thank you, Neil.

DR. GOLDMAN: You're quite welcome, Les.

Now, we look at this Committee as potentially analogous, at least in constitution, to that proposed by Chuck in his presentation as that Center Scientific Review Panel. That's the one that he said would provide advisory function to the Center director.

Now, for us, we see this Committee as a One-Time Committee, but we could imagine that this Committee could evolve into that Center Scientific Review Panel; that is, members who are on this Committee could migrate over to that; in fact, many of them could.

So what is the proposed process for the review? Well, we asked ourselves, in essence, what questions should we pose to this Committee that we'll be doing an overall review and upper level review.

These two questions that we came up with were, in fact, ones that we felt could end up as a charge to the Committee, and they include, and you have these in your packet, for example:

Is the scope of CBER's research programs appropriate, for example, as Dr. Friedman said.

Are existing programs relevant?

What is the quality of the existing research programs and can you identify their strengths and weaknesses?

What can we do to strengthen the culture of science and scientific leadership in the Center?

This was brought out by the Korn Committee.

Are we adequately coordinating our research to minimize duplication and omissions and to maximize productivity?

Are we providing adequate resources to our research programs so they can truly meet their goals?

Are we adequately maintaining our scientific disciplines?

Those are the ones I mentioned before. Those are the immunology and chemistry, biochemistry. But also our specialities, because we have certain specialties in our Centers that we need -- hematology, rheumatology, allergy.

We also would like them to comment on the process that we are using now for evaluating and prioritizing our research programs which has been outlined in our concept paper, in our White Paper.

And, lastly, we'd like to ask them to give us input on the way we are fostering interactions between our research laboratories and the regulatory process. And when I refer to regulatory process, I mean those doing lot release testing, as well as product reviews.

And this last question is, in fact, going to be addressed in our upcoming science forum in December, so it's an important one, and also one that was likewise pointed out by

the Korn Committee.

In addition, we are going to send background information, and this should be sent about six to eight weeks in advance, to the Committee members. This will provide them a background of the Center, provide them organizational structure, personnel and location, logistics.

We also want them to know the budgets that we're operating under and then how we're allocating those budgets.

An annual report of the research at CBER; this would include the office division and laboratory summaries of current achievements.

We also want them to see our current White Paper on the coordination of research. This is the models that we're using for prioritizing and evaluating research at CBER.

And, lastly, a description of CBER's research programs.

Because this is going to be an upper level review, and that is, not get down to the

individual scientists, so we'd have 130 or 150 of them making 30-minute presentations each, this will hopefully give the Committee members some idea of what kind of research is actually going on.

We're going to ask the laboratories to write up, based on their research program, a synopsis of the work they've done up to the current time, giving, thus, the sort of retrospective look of what's going on, but also in this, we're going to ask them to provide also a short amount of information on their prospective view; in essence, where are they going.

And we'd like this to be provided. This is going to be only maybe six pages long per research program. And we have about 40 or 50?

DR. CUATRECASAS: 40.

DR. GOLDMAN: So this won't be too much reading, but I think what it'll do is give them a good sense of background.

Lastly --

DR. FRIEDMAN: Can you restrict those words, the 200 words, to only being nouns and verbs, no adverbs, no adjectives?

(Laughter)

DR. FRIEDMAN: I'm serious.

DR. GOLDMAN: I think we could -- the intent would be to restrict the reading so that it's doable.

DR. FRIEDMAN: Just the facts. Yes.

DR. GOLDMAN: Just the facts.

DR. FRIEDMAN: Okay.

DR. GOLDMAN: That's doable.

And, lastly, we've proposed a daily review schedule, and this is only a proposed schedule, so it certainly is very flexible.

What we had in mind, actually, for our review, was to have two teams of reviewers. Now these are, again, our six basic disciplines, and we'd like to have two reviewers from each discipline, and they would constitute a total of 12, and that would be one team.

And what we have here are two teams,

and I'll show you why the intent for two teams.

As you remember, the presentations will actually be from the Center. We have actually a Center office, but also the four offices that were listed in that first organizational chart, as well as we're going to have presentations from the actual divisions where the research programs occur.

Now, I say divisions, plus laboratory designees, in that the concept that we have is that a division director will give a presentation, indicating his or her needs, regulatory needs, and how research is needed and helping making those decisions.

And then, behind that, would be followed by three or four people from the laboratories who are actually carrying out these research programs, so that one can get a sense.

Now, like I said before, we roughly have about three or four laboratories per division, so that's going to be roughly one per laboratory, and that will give the sense of the

actual research that, in a broad sense, that's going on.

Now, it's timing that counts so we are thinking of, potentially, a morning and afternoon session. Those sessions will be three hours. We'd like to have two hours of presentation and provide the members of the Committee one hour for discussion.

So in the morning of the first day the Center and Office directors will get together and make their presentations to the combined teams A and B. In the afternoon, Teams A and B will split. Team A will go and review one division. Team B will review another division.

In so doing, they can cover all 10 divisions. Now, actually, there are 12 divisions. We're going to consolidate a couple that it's possible to bring them together, and actually will tend to shorten the amount of time that we have to keep the Committee members present.

Anyway, we can see that over the course of the three days we could finish all 10

divisions and on the fourth day provide them an opportunity to draft a report and, at the end, hopefully have a close out meeting to review that report.

So this is the process that we have in mind for this kind of larger review of the entire Center.

So what I'd like to do is then stop here and thank you for listening and ask your considerations in helping us achieve this, since this would, in fact, be a Subcommittee of your Committee.

So I turn this over to Dr. Langer.

QUESTIONS AND COMMENTS

DR. LANGER: Well, basically, what I'd like to do now is just call for comments or questions related to the peer review process in general and also the formation of a CBER peer review subcommittee.

DR. FRIEDMAN: Let me just say one thing, if I may.

DR. LANGER: Sure.

DR. FRIEDMAN: Unfortunately, I've got

another commitment that I've got to leave for, and I apologize for that. This is very important, and Bern and I have talked about how your comments and your suggestions will certainly be conveyed to me through him and through others.

I didn't want any misperception about the fact that I'm not going to be able to be here for the whole discussion to indicate a lack of interest. I apologize. My schedule is not under my control anymore.

I appreciate very much the seriousness and the care with which you're looking at this and I encourage you to ask the most probing, most difficult questions you can of us as an Agency because we want a process just as good as we can make it.

This is an important thing to the scientists, but it's important to everybody within the Agency, and I apologize that I can't be here for the full discussion.

DR. LANGER: Thanks.

Les.

DR. BENET: I was a bit shocked to find my name as "filler" on this report, but since it's there I want to ask a critical question and I want Mike in the room for: What kind of staff support is such a group going to give?

I know David Korn wrote his own report, but this requires significant sport, either from CBER or from the office here.

DR. FRIEDMAN: Well, I this is a very important question, and I'm glad you raised it. I have the sense that there's not only certain efficiency that can be achieved but a certain standardization that can be achieved by having many of the peer review activities handled through the science office.

But that's not the only way to go. One could say that one will do it individually from Centers. I think it's a really fundamental question.

Your point, you know thinly disguised, is, it's got to be staffed properly. If this is going to be not just a One-Time

extraordinary effort but an ongoing effort that's going to have meaning. I completely agree with you, Les.

You know, my own leaning is toward having this as a centralized function within the science office, but I'd ask the Committee to give us your advice and your thoughts on that.

DR. GOLDMAN: If I may, I think that's a very good question. In fact, the Office of Science has been discussing that with us in CBER, and certainly we will provide -- we have a scientific advisory committee staff that certainly, as we do peer review, handles many of these logistic questions.

It's not unusual, at least, for example, at NIH, that the scientific director of an institute is, in fact, the ExSec of a large review.

This review, by the way, is not novel. This is exactly the kind of review that NIH does for each of its institutes, each one. They've already done three. They're on their

fourth one right now, which is the Genome Institute.

So you're right. We can provide -- I'm sorry. Go ahead.

DR. BENET: But I'm spoiled because I've chaired three IOM committees, and this staff support in your IOM reports are really the kind of support that makes outstanding reports come out.

And I've also been on NIH review committees, and you don't see the same kind of support.

So I think if we're going to have the kind of input that then gets translated into a report and certainly Elkan knows about this, I want to see the level of support that justifies the kinds of people you're planning to put on this Committee so that you really get an outstanding product.

DR. LANGER: Pedro is next.

DR. CUATRECASAS: This was a terrific presentation and a terrific proposal, down to the detail, and I complicate you for a lot of

work, a lot of thought.

I have one issue that I'm struggling with or agonizing with and I'm not sure how to reconcile this, and I certainly agree with the purpose and intention of reviewing the programs and asking the questions that you propose here, and I think there's real merit to that.

On the other hand, we're also saying that the detailed review of the scientific programs, specific programs, will come later.

Now, what I'm agonizing with is whether it is possible or wise to make the decisions about programs in the absence of knowing the quality of those individual programs, because it is the quality that is most important.

You can have wonderful programs, but if you're lousy or they're incompetent or they are whatever, they may look relevant, they may look great, but if the science is not good, if the investigators are not committed, if they're not publishing, they're not consistent with the overall scientific movement and they're not

integrated with overall science, then it's a whole different picture.

So you're asking people, I think, to make judgments with incomplete information.

Now, on the other hand, you're tantalizing them because you are also going to give them 40 or 50 detailed reports. And the kind of people you selected are good scientists. They are the people who are able to make judgments and decisions.

They will not be able to look at these things and not get into details. So I'm struggling on how to realize the enormity of the task if you're going to do the comprehensive review of the science, bottom up.

Yet, is it really possible to do it in the absence of that? I don't know.

DR. DOUGLAS: The department is similar, so your answer will probably apply to both, and it gets back to the discussion we were having before.

But this is always the dilemma. The dilemma is you've got to reduce -- and I'm

going to make it practical -- you have to reduce 80 people. Now, you can do it one of two ways.

You can go through and say which are the programs that really don't fit or fit least, because I think you'll find all the programs fit. Which are the ones that really don't -- you know, are the least fit, and those are the ones that we probably reduce.

And in that process, you reduce, as Pedro says, you reduce programs that perhaps you have quality scientists, could be very successful, and you maintain programs in which you don't have the best scientists that are ultimately going to fail. And that's one approach you take.

Another approach you take is to basically go through and say, I'm going to review, do the detailed review of the projects and the scientists and cull out. And then you look and say, okay, now that I've done that, do I still have viable programs?

And it's a dilemma. I support Pedro.

It's an excellent approach and excellent presentation. Detail, everything, but it is a dilemma that you have and you may very well end up, unfortunately, with programs and then later on somebody saying, but you got rid of some top scientists, and the programs you have you don't have the best scientists.

DR. CUATRECASAS: I agree completely, and it's particularly important since we have all agreed that the science which is being done within the Agency, the primary value is one to affect and to all influence the culture of science.

It isn't so much the content. The content, of course, is important, but good scientists will seek good science, and they will do things well, and they will find things which are appropriate and are pertinent and relevant.

So it's the quality of the people.

So it's those people who create and influence other people who then in turn will create and turn on the world an atmosphere to

foster good science, who will attract other scientists. And that's what we're trying to do.

That's the fundamental issue of how to do that, how to foster a scientific environment that perpetuates, and I think the way to do it is by having people who are excellent, the best possible people, those particular individuals.

And if you do it superficially you may get rid of programs, so you may get rid of very regular people.

The peer review, in my opinion -- we haven't talked about this but it's another comment -- I think the peer review, which is most important, particularly in its approach like this, where everybody is not independent to be reviewed by the NIH or NSF or something else; the most important review is the ongoing peer review by peers who are your neighbors and your colleagues from day to day.

So as the open science carries out within the institution, so that you depend once a year, once every five years on a group of

people coming in, spending three or four days, but it's the influence that we place on each other as working scientists.

So I think that's the other that has to be considered.

DR. LANGER: Okay.

DR. GOLDMAN: I couldn't agree with you more, Dr. Cuatrecasas. In fact, one of the biggest predicaments was in making decisions, as was pointed out by Dr. Douglas, in making decisions, you don't want to make the wrong decisions, so you would like actually to go down to the individual level.

The problem is we have so many people it would be impractical to try to do that.

Generally, that's why these kind of reviews occur over, say, four years, say when they start doing a review of an investigator.

If we did this, we would probably do roughly, say, three divisions a year over the course of four years and do 12 positions, and this would be manageable, considering all the numbers of people. We said we had 177 FTEs in

research.

So not giving the opportunity to really make decisions, we actually have to start losing today -- no, actually, tomorrow; October 1 is tomorrow. We have to start deciding to lose people, starting tomorrow.

If I had five years or four years, you would absolutely be right. That is the best way to do it. Unfortunately, I have to lose starting tomorrow, and by the end of those two years, there has to be -- those 80 have to show up as a loss.

So I would very much like to do it that way. I can tell you -- one second.

I anticipated your question, because we struggle with this same question all the time. So what we felt was, when we're making decisions, the final prioritization decisions, we use a number of pieces of information.

We would use the information we got from this internal review. They at least would be able to look into. They are able to look at the large programs and say, these are

necessary; these are very important. In fact, without these, you probably won't get your work done. That's the mission relevant part.

They can also take it with those research description forms, even though it's 40 or 50 of them, they can get a sense of just an overall quality. Not the individual but an overall quality.

That will weigh in. That's a mission relevance, and as the quality of the research program.

You'll also want to be able to look at the quality of the research scientist, and we have been ongoing since I've been at CBER over the last 18 years, we've been doing peer review. We do site visits. We do them all the time. Every one has the site visits, at least it's update for four years.

That will also play a role in our decision. We already know the quality we have. All of our site visits are done by outside reviewers, experts in those fields.

We use no one from internal, internal

to FDA.

In addition, we have another responsibility. I said we are not just researchers, we are research and reviewers; in fact, we are researcher, reviewer, inspectors. It just goes on and one. We do more than just research.

In fact, when we're really reviewing these people, we have another consideration because they do another job. In fact, half of their job may be in the regulatory area.

Now that impinges on the amount of the research they get done, and we have to weigh that in, and how important these people are.

So you can see that the decision, as you pointed out, is not an easy one. In fact, it's quite complex.

Or we think if we at least start with an upper level review, supplement it with the reviews that we do of all of our people, anyway, bringing in the regulatory part that these people also play to carry another job on their back, I think we can make those

decisions.

So I would still think that this would be a valuable review.

When NCI -- I remember when the new NCI director came in, he told the science -- the person who handles his scientific reviews, to go about doing an upper level review of the Institute and keep on going the lower level review which they do every four years, so that's how they maintained it.

They understood they could not get down to the individual, but they still did an upper level review. The Kasall-Marks (ph) report in '93, sent to NIH, you should review each of your Institutes, in fact, is being implemented, and they do the upper level review. They go to the, what they call lab sheets.

For us, the lab sheets are equivalent to a division or a division director. That's why we've come to this level. They do it exactly the same way.

They know that they can do the review

quickly to that level and the other would take much longer, so they have the ongoing four to five years. I think that was sort of the model that we had in mind, when we proposed this.

DR. LANGER: Neil, I assumed as we've talked about this, that those reports from the reviews of individual laboratories would be made available --

DR. GOLDMAN: Yes.

DR. LANGER: -- to the reviewers in this process.

DR. GOLDMAN: Yes.

DR. LANGER: So you would have information that's less than four years old that is a very specific review of the individual research projects, and I would assume that that would be helpful to the reviewers in looking at this bigger picture to have those individual detailed ones.

So we wouldn't just depend on the reviews that would take place over the next four years.

DR. SCHWETZ: Yes. We do reviews of

whole laboratories, so it's several investigators at a time, and we can provide that easily because -- actually, these are things that are reliable. We actually have to provide them.

DR. CUATRECASAS: My comment -- don't misunderstand -- is not meant to say that I was not in favor of what you're doing but simply to say that it's an approach that still leaves something to be desired and it's --

DR. GOLDMAN: It would not be done this way if we were given -- originally, we were told that we were going to have five years in which to lose these 80. If I had five years, this would not be a problem.

It was when I was recently told that we only had two years to do it.

DR. CUATRECASAS: That's important, I agree, to get on with it. I think it really is. It's very, very important to get on and get started.

I guess in part I would rationalize my concerns again by saying that the kinds of

things that I am concerned about is, you are and all of us, are things that are likely to come out from the reviewers as well; that is, those individuals, if they are the kind of people that we chose, will express those kinds of apprehensions and perhaps will suggest approaches to make judgments of quality.

And that may not help you in deal with those other issues.

MR. LIEBLER: I've been sitting here dying to speak but not wanting to abuse hospitality, but I do have a question on this last slide.

It seems to me that a program could pass all the tests, quality reviewer, quality scientists, relevant and good quality work, and still be a duplication of work being done elsewhere.

Does your review have a method for catching that? Because I know that would be a concern of the industry, would be the industry spending money to do research that they're doing and that doesn't need to be done within

the FDA.

DR. GOLDMAN: Well, I think that was the reason for actually asking that this Committee be manned -- the members of the Committee actually being people who included people from industry.

I know that on that list are a number who are currently in industry right now, so that they can actually address that question of whether or not they see duplication.

So the answer is, I think we have, by having people in the academic world who know what's going on and would see a duplication within the academic world as well as in industry, I think that we're covering our bases there.

DR. LANGER: Yes.

DR. COLWELL: I don't mean to be light-hardy, but I would like to say that, taking the long perspective, things are tough, Neil, but they were a lot worse four or five years ago when the Blue Ribbon Committee was deliberating the question was whether there

should be any research in FDA, and some of us fought like hell to make sure there was.

So it's good to be reviewing the research.

DR. DOUGLAS: I'm trying to look at this in perspective. You've got three problems.

One: What is the mission; is it still appropriate within the present constraints.

Two: For the programs we're doing do we have the relevant quality, and

Three: I've got a problem. I have to lose data people.

This is excellently presented, excellently construed, but I'm starting back asking myself, is this going to get you what you want.

I'm not suggesting this, but could a number of your senior people sitting in the room, reviewing industry concerns, reviewing the Blue Ribbon panel, reviewing the mandate conclude that, you know, here are the areas that we can defend, that make sense, support regulatory, and here are the areas that are

somewhat iffy that perhaps have some overlap, and that group, without this detailed review, could identify that.

And then what the review really is and the notion, it's the day-by-day, neighbor-by-neighbor review that's really the important peer review that we do, and you already have those records.

If you have to start losing people tomorrow, as you've said, you will probably go into the various areas and say, let's look at performance evaluations, et cetera, is what you probably will do, whether some combination of those things can get you to where you want to get to instead of this review.

I'm not even sure I'm offering that. I'm just trying to look at this from a different perspective. That's all I'm trying to do because I find this very useful, very appropriate, but I'm just trying to throw out a what if.

DR. GOLDMAN: I must admit that you are correct. Our upper management could take

the information that they have at hand to make decisions, and I think that in some cases that will have to occur, certainly between now and the time that the review actually takes place.

I also think that the intent of the review should be to start to have the Center looked at by outsiders, and in that way I think it becomes more -- what we think is mission-relevant, what we think is high quality is meaningless.

It's what your peers on the outside think. Dr. Cuatrecasas rightly pointed out, that's what peer review is all about.

It's not what you internally think, it's what those on the outside think. We would like to have that looked at from the outside.

I think it would provide a great deal.

DR. BLOUT: I think this review could be very important to the Agency because it might set a model for other Centers to do. In fact, we have in this room the senior scientists from most of the other Centers, and if the Board wishes to, I think one or more of

them might be willing to comment on the relevance of this kind of review to their Center, so we're not doing something that's specific to CBER.

DR. DOUGLAS: Let me add, as I said: I think this is excellent and I support this. I was just trying to step back and do a "what if." I accept your answer in terms of what really is relevant with respect to the mission, not what we sitting in CBER think is relevant but is also what externally thought as relevant.

But your comment, Elkan, in terms of a model for the other Centers, I absolutely agree. I mean, I was getting very excited within the context of the previous discussion we had, the previous presentation.

DR. LANGER: Do we want to hear any comments?

DR. BLOUT: Anybody from one of the other Centers want to start?

MR. MacGREGOR: Can you hear me without this?

I'm Jim MacGregor. I'm the Director of the Office of Testing and Research in CDER, and we're essentially facing a very similar thing. It's not a PDUFA-mandated reduction but currently there are 126 research and testing positions within CDER, and we're facing a 34 FTE reduction most likely, although the budget isn't set firmly in the upcoming year, so about a 27 percent reduction.

And so we're facing very much the same kind of thing in terms of looking at our programs and deciding how to make these types of decisions.

In addition, I'm relatively new to the Agency, and we're actually in the process of restructuring our Center-wide research prioritization procedure and reformulating our internal Center structure for what we're calling a Research Coordinating Committee for the Center, including a process for plugging that into outside input on a periodic basis of once a year or so.

So this kind of process from my

perspective, would be equally relevant and meaningful relevant for CDER.

DR. CUATRECASAS: Excuse me. Is there a thought perhaps of doing another exercise like this, virtually simultaneously or in parallel?

The one thing, of course, is to do this as an experiment. When it's finished, analyze it, digest it, and so on, and then go on to another.

But CBER is also fairly unique, it's quite unique. So it may be quite valuable, I would think, as part of the evaluation itself as well as an example of the overall review, is there were at least one other process like this, ongoing in another Center, I would think.

DR. JACOBSON: I'm Liz Jacobson. I'm the Deputy Director for Science in the Center offer Devices and Radiological Health.

Not commenting directly on your question, I just wanted to give an overall comment.

Probably the field and CDRH labs are

the leanest lab operations in the Agency, and we have doing, in CDRH, ad hoc peer reviews for a long time now, and we're going to be very interested in looking to see how this kind of a peer review system goes for CBER.

I think we can learn a lot. We're very concerned about how we do the peer reviews.

Dr. Benet, your question of support, how do we handle just the logistics of getting these kind of things done is a really important question for us, and we'd like to fold the results of how CBER runs this into the discussion of peer review as a whole.

We've sort of seen a couple of different models this morning of how to do this Agency-wide, and I think it'll be very interesting to see how you're kind of being driven here by outside forces here in a relatively constrained time period, but I think it'll be a terrific laboratory, in a way, for peer review for the Agency.

DR. CUATRECASAS: I think the issue

Leslie raised and you reiterate, one of resources, is really an important one, because this review processes are really quite big undertakings and they will take a lot of effort and cost a lot of money.

Yet, they are really so important, again, that's why I would think that having two or three, because I have a strong sense of this that out of these reviews, it's much more than -- what will happen, it will be much more than simply help you with deductions.

But I think we're going to see the judgments come out that there is excellent science within the FDA, that it is appropriate and necessary to the functions of the FDA.

It will be an outside reinforcement of the things that we're saying to the Subcommittee for research and which I serve, what they were saying, and I think that this will reinforce also and perhaps help, ultimately, with reinstituting some of the resources which are being taken away for these purposes.

There is a degree of skepticism in the outside world in many parts, and this is serious, a skepticism, by the quality for science. And there's a great misunderstanding about that, and I think having these outside panels of experts who have nothing to gain, I think perhaps will be a dramatic way to reinforce what we're trying to do.

MR. FULLEN: I'm Al Fullen. I'm with the Center for Food Safety.

I agree with what you've said, and all of the Centers I think would tell you, yes, we need that outside review. We need the comments from outside reviewers to help us defend our programs.

Yesterday, we had a meeting within the Center, which was precipitated by a 40 percent reduction in our staff by the year 2002. That was the planning process.

Now, in the process of planning that reduction, in that total staff, we were given a suggestion, two of three suggestions we were given focused on research, meaning if we're

going to look for reductions, we're going to look for them in the research area.

Now, you should also know that over the fact of the last five years, we haven't rehired a significant number of people who have left from our laboratories, so our laboratories are becoming very thin.

We need to have support for why the laboratories are important and we need to have a budget.

One of the things that always impresses me about FDA is that people think we have this huge research effort and we've got labs scattered all over the world doing research. In fact, we have a very small research effort total, and most of the lab work is done on routine sample analysis and that sort of thing in our field labs.

On the other hand, we do spend a considerable amount of money on research, and we do need to defend why we're doing that. So in this case, Dr. Goldman, I think all of the Centers would be interested in seeing how this

works out, with the idea that you would evaluate how much it's really costing us to do that sort of thing.

Is it costing us more than we have research going on?

I think when you consider all of the expert committees that we have, ever Center has an Advisory Committee, we have this Board, we're spending a considerable amount of money being reviewed, and on the other hand, our research people in the labs are losing support and are leaving.

And I think we need to reverse this loss of research effort from our laboratories as much as we do to review the research effort that we've got ongoing.

DR. LANGER: Other comments?

MR. ALDERSON: I'm Morris Alderson from the Agency's smallest Center, the Center for Vet Medicine.

The research office only has 40 people, so we continually struggle, even with this small staff, on how we go about

prioritizing work, because the dollars continue to diminish.

My research budget has gone down in the last four years probably 50 percent.

But, at the same time, we've got food safety initiative coming in this next year, it's probably going to quadruple it. Congress has appropriated $40 million to come into the Agency this next year for food safety programs.

My Office of Research gets -- at least Congress has appropriated it; we haven't seen how many dollars we'll get yet, about $2.5 million.

But prioritizing the work and how best to use that becomes a real issue very fast for me in the next few days to get this money obligated before next September 30th.

So it's a continuing changing picture for all of us, and certainly the process is for prioritizing our dollars and how we get the best utilization of that is a continuing issue for us, and I hope Neil's process lends some light on how we can all best do that.

But I would emphasize, also, what Al just said. It's a continuing process. We continue to deal with, and almost every year is different.

So any help we can get from you on how to do it we'd appreciate it.

DR. LANGER: Elkan.

DR. BLOUT: I think this has been a very good discussion so far, but one thing I haven't heard is how do we communicate to the outside world? What's going on in the FDA and what these evaluations mean to the outside world.

One of my hopes when we set up the Science Board was that the Science Board would be a means to communicate to the outside world, to industry, to the Congress, to the staff of Congress, it hasn't worked out.

But I think it's up to the Board to consider that aspect of our work, and I would urge you to do so.

DR. LANGER: Rita.

DR. COLWELL: It may sound a little incongruous and not part of the standard operating procedure, but it would seem to me as we come to closure on this process and agree to go forward that it would not be unseemly for the Science Board to have a press conference and to announce that that, in fact, is what's going to happen, and we stand behind it, and we feel that whatever conclusions we've drawn we share with the public.

I think that's a perfectly suitable way to go about it.

Another is, certainly, not to hide the reports under a bushel basket but to not rate, you know, as graduate students do, they always want to do the perfect experiment and cure cancer in one go, but rather to break the task out and that increment that are appropriate and reasonable to have either an announcement or a report, or at least a section of the report released.

But there are ways that one can operate in a very suitable and information-rich

process.

DR. BENET: Elkan, to some extent, that's why I asked about the resources, because I think you do need a quality report that has an impact and is not just the chairman writing up what his secretary can type that day.

But to follow-up more on the interactive nature and getting this kind of information out, repeatedly, in the Science Board I've brought up over the years what I thought is a lack of a strong interaction between various scientific disciplines within the FDA and their home societies.

What I think a report like this -- if I actually was stupid enough to do this or being selected -- I think what you want to do is not only prepare the report and have a press conference, which I think is good, but I think what you want to do is ask the scientific disciplines who are represented by the areas that are of importance to CBER to take this in their national societies and to comment on this, and to get the input back from these

scientific associations, either by holding workshops, which the American Association of Pharmaceutical Scientists have done very well, or to have an input back that then not only do you have this Committee making a report but you have the Society of Microbiology and FASEB societies also making directed reports as requested by this Committee and by this Board.

And I think that could have a significant impact beyond a single Committee report.

DR. LANGER: Other points?

DR. BLOUT: I agree, Les, but there are two other constituencies I'd like to see respond, namely, the industrial scientific community and the Congress, and I'd like to see somehow this proposed activity directed at those two constituencies.

DR. LANGER: Any other?

DR. DOUGLAS: I just think it's very important to have those constituencies and particularly the industrial community, particularly since one part of the industrial

community, the pharmaceutical part, probably is relatively critical of some of the activities.

DR. BLOUT: Exactly.

DR. DOUGLAS: So it becomes extremely important.

DR. CUATRECASAS: I agree, and I think that that's not so difficult to communicate, because that community will know that such a process is on the line, and that alone is going to be very important for that sector.

The other inquiry, I guess, is whether or not any thought has been given to trying to get the IOM to help.

In thinking about Leslie's comment and yours, too, Elkan, about disseminating information, inviting reports, and getting staff assistants, and so on, is it possible that the IOM might be a vehicle that could help us with has and would be complicated?

DR. GRIESHABER: Glad you asked.

As all of you know in this room, better than I, the NRC sponsors reviews at various governmental and other research

programs throughout the country.

We've been in contact with the NRC, and we're just, in preliminary discussions, asking how they would carry out reviews, the staffing situation that Dr. Benet mentioned.

The Academy really has a wonderful system in terms of making sure the final report really is the view of the Academy and so forth, and we thought that that would add not only a touch of external review but certainly a highly-regarded professional review.

So we are discussing that. That's what I wanted to say, and that's in alternative form, then we mentioned establishing of the Committees that I mentioned earlier.

DR. LANGER: Any other comments?

MR. DIEGO: Yes. I'm Jim Diego from ORA, the Officer of Regulatory Affairs. Although I haven't had the opportunity to give our input, we did -- unfortunately, we didn't have the opportunity to be reviewed by the Subcommittee on Research.

We do have about 80 FTEs that we use to conduct research in the field. It's mostly method development research, and we would like to have the opportunity to have the Subcommittee take a look at the work that we've done.

Back in 1992, we had some science advisors from academia put together, along with us, an FMD, field management directive, to allow the review of our research by outside academia and by a research Committee.

So we'd love the opportunity to have review of that work.

DR. LANGER: It's getting near lunch time. One of the things I was asked to do is, is there, in general, a recommendation to approve the process and general framework for the external peer review and CBER review and to establish a Subcommittee to conduct a CBER review?

I think a lot of very good comments were made, and that can perhaps be taken into account.

Why don't we adjourn for lunch, continue these discussions over lunch, and then we'll start talking about the FDA Science and Research Programming and Planning, exactly 1:00.

Checkout, I'm reminded, is at noon. So if anybody hasn't checked out, you should run up to your room.

(A luncheon recess was held.)

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

[1:10 p.m.]

DR. LANGER: We're going to get started.

FDA Science and Research Program Planning

DR. SCHWETZ: We need to give credit to Dr. Setlow for the role he played...for the peer review of the whole center, which was something that is the counterpart to what Neil proposed, except we not only looked at the proposed strategy for future research, but we looked at the use of money for contracts and for everything else that represented the total performance of the Center.

So it was a very effective tool for us through the past years, going through that cycle and finishing with a complete review of the overview of the Center, to help make the changes in programs and the reallocation of resources that we've gone through at the Center in the last few years. So we know from our experience that it can be a helpful tool.

Let me talk a little bit about the

program planning in research. We've made a change in the program today; we had a fair amount of time allocated between the end of the morning and the beginning of this afternoon to do that. We have truncated that so that we can preserve time for other discussions yet this afternoon and not shorten them, because this is a topic that I will now just talk two minutes about, but we'll bring it back to the Board next time for more discussion, and the part that we took out today was the part that was the linking between research planning and GPRA, the Government Performance and Results Act. And we didn't want to try to squeeze that in in just a couple minutes' talk today, because I've never been part of a short discussion of GPRA.

(Laughter)

And as it relates to research. And we thought that needed full time, next time.

Let me just summarize where we are in trying to respond to the recommendation from the report of Dr. Korn's committee that we move

toward developing more of a research planning function within the total agency, and moving toward this virtual science center.

The centers individually and ORA go through a research planning process at this time of the year, every year, in preparation for the new fiscal year, so over the last couple of months, every center has asked for the proposed projects for next year for our research programs. They continue to come in throughout the year as needs dictate, but the largest bulk of that planning occurs in these last couple of months at the end of the year. So one of the things that we have done to try to move us forward in planning an FDA research program was to reach agreement on the format for all of those proposals which, by itself, was a little bit of a task because each center has its own way of coming up like with a two page description of research proposals that can be reviewed by management of that center in deciding whether or not this is what we want to support; and do we have the resources to do it

if we do want to support it, and what's the relative priority.

So in the have had centers, there would be anything up to dozens of these proposals, several hundred agency-wide would be brought up for review at this time of the year. To facilitate the review of those by a smaller number of us who look over the whole agency, what we did was to reach agreement on a format for those proposals so that we can get them entered into the FIRSt data system that you heard about this morning, in the context of the expertise database, while we can get these same research proposals into that computer system and make them searchable.

So that if we want then, when all of these are entered from the centers, if we want to ask, for example, what research proposals are there for work on thalidomide, or Cyclospora, or pfisteria, whatever the case might be we can go in and find out through this computerized set of proposals, then, what kind of work is proposed so that some of us can look

at it and see whether or not there might be duplication or in fact there isn't anything proposed on something where there should be, so we can begin then to interact back with the centers to discuss the nature of the proposals that have come in from throughout the agency.

So as a beginning tool this is at least a way to get all the proposals in front of a small group of us at one time during the year to look at this bulk of proposing for the research planning that comes at this time. This obviously lends itself to several further uses; and one is, if we design this so that we can capture the proposals throughout the year, it becomes a complete centralized tracking system for research within the agency that would permit us to ask those kinds of questions at any time during the year and to get an idea of the resources that are being allocated to these various kinds of research projects and to be sure that we bring it to the attention of others proposing the same kind of research, that they need to be aware of what's being

proposed elsewhere in the agency, to get the groups of people working together.

It has the possibility of becoming a management tool that, if we see that there are things being worked on that don't necessarily represent a high priority to the agency, we can begin to question some of the kinds of work that are going on. Not to tell the Centers what their research programs need to be, so it isn't a matter of micromanaging and saving a thousand dollars here and a thousand dollars there by challenging this and second-guessing everything, but there's more to be gained by improving the efficiency of the agency, by increasing the communication process so that somebody's at least aware of what the total picture looks like.

Then the other natural extension of that, having pulled together information on what we're doing, a natural step that goes beyond that for the future, is to begin to identify prospectively FDA research priorities. And the hopes that in the process of laying

this all out for us it will be a lot easier for us to get the centers to communicate with each other to begin to identify prospectively -- not in hindsight -- what the priorities are, not what they must have been based upon what proposals were submitted.

So we see that as another aspect of this that will unfold once we get the process in place so that we can for the first time electronically review of the work that is done and begin to query it and draw some kinds of analytical kinds of information out of it so that we can review the proposals on an agency-wide basis rather than just center by center.

So that's kind of where we're at, and we will come back to you with more information next time, and then tie this together with the discussion of GPRA, which we would like your input on that as well, because the question of how do you plan in the research community for what expectations there are through GPRA or something that we have kept deferring as long as we could because we don't know how to deal

with it, and we're coming down to the stage where we can't ignore it anymore; we have to deal with it.

So I would be happy to answer questions or receive your comments on where we're at on this.

DR. LANGER: Gil?

DR. LEVEILLE: Bernie, have you thought about the next step -- well, what seems to me to be a logical next step, of not only getting proposals in and projects, but progress on those, that would be fed into the system on an ongoing basis.

DR. SCHWETZ: Yes, and that is the next phase that we're talking about, not only looking at the proposals, but then this becomes a tracking system; and you can get a lot more information because a lot of these proposals -- well, not a lot, but a certain percentage of the proposals will either be dropped or they'll be changed during the year, or they'll be deferred for something that's a higher priority. So this One-Time look in the year

isn't enough. We need to be able to track the process, but also then the progress; and the progress becomes, in the context of what we were talking about this morning and at lunch about our need to get more information out about what we accomplish, this also becomes a tool for identifying what it is that's being accomplished in the research community within the agency from the output from this tracking system.

DR. LEVEILLE: But as part of the development of the system, there has to be a mechanism for ongoing input that becomes critical.

DR. LANGER: Other questions or comments? Including from the audience.

No; okay.

Anything more you want to --?

DR. SCHWETZ: No, I don't think so.

DR. LANGER: Well, you've gotten us back on schedule and then some.

So we'll go on to the Subcommittee on Toxicology; and Dick Setlow, who is the

chairman of that subcommittee, will give us an update. Dick?

Subcommittee on Toxicology Update

DR. SETLOW: The committee met yesterday; the Subcommittee on Toxicology has had a problem in trying to develop a mission statement and objectives because we have a lot of verbal members to the committees with very definite ideas. So we've been talking around this particular problem, and the breakthrough came by initially setting up a web site so that people could write in all their proposals and thoughts and so on. And the first step, then, in trying to break this logjam of getting a vision statement and so on was for the staff -- mostly I guess Neil and others, to look at all the things that were sent in, and tried to sort of get a consensus of the vision statement, the mission statement, and possible goals.

[Overhead]

So you see written here, the vision is to improve public health through improved toxicological assessment models, and the

mission is to coordinate a collaborative effort between public and private sector stakeholders to identify and promote product safety testing that is more predictive of human endpoints. So those are great motherhood statements, and the question is how do we get there? What are the goals?

Neil and his helpers identified a number of potential goals for -- think of them as A, B, C, and D. You'll see them again. And now, how do we get people to buy into these goals, tell what we're going to do about the goals, and how do we get action, which is the key to all this; how do we get action.

The key to getting action was to force the committee to make a decision, and the way that the committee was forced to make a decision was to have a facilitator, and the facilitator in a sense forced everyone to make decisions by the following mechanism.

There were four general goals there; I've mentioned them, A, B, C and D. We went to the next room, and there were four tables; A,

B, C and D, and the members of the subcommittee and the FDA committee on toxicology itself sort of had a group and arbitrarily somewhat the whole group of individuals was divided into four parts; one part sat at Table A, one part sat at Table B, one part sat at Table C, one part sat at Table D.

And we were given, at each table -- those sitting at Table A had to come up with concrete statements for the goals, which I'll put it up again. For goal A -- those sitting at Table B had to come up with concrete statements for the goals on Table B and so on, and at the end of ten minutes, all change. That is to say, Table A then went on to the next goal -- actually, it turned out to be D and so on.

[Overhead]

So the net result of that was that each of the four tables considered each of the four general goals. You don't want to read all this; just so that you can see. So there were four goals, roughly speaking one goal from each

table for this building, and then there were objectives, improved human risk assessment -- these are kind of motherhood statements, you understand -- to identify information gaps.

Don't read them all because we're going to get them boiled down even a little more. But just to show that for each of these goals, how would we facilitate bridging the gaps through mechanism-based research and improved models in predictive toxicology?

[Overhead]

And the objectives were, for example: To develop workshops, to determine programs, convene researchers and regulators, and establish agency-industry consortia. So these were all the things that came out that people agreed to. A very disparate group, I assure you, agreeing to this particular set of comments.

Then we had two other tables, so to speak C and D. C was to promote development of cost-efficient product testing methods; that's the goal. How would we reach it? And you can

see four reasons, four ways to do this. And likewise for Goal D, encourage acceptance and integration. And how would we do this? Organize workshops, establish international frameworks, facilitate and so on. As I say, you don't want to read every one of these because they're in a flux. But these are what the objectives are. And of course the question is, how do we reach the objectives? We have to have action for each of these objectives.

[Overhead]

So the facilitator laid out interim work that the subcommittee is supposed to do. First of all, review what I've given on these overheads, and then isolate the objectives; which are the most important? Under each of these goals, there were four objectives. Put them in some sort of priority order, and more importantly, as I say, for each objectives -- how should they be prioritized? What are the appropriate timelines and measures to reach the objectives, and how do we do that? The appropriate action items.

Now this is not open-ended. My recollection, and actually I've written it down, my recollection is that we were given three weeks to come up with all these things, prioritize the objectives, estimate timelines and measures, and what would be the appropriate actions to take to reach these objectives.

As I say, we have three weeks to do that and that means that each member of the committee is supposed to send in his or her thoughts by E-mail to the facilitator, who will collate them, summarize them, send them to Neil. We'll send them out again, reach some sort of conclusion, without coming to a meeting in Washington. My guess is within two months we'll have a consensus statement from the committee as to how we're going to reach the objectives so as to reach the goals, to satisfy the mission statement and everything else.

That took just the morning, all this was done in the morning. And I assure you, it was done quickly, thoughtfully because there were groups of four people sitting around

tables saying "Okay, what do you think we should make for the objectives?" And we would go around and around and finally something would spin out of this circular process. So that was the morning.

[Overhead]

We had new suggestions and so on afterwards, but I wanted to finish up my remarks by indicating that there was more than just the morning. So this was all the subcommittee's identification of objectives and so on. And in the afternoon, we heard a series of talks from individuals from FDA on actually three kind of separate topics.

There was a group from some of the centers dealing with neurological toxicology, and that's a can of worms, I can assure you. It's the same problem for neurotox as existed 20, 25 years ago for carcinogenesis. How are you going to develop, if at all, short-term tests, if there are any. How do you do the same sort of thing that we worry about for carcinogenicity?

And there were a number of interesting points that came up, and they'll appear in the minutes, I'm sure, of some sort. So those are real problems in toxicology that will be discussed separately from carcinogenicity testing. Our major emphasis is mostly on carcinogenicity testing. It's easier to get our hands on that particular subject.

So even though this was backwards, redeveloped notions as to gaps in the information, we heard more of these from CBER and CFSAN. And we ended up with Rosalie Elespuru, who was not representing one of the centers, but I guess was sort of representing her position as the incoming president of the Environmental Mutagen Society. To think about future approaches and what the problems are, and how the best thing we have to aim for is real collaboration and interaction, intellectual interaction between industry and FDA. It's the only way one is going to get some new methods.

It's a complicated problem because

existing methods for example of carcinogenicity testing use certain animals, which sort of appeared, you know, out of the blue but were used by everyone, and so they became set in concrete, if I can call it that.

Now new animal models are developing all the time; transgenic animals of various sorts. How do you integrate these into the overall scheme? Will they give the same results, different results, which are better, which are worse? We don't really know. And that's for an easy problem, such as carcinogenicity testing.

We got to the end. So the floor is open for questions.

DR. CUATRECASAS: How many members are on this committee, this subcommittee?

DR. SETLOW: About nine. There are academicians, there are industry people, yes.

DR. CUATRECASAS: And the industry people are heads of toxicology departments?

DR. SETLOW: Yes; they're top people in that. And as I say, the old question is of

course, how much information is proprietary, how much is not; questions that always were discussed at length is, how to put a lot of this information on a web site or something of that sort so that it's available readily, without compromising proprietary information.

But again, there's a lot of information, there are a whole bunch of databases out there, and they're not communicating with one another. They really have to be integrated sometime, and that's a big effort to integrate all these; but there's a lot more information in the agency than is in the individual center, and one has to be able to tap into that information.

Neil, do you want to add? I mean, he's the architect, you understand.

DR. WILCOX: Thanks, Dr. Setlow. No, you've done a very thorough job describing a meeting that was difficult to orchestrate but I think most successful; and we made great strides into identifying the products of this committee and I think moving ahead and trying

to bring experts from industry and the public sector together. Thank you.

DR. CUATRECASAS: Did you also discuss, or I guess you'd have to do this within the context of the harmonization efforts as well, with European and Japanese --

DR. SETLOW: Yes, that was one of the things that we have to --

DR. CUATRECASAS: -- major constraints there, I would think, too. And opportunities.

DR. SETLOW: Well, the harmonization, yes, was emphasized by Dr. Elespuru.

DR. SCHWETZ: The harmonization is an interesting issue, because this in effect -- it might appear as though we're going against the harmonization effort, because the harmonization efforts are to fix in some stated agreement how it is we're going to do things. So now we're going beyond that and asking, can we do things better? And one of the problems of reaching agreement internationally with what you're going to do to answer a particular question, it discourages the flexibility of looking forward

and how we can do it better.

So while the FDA is committed to the ICH process, we're also committed to this process of realizing that what we have reached agreement on internationally is what we've been doing in the last couple of decades, and we can't stop now and just continue to use that without asking these other questions.

One of the things that was discussed at a lot of length yesterday, I think we've talked about here before and I would bring it back because it's still an important question to us, is the question of getting data that the FDA has that is protected because it's proprietary, data that exists in industry that's also held there and not shared by anybody else; but the collective knowledge that all of that represents would represent big steps forward in understanding our ability to predict toxicity.

But there is an awful lot of information that we can analyze that is available through Freedom of Information.

There's a certain level of information that is being analyzed to share what it says, and how it can be used for predictions. But in addition we continue to ask how, when it comes to structure activity relationships and some of these other predictive tools, there's an awful lot of information that has been learned by industry that is intentionally -- not put out there, because it is part of your architecture within your company, and it supports decision-making that makes your company different from somebody else's.

So obviously some of it's published, like in the carcinogenesis area. Eventually a fair amount of that is published, but not in other areas. So when it comes to developing predictive tools for some of the other endpoints, the data are out there to improve the process considerably, but we don't have access to it. We as a community, not just the FDA but none of us, have access to all of what it takes.

And to the extent that these

discussions have been taking place, we're seeing some softening in that more people are volunteering and looking for ways to bring that information forward so that it can be made available to people who couldn't analyze it and develop better tools, or develop a better appreciation for the limitations of the test models that we have been using for the last 30 years.

So it continues to be a viable discussion, but it's a very slow process to reach agreement on how can we get data brought into a group of people to analyze, what kind of data could we get; and if we could ever get that agreed upon and maybe through some partnerships and some sharing process, I think some important steps could be taken forward; but we're not there yet.

DR. CUATRECASAS: I agree with you; I think that is, perhaps in my mind, the largest or the most important anomaly in toxicological science. Because science advances through openness and through publication and through

sharing of all the data with colleagues and people in the field. And here, in toxicology, we have very major spheres of data that are not being shared, not being published, yet are essential for decision-making. And altogether, if they were made public, there's no doubt it would advance the state-of-the-art very significantly.

Now how to resolve that dilemma, it's understandable. So there must be a way, and I'm not sure what that is. But surely I would urge you to continue to press for this. Perhaps it may be that some sort of reward -- you know, in the broadest type of sense, may be necessary to encourage sponsors with such data to make it all public. Or at least to allow the FDA to make their part public, which they submitted, at the very least.

DR. WILCOX: I found it interesting, Pedro, that -- and again I was quite excited yesterday. It was brought to our attention that there is such a process going on in Europe right now, where they're working out a model by

which there are data shared between government and industry. And they're doing it by coding and so forth. But they're working very hard on it; and hopefully we can look at that and maybe use it as an example to move forward. That was the first I'd heard of that; it was called the LHASA program or something like that.

DR. SCHWETZ: In that case the incentive is that I put in one piece of data from my company and I get one piece of data from each of the other nine contributors. So it's a 10 for 1, assuming that you have some value in the other nine.

DR. CUATRECASAS: Well, that's a start. I'm encouraged by that; I had not heard of it. I'm pleased to hear that. Again, it's not only what regulatory agencies have they cannot share with others, but this is an enormous amount of data which companies have that they have never shared with FDA because they have been either controls or in substances that have failed, have not been submitted, and also tremendous background data on control

animals, in controlled species which hasn't been submitted to the FDA.

So hopefully those things will remain available to the public.

DR. LANGER: Any other comments?

DR. SETLOW: I would say this is a real problem. The problem exists, and the existence of this problem is one reason why the FDA has to also be in the forefront of science, so they can understand the nuances of every one of these new things that comes up, so that it has some way of evaluating it. Without that background knowledge, they'll be helpless.

DR. LANGER: Any other thoughts?

DR. SCHWETZ: There's another -- the analogy I would use for what this subcommittee is trying to do is that the dog has chased the car all these years and now it's caught it. You know, we have said for a lot of years that we wanted more mechanistic tests to use to make decisions; and when none of those tests were on the horizon it was an easy thing to say that we would really love to have those tests, and we

would use them if we had them. Now they're on the horizon and they're being used, and now there's an awful lot of discomfort with the fact that we might use them; discomfort from within the agency, discomfort from within the industry.

Because now we're back to an unstructured situation where it's a lot more difficult to tell in advance what set of data would most accurately predict the potential toxicity of a substance, and these tests are being, the transgenic models, for example, are being developed faster than new drugs are being developed.

So before one goes all the way to completion, there may be a better animal model that was surfaced that would have been great for this particular molecule. And I think we're going to have a difficult time knowing what to do with the car now that we've got it. Hopefully this subcommittee can help sort that out.

DR. LANGER: Sounds like a good

challenge.

Okay, why don't we move on to the Biomaterials Forum. There's actually an update, written report in the briefing book, but I want to also introduce Bernie Liebler, who is the Director of Technology and Regulatory Affairs for HIMA, who has actually really spearheaded this effort, and -- do you want to make any comments or just answer questions, or what would you like to do?

MR. LIEBLER: Well, briefly, we have not be able to meet since the last meeting of the Science Board. The group that's been working on this is very hard to get together most of the time, because half of us aren't around at any given time. And not consequently made great progress.

Our big stumbling block is still how to fund it, and I'm still not sure how to do it. We toyed with the idea of creating a corporation; it turns out that that in itself would create more difficulty than anything else.

I've got a letter two-thirds written -- I hope two-thirds written because I don't want it to be that long -- trying to determine and gauge somehow the interest of appropriate organizations, be they companies, government agencies, trade and trade associations, scientific societies. And I got a little block on how to finish that letter about a month ago, so I just dropped it and left it, and I'll be going back to it.

Hopefully if we can get that out and get some response, we'll actually know whether we have, rather than playing "build it and they will come" we'll find out if we have somebody coming and then we'll know what to build, and maybe we'll get their help building it; and that's basically where we are right now.

DR. LANGER: Why don't we see if there are any questions and then any suggestions on how to raise money.

We'll first do questions and comments.

DR. BLOUT: Bernie, what's the status of industry interest in biomaterials? Is there

any profit to be made by industry in biomaterials?

MR. LIEBLER: Well, my industry uses the biomaterials.

DR. BLOUT: I know.

MR. LIEBLER: And, yes, they're critical. They're critical for -- essentially for implants, that's the basis of having the implant industry.

So you've got all of the orthopedic people, the pacemaker people, God knows how many else, that really care about that. Is there profit to a manufacturer or a supplier to sell to our industry?

DR. BLOUT: That's the question.

MR. LIEBLER: No.

DR. BLOUT: And that's a basic problem, isn't it?

MR. LIEBLER: Essentially, that's why we've been on the Hill with our biomaterials bill. Essentially, when you go back over the problems with Dow Corning leaving the industry -- leaving the market, I should say; Dupont

leaving the market -- we were discussing this at lunch. There's probably more Dacron in this building in the form of carpeting that then can be sold to the device industry.

These are companies that are used to orders by the tank car, the railroad tank car. And we're talking about selling to an industry that essentially needs orders by the pitcherful or the bucketfull, a few pounds. Even at a 9:1 ratio, which is I think the ratio is given for a vascular graft for Dacron, you're talking of maybe an ounce per graft. This is not a lot of material; it is not worth the liability, it's almost not worth the postage, frankly, for a big chemical manufacturer to sell to us. That's a political and social problem.

But they're vital for the industry. The idea of the forum was, going back to the start: How do we deal with regulatory and technical questions? I think the industry is interested, but I don't know how many others are going to play. I think we have to find out. And again, I can't say in advance,

regardless of the level of interest to the industry, how quickly they're going to reach in their pockets for a checkbook. I mean, I've learned that; I don't know. You never know.

And representing the association, I would be foolish to predict anything.

DR. LANGER: The big issue probably is the liability laws, and --

MR. LIEBLER: Yes.

DR. LANGER: -- the question is whether that bill will passed.

Other comments or questions on this?

I also wanted to turn on suggestions for money. I'm not willing to leave this yet.

DR. SCHWETZ: But another question regarding a host for the forum. I know there was some discussion with the toxicology forum and their potential interest in helping to provide a place where this communication could take place, has there been any progress there?

MR. LIEBLER: No, I really have not been able to pursue that over the last couple months.

Can I just take this opportunity -- the toxicology forum has a web site. Does anything know the address so I can look at it?

DR. WILCOX: You mean the subcommittee?

MR. LIEBLER: Excuse me. Yes.

DR. WILCOX: Oh, sure.

MR. LIEBLER: I'd just like it so I could get a chance to look at it.

DR. LANGER: Other questions before we get on to suggestions on possible routes of raising funds?

We'll turn to that. Does anybody have any creative ideas for that?

DR. COLWELL: Sell cookies.

DR. LANGER: It's not a bad idea. How man boxes can I put you down for?

(Laughter)

Are there foundations like Whittaker Foundation that might help get something started? Have you talked to them?

MR. LIEBLER: Actually, that was the latest thing that's been floating around in my

brain; was possibly to either look towards some sort of an NSF educational grant or possibly going after the Whittaker Foundation to get it started.

DR. LANGER: Yes. Because as you were talking, that seemed to me like that might be a strategy. You know, at least to get some seed money to get things moving.

MR. LIEBLER: That's my latest idea. I had originally hoped that I would have some company like -- well, I won't mention any -- but some company would decide that this is a wonderful idea and agree to put up five or ten thousand dollars. That hasn't happened yet.

That's the point of the letter, seriously; I'm fishing.

DR. LANGER: Yes.

DR. COLWELL: I think you ought to consider the Wellcome Foundation, the North Carolina branch of it -- not necessarily the -- even possibly the Burroughs-Wellcome in Britain, but they are very much medical associated; this fits their -- Bond is the

president of it. I think you really ought to approach Gay. And I'd be very happy to go with anybody who wants to.

DR. LANGER: And in terms of companies, you've probably talked to Johnson & Johnson or Monsanto; I was just thinking of companies that are heavily materials oriented. To answer Elkan's comment, there's very interesting things in biomaterials going on, new sealants -- but I don't know whether Johnson & Johnson would be contribute or not, as an example.

MR. LIEBLER: Probably once -- you know, this is one of those situations -- and again, you've got me talking about what my members are going to do; it's a little hard.

DR. LANGER: Sure.

MR. LIEBLER: But I can think of a few that probably will. The question is, to what extent, how much money? It's almost going to be like a poker game; if somebody antes, then somebody else will ante.

DR. LANGER: That's why I was thinking

if the Whitakers seed it, maybe that's the way to get the ante started.

MR. LIEBLER: That's really going to be the key, is to get somebody to write the first check. Once I get the first check, then it's probably not going to be too bad.

DR. LANGER: Well, if I can help with the Whittaker stuff, let me know.

MR. LIEBLER: Okay.

DR. COLWELL: Another source would be the Sloan Foundation, because they're supposed to be enhancing industry competitiveness, U.S. industry competitiveness, and I think you could certainly fit into that category.

MR. LIEBLER: Now all I have to do is find the time to do this while I do the rest of my job.

(Laughter)

DR. LANGER: Yes, I guess that comes to the second thing. Is there any help that you can get or that we can somehow provide; I'm not sure.

MR. LIEBLER: Actually, well, we have

FDA participation. And it's really a question of just everybody finding the time within their schedules and getting everybody -- you know.

DR. LANGER: But the fund raising thing sounds like a particularly --

MR. LIEBLER: I think we need to do that.

DR. LANGER: -- key thing. So the question is who makes the calls and how do we do that; is the burden solely on you or -- but maybe there's a way to split it up or something like that.

MR. LIEBLER: What I was hoping, as I mentioned to Susan on the way in this morning, was to use a report from this meeting back to the committee to try and see if we can get together another committee meeting and parcel out some tasks.

DR. LANGER: Because the other thing that occurs to me, on the one hand you've got a committee with some fairly high level, busy people; but it might be worthwhile say adding just some junior people who were willing to,

you know, spend some time, make some phone calls. Just a thought -- who could really help on some of these things.

MR. LIEBLER: Yes. Again it's a question of -- you know, these people can generate the people out of their companies. One of the problems, I lost Stephie Burns; she's now in Europe, which is unfortunate for a couple of reasons, although good for her.

DR. LANGER: I know.

MR. LIEBLER: Ed Muller's been always an active participant.

DR. LANGER: I know that.

MR. LIEBLER: Again, I think we can do it; we just need to plug ahead, get the letter out, and line up some of these contacts, and I'll even push my boss to make phone calls if I need to -- although he usually pushes them off on me. We'll try and do it the other way around.

DR. LANGER: I think what you are doing is great; if you look at where we were a year or two ago, a lot of progress has been

made.

Any other questions or comments?

From the audience.

Okay, we'll go on. The next topic is Collaborative Research Efforts and Partnering; and let me again, Bern Schwetz and Sam Page, who is at the FDA Center for Food Safety and Applied Nutrition will present the Collaborative Research Efforts and Partnering part.

DR. SCHWETZ: Let me just take a minute to introduce this, to remind you that we've had discussions with you and we've had a lot of discussions internally about, how do we leverage the research capabilities that we have to be able to do more work than our actual number of people and resources would permit; how do we reach out to organizations where we can take advantage of experts elsewhere that we wouldn't have access to otherwise, and increase the cadre of people who can do work that relates to the questions that we have; and then how do we deal with some of the questions that

we've been talking about this morning, the planning process for research, how do we deal with peer review of scientists? These things become more complicated as you have successful outreach programs that head in a particular direction of getting work where you may be going outside the FDA to get some of this work done.

We have had a lot of effort within the agency in the last -- see, I don't know how long this planning has been for JIFSAN, but it's a joint effort between the Center for Food Safety and Applied Nutrition and the University of Maryland in developing a new joint research program, and Sam Page is with us to share the dimensions and the purpose of this joint effort.

Sam?

DR. PAGE: The joint Institute for Food Safety and Applied Nutrition was established by a memorandum of understanding between the University of Maryland and the FDA in April of 1996. Currently, the Center for

Food Safety and Applied Nutrition and the Center for Veterinary Medicine are the participating centers in FDA.

What this is an enormous opportunity for us to improve the science base, particularly in the area of Food Safety and Applied Nutrition, that we are being very enthusiastically received by the University of Maryland, and "Bee" informs me that the cooperative agreement, which was approved by the NIH grants review committee has been implemented as of this week, so we're formally in business. The other important point to note is that funds have been committed for the construction of the new building, which will be adjacent to the University of Maryland campus at College Park. This will house all of the headquarters, CVM and CFSAN review staff as well as the SIPSAN-JIFSAN research operations. JIFSAN will also include the SIPSAN Mod 1 Toxicology Research facilities and components of the Mod 2 CVM research facilities in Laurel, Maryland, which is in fairly close proximity to

the University of Maryland campus.

The mission of JIFSAN is to ensure the safety of the food supply and advance new concepts of applied human nutrition and animal health through cooperative research and education programs. The basic concept is that this is a multidisciplinary research and education program, jointly administered by the University of Maryland and the FDA; and the key part of this, this is to form a foundation for partnerships that contribute to the science base for food safety, applied nutrition, and animal health.

This gives us the opportunity to bridge the departments at the University of Maryland and more importantly, to leverage resources from other sources, meaning other government agencies, other academic institutions and particularly the private sector.

One of the questions that's often asked is, what does the private sector, what do they get out of this? The basic answer to that

is that they would do this as a possible way of influencing FDA policy.

We are a science-based regulatory agency. Anyone who is willing to contribute to the development of good science to drive regulatory policy would be welcome. Obviously there will be a number of ethical considerations which we have to address; the command from Dr. Friedman was to be creative. Obviously we have to be very careful about being creative, given the congressional and federal regulations, but I think we do have an enormous opportunity to do this.

One of our major emphases will be on risk analysis, which, according to the WHO definitions, will include risk assessment, risk management, and risk communication. We have been very fortunate to have been recognized in the president's food safety initiative as the lead organization for the interagency risk assessment consortium under the food safety initiative. We also are being recognized by the World Health Organization as a WHO

collaborating center for risk assessment in food contaminants.

We view this as probably one of the key areas of emphasis, because this gives us the opportunity to drive national food safety programs and international food standards. With the recent passage under the food chemical codex of the requirements for mutual recognition and the food safety standards and inter-laboratory validation and testing programs, I think we will be in a very good position to drive international food regulations by requiring that any standards be based on science-based risk assessments. We think this is very important to the industry for a level playing field in the international arena, and it's becoming very obvious.

For example, in the past two weeks, the European Union is essentially establishing an embargo on raisins because of the mycotoxin contamination. This is Ochratoxin-A {ph} for those of you who might not be familiar with the

situation. We have no idea of the potential contamination of the U.S. raisin supply; this was based primarily on raisins from Iran, and in fact the U.S. is probably a major producer.

So the industry is extremely interested, along with U.S.D.A. in partnering with us to develop the data to drive an international regulation on the basis of risk assessment, science-based risk assessment. So I think we're going to have an enormous number of these types of opportunities to partner both with the public and the private sectors.

In the environment there at the University of Maryland, we're in close proximity with the U.S.D.A., ARS research laboratories, Human Nutrition labs, and we're already moving to partner with a number of these in the development of research programs. So as I said, we're just starting the cooperative agreement we just implemented this week, which gives us the go-ahead to start full-scale development; although we have a number of issues already underway. But I think

I would stop at this point and welcome the opportunity to answer any questions; and to point out the brochures which were in fact developed by the University of Maryland staff, and this is certainly a major advantage that we have, that we can move very rapidly with the University of Maryland to address emerging issues as they occur.

The other thing I would like to point out as far as the international, before I close international situation; that we're already making preliminary negotiations with other similar organizations throughout the world, such as the Carolinsk Institute {ph}, the National Institute for Health Sciences in Japan with similar institutes in Australia and the United Kingdom.

We had hoped to be able to more rapidly respond and develop critical mass to very rapidly address emerging issues of human health concern on an international basis. We view the potential and the extreme power, within a matter of a week or so to call these

institutes and assemble a cadre of scientists from throughout the world at the University of Maryland to develop joint research programs, to establish these collegial relationships, to move very rapidly on an international scale to address human health issues. And with the flexibility that we have, through the university systems, these mechanisms are already in place.

I certainly welcome the opportunity to address any questions now or certainly in the future. All of my addresses are on the back of the brochures.

DR. DOUGLAS: Sort of a very layman's question here: Last night looking at the news I saw a piece that commented on the continuing import of fruits and the like from other countries which carry various microbes, that's endangering the health of Americans, and apparently the public policies are such that there is nothing that can be done to effect that.

Will the Institute be looking at

issues like that from a policy perspective.

DR. PAGE: Certainly for the long term we will become more and more involved in policy issues, particularly the ability to examine these in an academic environment; meaning removed at least one step from the regulatory perspective and one step from the private sector. I think this will give us a neutral ground to really examine a number of these issues in detail.

But to specifically address the types of issues that you're referring to here, I think as we move very rapidly to an international marketplace, and the requirements for mutual recognition with the international trade agreements, we are going to have to assist many developing countries in the development of their programs. If we are ever going to be in a position to accept their data, we're going to have to participate. And that's one of the main reasons for our involvement with the World Health Organization and the Pan American Health Organization, and certainly

from some of our initial discussions with the International Life Sciences Institute.

We would very much like for those individuals to participate in our programs, our outreach programs. As visiting scientists, we are working currently with U.S.D.A., the Foreign Agricultural Service to develop programs where we can have these types of public outreach programs internationally. And we look forward to, in the very near future, being able to be a major player in this arena.

DR. LANGER: Gil?

DR. LEVEILLE: This is the second program of this sort that CFSAN has embarked on, and I think FDA and CFSAN are to be commended for moving in this direction.

I notice you didn't mention a Moffit operation. How do you see the interaction between these two programs, and are there lessons learned from the Moffitt operation that will help the Maryland program develop?

DR. PAGE: the Moffitt Center, the National Center for Food Safety and Technology

in Chicago will primarily focus on food processing techniques. While we'll be more involved directly with the food safety aspects, and to a much lesser degree, in processing technologies.

The major difference between -- operationally between the Moffitt Center and our center, we will not be requiring membership fees or that kind of participation. Our types of partnerships will be specifically aimed at direct projects, although we are certainly moving to encourage participation in such areas with the university as endowing chairs in specific areas in the joint institute and the University of Maryland, to endow both research professorships as well as visiting scientists, staff fellows and graduate students.

And we certainly aren't restricting our efforts to the University of Maryland; I wanted to emphasis we're looking at partnerships. And these will be also with other academic institutions in order for FDA to obtain needed expertise. I think obviously the

University of Maryland doesn't claim to have top scientists in every field; you can't do that, you have to specialize. What we would like to do would be able to use mechanisms to recruit scientists from other academic institutions, to come to FDA either as visiting scientists or to participate in our research programs. And this will be I think slightly different from the way the situation is handled at Moffitt.

DR. LEVEILLE: I guess what I'm looking for is more and more of these collaborative arrangements sprint up, which I think is a desirable thing. But the importance of it, it seems to me, is to have some integrative mechanism that brings the power of all of those individual centers together rather than creating another situation where there are a whole array of independent laboratories sprouting up around the world in this case.

So my plea, and what I was looking for, is whether the Center has thought about an integrative mechanism for these things.

DR. PAGE: Well, we certainly have with the Moffitt Center, as far as I'm aware, is for the food safety; we're dividing the research areas primarily between processing and --.

DR. LEVEILLE: What I'm looking for is a communication link between these various programs.

DR. PAGE: Particularly David Armstrong and myself work very closely together. So certainly we'll go into much more research planning as the Joint Institute gets established.

DR. LEVEILLE: Good.

DR. PAGE: And we'll in fact be transferring some funds that are coming in to Moffitt in those areas which are involved in processing. So that those types of joint programs are going to be developed.

DR. LANGER: Dick?

DR. SETLOW: What type of training will there be for undergraduates and graduate students? And if at all, what types of degrees

will they be receiving?

DR. PAGE: We have a meeting tomorrow with several of the academic deans to start putting those into place. Obviously our main departments that we're interacting with now are the departments of chemistry and biochemistry, departments of food science and nutrition, the department of microbiology and the school of veterinary medicine.

We do have a limited involvement in other departments. For the long term, we hope to have a degree program in risk analysis, for example. Those particularly crosscutting programs. We were talking about bridging various departments. These types of details are obviously fairly creative and need to be worked out. But we will be supporting graduate students, postdoctoral fellows, a number of visiting scientists. We are looking forward to sabbatical leaves from other academic institutions as well as the private sector, and this is going to be very strongly encouraged as far as integrating them into our research

programs.

One of the things that we have inaugurated, just in trying training course to be able to respond very rapidly to problem areas, for example. This past spring there was a major problem in the dietary supplement arena because of misidentification of plant material coming in. And this was primarily because the quality assurance programs were not in place.

I gave the word that I wanted a program carried out as soon as possible on the microscopic identification of plant material, a practical course for industry scientists. And we were able to work with the university within two months to carry this course out. It was fully subscribed, we have enough inquiries to run it twice again; it was very well received by the industry.

We look forward to carrying these types of training courses out, both for hands-on training as well as education. For example, if a regulation is coming up, it will be very useful to have basically an interactive forum

with the industry, and a neutral ground to handle these types of questions through the university system.

So we hope to be able to respond in a much more timely fashion to these emerging issues and questions. And the university gives us the flexibility to do that.

DR. LANGER: Pedro?

DR. CUATRECASAS: How do you interface with Food and Nutrition Board of the IOM?

DR. PAGE: Primarily through Dr. John Vanderdam right now. We will -- to be honest about it. There are a number of these issues; we're just starting out. And there are a number of these contacts which we're going to have to develop formally.

It's my understanding that that's in a period of reformation now, and I was actually stepping back until the decisions were made where that was going, before we moved forward to -- obviously there are a number of organizations like this that we're going to have to integrate with very closely, and it's

certainly our intention to do that.

DR. CUATRECASAS: So so far you haven't tried to influence their programs or to initiate --

DR. PAGE: And vice-versa. Obviously we are going to have to be working very closely with them; with the National Institutes of Health, for example, and other organizations as far as very strong partners. Obviously we're counting on U.S.D.A. as a major player whether or not we're combined into single foods organizations, we're already becoming involved with joint programs with a number of -- ARS and AMS and most of the U.S.D.A., in both education and research programs. It's just an enormous opportunity and we're extremely excited about it.

DR. LANGER: Any other comments?

DR. BLOUT: One question, Sam. Are you involved at all in sort of post-marketing problems?

DR. PAGE: We probably will be. Again, there are a number of issues that we're

going to have to work out as far as how these are handled ethically. Another problem will be in free market. Obviously, we would not want to be carrying out research that is going to be submitted in a petition to FDA, for example. I mean, there are ethical issues which, we're going to have to sit down with the university. We will have a joint ethics committee with the university to handle these kinds of issues.

But it's a learning process; we are being as creative as we legally can be -- (laughing) -- she would kick me under the table if I said otherwise. But as I said, we're being as creative as we can and are really looking forward to expanding our horizons on a number of fronts.

DR. SCHWETZ: Just a question of where this takes us in the future, as a research community within the FDA. Because if you assume that this is successful and it's a wonderful opportunity for us to extend our research capabilities, then this becomes

repeated with other centers, that we have these kinds of connections.

If you have this group, in this example researchers from CFSAN who now become part of a new research community, the possibility that they become more distanced from the innards of the FDA; and if you have now a number of these research opportunities being developed, what is the chance that you begin to have the core of the FDA now located in our communities, and it becomes more difficult for us to have a concentrated research community within the FDA, because it's dispersed.

I don't mean to suggest that this is anything but a wonderful opportunity; but how do we prevent that and is there any risk of that?

DR. PAGE: Well, I like to comment on that for a moment. Basically our concept is that all FDA employers participating in JIFSAN research will be both FDA researchers and have a significant review function. We have change

our peer review system to incorporate a mechanism to give credit for regulatory review, whether it be for petition review or participation in one of the various program office regulatory activities.

But this is going to be a mandatory function of all CFSAN researchers, to have a significant role in the review side. The way we're going to be able to do this is to support these scientists with graduate students and postdocs, so their regulatory load will be comparable to that of a professor having a teaching load. It is really unrealistic to expect an individual to carry out a vigorous research program and have a significant regulatory review function and not have this kind of support; you just can't do it. You can't dabble, that's the bottom line.

In order to have a vigorous program, you're going to need this type of support and through the university, through the Joint Institute, we're going to be in a position to offer this. We think this is going to give us

a major advantage in recruiting top quality science into the FDA to offer this kind of opportunity.

But the bottom line is, you're absolutely right, we are very concerned about the integration of the research into FDA program function; and certainly the design of our building at College Park is going to reflect the integration of research into the regulatory function, and we're quite excited about where that's going and the impression there.

The other advantage that that does give us is access to a lot of very cheap or free consultation in the university system, and likewise. It also leverages a lot of the major instrumentation resources, particularly through the instrumentation center of the Center for Biomolecular Structure and Organization which was recently formed at the University of Maryland.

All of our major instrumentation will be integrated into the instrumentation

resources of the University of Maryland for those types of joint support activities.

DR. LANGER: Any other comments or questions?

Is there any motion or recommendation you're looking for this section? No.

DR. SCHWETZ: This was for information; this is a done deal. I guess if I was looking for any input other than just sharing with you this example, whether or not we should aggressively as an agency pursue more of this.

This was primarily for information, but also the question to you for discussion of whether this is the direction to go in, and we should be seeking more of these opportunities.

DR. DOUGLAS: I was a little bit impolite and had a cite bar with Pedro precisely around that, whether it made sense at some time having a discussion as to whether we should do more of this; this is a type of a model. I don't know if this is the time to do it; I feel I don't know enough to add more, but

it just struck me that it might be a useful model.

DR. LANGER: Yes, Rita.

DR. COLWELL: What has happened to -- is it deep-sixed, the concept of a campus for the FDA being in one location? I know that there was a lot of political to-and-fro'ing, but shouldn't that be something that is kept in abeyance rather than discarded?

DR. SCHWETZ: There's still a lot of political to'ing and fro'ing. And as those discussions go on about consolidating and where it can happen and who comes in, these kinds of opportunities come up and it automatically impacts CVM and CFSAN's contributions into whatever the plans would have been for consolidating, and with the prospect that the to'ing and fro'ing in developing a centralized FDA facility someplace, with that ongoing, we can't hold these up because of the prospect that some day the FDA would be under one large roof someplace. So I think the prospect is that that probably won't happen, because we're

going to continue to have these kinds of opportunities that speak against that.

DR. PAGE: If I might make one additional comment here to address that issue, we are certainly including the other considerations for the other centers in this. For example, we're doing some negotiation now for imaging equipment that would be in the University of Maryland center to support both CDER, CBER, and CFSAN, requirements from the toxicology side.

I think there are a number of these issues that are, that even -- I think the current plans are both for the White Oak facility for most of the rest of the agency in College Park, for CVM and CFSAN, and that's relatively close proximity, particularly if we're talking about the expense of the major instrumentation required and shared by all of these centers. I think through the University of Maryland we have a significant opportunity here to develop these types of joint resources.

And obviously while CVM and CFSAN are

the major players with the University of Maryland, we're certainly taking into consideration the needs of the other headquarters personnel, in as many areas as we can. To include funding for various projects through the University of Maryland that these centers might have.

The MOU is with the Food and Drug Administration, not just CFSAN and CVM. So the opportunity is certainly there for all the other centers to participate in the university system.

DR. DOUGLAS: Of course the two sides to the success is that one could ask the question: If one is really squeezed for budgets, et cetera, should all centers basically transform into these joint efforts?

No response is needed.

DR. PAGE: Well I think that, as Dr. Schwetz pointed out, this is more of a political issue than -- than a scientific or programmatic issue for that point.

DR. LEVEILLE: Let me come back to the

point Bernie was raising. I'm an enthusiastic proponent of this kind of model. I think it offers a lot of opportunity to the agency, and I think this particular one provides a lot of opportunity to study all of the issues that may be associated with moving in this route, so it should be followed very carefully.

The concern is the one you raised earlier, of how do you maintain the integrity of the research and the regulatory functions? And I know it's being addressed and an attempt will be made to do that, but recognizing that you now are putting people in an environment where on the one hand, on the academic side, they speak very freely about everything they do; and on the other side, they need to maintain some degree of confidentiality and you create a schizophrenia within each of the individuals that you place in those centers. It probably can be managed, it probably can work, but I think it's something that will have to be observed very carefully over time.

So I think it may be a desirable

direction to move in, and I suspect it will be over time; but this will be a good model to watch for the short term; and it probably would be very valuable to this board to have CFSAN come back and review the ongoing programs that they have in a year or so in considerably more detail if we can give it that time.

DR. DOUGLAS: I would like to make it a little stronger. I'm sitting here, just reflecting the whole day, and I would like to, without saying much more, I would like to propose it a little bit stronger, that this Board actually in a proactive way look at this model and look at what are some of the strategic issues involved with the model, what are some of the administrative regulatory issues, what are some of the issues that affect the research side of the FDA, and how does this model impact those issues.

I would like to recommend that this board do that in a very proactive manner.

DR. BLOUT: Are you ready for that?

DR. PAGE: We certainly welcome that.

I was actually going to volunteer to, if the committee so desired, to essentially issue a monthly update, progress report of where we are, and to include in that some of the issues that have come up. We would certainly appreciate the advice of the Board.

Obviously there are a significant number of issues that we will be breaking new ground on, and certainly with the wealth of experience with the Science Board, we would enormously appreciate that, because that would be very useful. This is both from the university and from FDA; there are, as you point out, a number of issues that we're going to have to address that we're actually having to address in the design of the new building, that obviously we're going to have a number of visiting scientists. We're going to have to determine how you handle security from the confidential information, a number of ethical issues --and we would certainly appreciate the advice of where things are going, appreciate support; obviously we have some problems that

we've already picked up on that you might be of significant assistance with us. And we'll certainly let you know those, too.

DR. SCHWETZ: There are a couple of other examples of MOUs, one that's been put in place just recently with one of the institutes of NIH, the dental institute and CDRH. And these are less dramatic than this one in that it doesn't lead to a building with a name on it, and they don't have these kinds of documents that really emphasize the joint institute nature; and I was hoping that Liz Jacobsen was still here, but she isn't, is she?

But what has come to be of interest to us is that institutes like the dental institute have recently come to us with the idea that "Gee, FDA, because we interact with you in the device area and we overlap to some extent, we have questions, we have applied questions, research questions that we'd like to share with you and discuss and talk about how can we get work done?" This is a relatively new mindset that comes to the table, because we did deal

with applied research questions. And for the most part, the institutes of NIH have not come to us and said "Could you please help us with applied research questions?"

So that has been a very positive thing that's happened in these past few months, that we would now develop an MOU to share information, to share research planning with institutes of NIH that again would represent an extension of our capabilities, and certainly brings to us a whole other set of experts who can help deal with the questions that we need to deal with.

The other one where we've had that kind of an MOU for a number of years, and I mentioned this at lunch to some of you, is between NCTR and NIEHS, primarily because of the national toxicology program, but there has been a large cooperative effort between that center and that institute of NIH to again foster research, the support for research at NCTR that is of need for the FDA, but through NIH funding.

So I think what we can do for you is bring back from time to time kind of a summary of how all of these interactions are working, and maybe pick pieces of them that represent the greatest successes as we look to how we can do more of this in the future.

DR. LANGER: Thank you. Any other comments?

@@ What I'd like to do is, we're sort of at the end of this before public comments is, just go over any recommendations that we might make. And so far there's been sort of one major one and I'll just summarize it and see if anybody wants to make any changes. This was from earlier in the day. That is that:

> The Science Board to the FDA endorses the external peer review process and framework for review of FDA research programs; and recommends establishing a subcommittee to the Board that will conduct the CBER research program peer review.

I just wanted to see if there were any changes to that.

DR. BLOUT: I'd like to see if the Board would go along with the thought that keeps surfacing, namely: Should we suggest that there be an outreach from this process? It's an important process, but should we designate that there be outreach positions?

DR. COLWELL: If I can translate, if you mean public education, I would endorse it.

DR. BLOUT: Yes, that's what I mean.

DR. LANGER: Attached to this comment, or more broadly?

DR. COLWELL: More broadly.

DR. LANGER: I agree with that, yes.

Do you want to have a recommendation that we put into the minutes, or do you --

DR. COLWELL: Could we put it in the minutes as a strong sense of the Science Board?

DR. LANGER: So how should -- if you could suggest some wording.

DR. BLOUT: After reviewing various

programs and activities relating to science and research at the FDA, it is the recommendation of the Board that -- what do you want to say, Rita?

DR. COLWELL: That the FDA undertake public education and outreach efforts to communicate the activities of the FDA.

DR. LANGER: Outreach efforts to communicate --

DR. COLWELL: Activities of the FDA.

DR. LANGER: "the activities of the FDA."

Let me read that back.

DR. COLWELL: Use "science activities".

DR. LANGER: All right, the science activities.

Okay, so here's this recommendation:

> After reviewing various programs and activities relating to science and activities at the FDA --?

DR. BLOUT: No.

DR. LANGER: -- relating to science at the FDA, that the FDA undertake public education and outreach efforts to communicate the science activities of the FDA.

DR. COLWELL: It's a little circular, but that's okay.

DR. LANGER: What's that?

DR. COLWELL: It's a bit circular, but it'll do just fine.

DR. LANGER: What do people feel?

DR. LEVEILLE: I think it's necessary.

DR. LANGER: Okay. No objections?

DR. LEVEILLE: I have no objection, but I wonder if it's adequate without identifying somebody who should do it.

DR. LANGER: Um.

DR. LEVEILLE: And I don't know whether within the agency, that would be the office of public relations or --

DR. BLOUT: It should come from the Office of Science and from the Commissioner's office.

DR. LANGER: Yes, I was going to say

that I think -- I think they could come back to us at a subsequent meeting with how this was done. I think it's certainly a well-taken point.

Any other recommendations that anyone feels we should make based on today's discussion?

DR. CUATRECASAS: I would suggest that perhaps we consider, to your first recommendation, adding the statement that -- we would urge the FDA to consider initiating a similar review of one or two other centers to be conducted in parallel, and as soon as possible, to examine the feasibility of doing that.

DR. LANGER: So, we would urge the FDA to consider a peer review process in --

DR. CUATRECASAS: Similar to the --

DR. LANGER: -- in other centers as soon as possible.

DR. BLOUT: To be initiated as soon as possible.

DR. SCHWETZ: May I ask a question of

clarification? Whether the intent of it is to gather more experience before we bring back to the Science Board a proposal for the, what you might consider the final version of our peer review process; or whether what you're recommending is independent of our continuing to proceed to define the peer review process within the agency.

DR. CUATRECASAS: No, I would not think of that being done independently, no more than the CVR proposal. Something similar to that would not be obviously in conflict with it; but I think both are helping to shape each other. Just to get things started, to get things moving.

DR. LANGER: Yes.

DR. SETLOW: I don't think that the words in your general outline are cast in stone.

DR. LANGER: Let me just read this back. The first recommendation was 1, I'll call this 1a:

We would urge the FDA to

consider a peer review in other centers to be initiated as soon as possible.

Does that adequately capture it, and are there any objections or changes?

DR. BENET: I don't object; but it's just -- I like to do stuff that's realistic. And it is obvious to us that CBER has put a lot of effort into this, put some information together, and we're just tacking on say "why don't other people do it?" I'd like to see -- I think we heard from the science representatives of each of the other centers that they want to see this, they would like to be able to use this as a model, and I think it's premature for us to say in parallel or we should be doing these other things. Although, as Bern has talked about, there are peer review processes ongoing; this is a different process of looking at the whole center as a group; and I think it's very unrealistic for us to recommend this at this time.

DR. LANGER: Elkan, you were going to

say something?

DR. BLOUT: I think it's unrealistic; we don't have the resources, both spiritual and financial to do more than one. But it is not unrealistic to plan for a second one.

DR. CUATRECASAS: Well, I think that's obviously that's what we're proposing, not that they should go off and start doing the review. What they will do is select one or two centers, they will begin to look at the feasibility of that. and to put together a proposal, and to see what's involved. It's going to be different from what we heard today, and it will be hearing what kind of process they would like to see, and what kind of constraints there are, what kind of costs, et cetera. And that's going to take a long time.

If we wait until the other one is finished, before anything else is done, we'll be here forever.

DR. LANGER: Let me see, I'll read this back again, see if there's any amendments. We can either not do it, do it, or make some

changes to it. I'll read it back again.

We would urge the FDA to consider a peer review in other centers to be initiated as soon as possible.

Everybody?

All right, so then we'll do this one, too.

Any other thoughts on any of the other things we went over today in terms of motions? I just wanted to check with Bernie about biomaterials.

DR. BLOUT: Is everybody satisfied, Bob, about the nature of this process? I know Mike wants it not as conventional as other types of processing. He wants to --

DR. BLOUT: The CBER --

DR. LANGER: Review process.

DR. BLOUT: Review process.

His concern is that we get input from many money places, not only. Should we say anything about that?

DR. DOUGLAS: Given what you need to

accomplish around mission, around quality, around the downsizing, I'm not so sure how innovative you want to be in your process.

DR. LANGER: Okay, any other comments on this?

At 3 o'clock we're going to have public comments, but I did want to see if anybody here wants to say anything? Yes.

AUDIENCE: I'm Jon Yohanssen, currently the cochair of the CAFTAS group.

There were three of us here today; and I think we were all a little disappointed, because we didn't hear the words "virtual science center" mentioned once by anybody today, and it seems that that's something that's almost -- well, I came in a few minutes late, so maybe I missed that.

And that a lot of the sort of structures -- while we realize that the agency is under a lot of pressure in terms of decreases in funding and people, and one of the recommendations that the Subcommittee on Research had made to sort of deal with those

was to find ways of increasing the collaboration between centers; so that where there are resources in a particular discipline, scientific discipline, and a problem comes up that maybe one center can't completely deal with on its own, that there is some sharing of those human resources as well as instrumental resources.

And I would submit that while clearly peer reviews of programs within a center have to be done, because that's how the budgeting is done and you have to look at how the money is being spent, and is this reasonable? I think that the members of CAFTAS in general feel pretty strongly that there should be some review of scientists by discipline across centers, because one of the goals, as my understanding of the recommendations of the subcommittee, were that the agency really get a better handle on the depth and the breadth of expertise in different scientific disciplines.

I would submit that if these peer reviews are being conducted strictly by center,

even though you have this Board of Scientific Counselors over the top, that the degree of sort of detail that's going to come out of that is I don't think that the Board of Scientific Review as a whole is going to have a sense, agency-wide, for example. What is the agency strength in this area or that area?

I would think that maybe you don't want to call it a peer review, but some kind of a survey and review of programs by discipline across the agency would be useful in the sense that it would give the agency a clear view of what's going on in a discipline across the agency; and at the same time I think it would bring those people together during the peer review process across the agency, and sort of mix things up a little bit.

And I realize that we will have this expertise database, and that that's going to be a useful tool, certainly for making connections. But I think what Dr. Friedman was alluding to earlier in terms of being a little non-conventional about this is that as the

crunch gets tighter and tighter, is that the agency perhaps as a whole at the agency level is going to have to at some point make a decision about, "Well, what's the most important thing coming down the pike? And what are the areas of expertise that we really need to increase our manpower, and what perhaps do we have maybe too much of?"

I think that there has to be some kind of a look overall at sort of the breadth of different scientific disciplines. Coming back to -- Neil and I had a discussion about this at lunch, but the process you're going through right now is you're having to decrease a certain number of FTEs in research. Well, it could be that there's an area where you have only a few people right now, but it's one that's very, very critical. Well, it could be that maybe that expertise exists somewhere else in the agency.

So I'm saying that doing sometimes these peer reviews in a vacuum without considering what's going on in the other

centers may not be the most efficient way to do things.

DR. LANGER: Thank you.

Yes, Pedro.

DR. CUATRECASAS: It seems to me that we -- by the way, Bern did talk about the virtual science thing earlier; I guess you must have missed that.

DR. YOHANSSEN: Sorry.

DR. CUATRECASAS: You raised a very good point, but it seems to me it was covered this morning. And that is that these reviews are not going to exist in a vacuum, and what we also have which is new is the Office of Science, and the Chief Scientist.

It is I think appropriately the responsibility of the Chief Scientist and his office to then meet and to actually put together and to formulate questions and issues and to go back to the counselors, and the things you initiate there, and then come back to the Science Board.

I think we all would expect that at

that level, there would be a coordination of all of the reviews, not only reviews but the activities that are ongoing. And that's one of the major functions, in my opinion, of the Chief Scientist, to see that there is, indeed, harmonization and coordination, and cognizance of all of the functions within the agency.

DR. LANGER: Any other comments? Yes.

DR. DOUGLAS: If I can just add, unfortunately the speaker missed a lot of the discussion this morning, which addressed many of his issues. What might be helpful as a recommendation I'm hearing from him, is during the program reviews, for example, that the external panel you get, you may want to reach in to other centers and select an individual with that expertise to be part of the review panel. And I don't think we covered that this morning; and I think it's a useful suggestion.

DR. LANGER: Yes.

DR. MACGREGOR: I'm Jim MacGregor from CDER, and I just wanted to comment on the topic of collaborative undertakings and point out

that CDER actually is embarking on two external collaborations, one in the area of product quality called the product quality research initiative, and currently is developing a CRADA with the American Association of Pharmaceutical Sciences, under which they would function as the administrative center of a collaboration; and in the early part of 1998 there's going to be a public meeting focused on that to try to focus on how that might go forward and get public input into the process and so on.

Also at an earlier stage is the idea of a collaboration for drug development improvement, which would be a collaboration with a center at Georgetown University and CDER on issues related to the drug development process and how to perform, establish a collaborative center and focus on research to support that process.

And personally, as we listen to the cutbacks in resources internally at FDA for performing and carrying out these research programs, my personal view is that this kind of

leveraging is going to become almost a necessity if we're really going to make impact.

DR. LANGER: Thank you.

Any other comments to now?

Why don't we take a 15 minute break, meet here at 3 o'clock, and Les Benet will chair the rest of the meeting. I know he's looking forward to that.

DR. BENET: We'll meet at 3 o'clock.

(Recess.)

DR. BENET:

Okay, we are calling to order my moment in the sun. I've been waiting to be the interim-interim chairman for a long time.

We have one item on our agenda and that is public comment. And since it's scheduled for 3 o'clock, it's now 3 o'clock.

Are there public comments? Going once. --

No public comment. I knew this was going to be easy.

Are there other comments or suggestions from members of the Board, or

guests that would like to say anything?

MR. LIEBLER: I'm going to say something. It will make you feel good.

DR. BENET: Okay.

MR. LIEBLER: Actually, this is a residual thought from this morning. Actually two. One is that, looking at the first plan for peer review, I did a rough back-of-the-envelope or the little scratch pad calculation, and there's a potential for people spending on the order of 900 person-days a year in meetings. That is a lot of overhead for a review.

So I would apply a heavy dose of Hakim's razor and look to make things as simple as possible, which would to me say, give the centers the responsibilities for performing the reviews -- I forget what the board was that sat above the red ones -- and it filters back up for the overall policy view up there, and make them responsible for deciding how to do it.

But I think what's got to be critical is that, Dr. Goldman answered me this morning

with the fact that he expected that the outside experts would come from industry. Rather than saying that you need world class experts, I think you need to direct the peer review to include industry experts. I think that has to be directed; I don't think it can be assumed. Because that's critical. These are the people that -- your primary customer, and they've got to be involved. End of statement.

DR. BENET: Okay, thank you, Bernie. Neil?

DR. GOLDMAN: Yes, if I can just respond to that.

Bernie, in fact what I was saying was yes, we intended to include in that review and have on our list people from industries that we engage with; that included Pharma and Bio. So in fact we have been in contact with them, first to make sure that they actually could be part of the review; that they would be allowed to participate and they supposedly are now allowed to participate, and we have actively been seeking them out.

MR. LIEBLER: I wasn't criticizing your activity; I was suggesting that the Board's discussion of any plan should include direction for it to be that way, as opposed to hoping that it would be that way.

DR. GOLDMAN: Ours was planned to be that way.

DR. BENET: Any other comments?

Bern, final comment?

DR. SCHWETZ: Just to thank you for useful insight and input today; and it helps to have this kind of advice. Thank you.

DR. BENET: Elkan?

DR. BLOUT: I recommend we adjourn.

DR. BENET: Very good. I was afraid to do that on my own, because I was only interim-interim.

Thank you all very much.

(The meeting concluded at 3:05 p.m.)