SCIENCE BOARD

to the

FOOD AND DRUG ADMINISTRATION

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P R O C E E D I N G S

CHAIRMAN KIPNIS: I'd like to call the meeting of the Science Board to order.

Today, on our agenda we have a number of very interesting reports, Biomaterials Update; a Subcommittee Report on Toxicology, and we'd like to do those at the beginning of this session.

Then we have a major report from the Subcommittee on FDA Research for presentation to the Board, discussion, and final action by this Board.

I'd like to call on Dr. Blout to make some introductory comments, as well as introductions.

OPENING REMARKS

DR. BLOUT: Well, I can only emphasize Dr. Kipnis' comments that, while not deprecating the other business of the Board, our main business today is to consider and hopefully act on the subcommittee report.

Just so everybody knows who everybody is around the table, on my right is Bern

Schwetz, who is Associate Commissioner for Science, and one of the six directors of the Centers. He's the Director of the National Center for Toxicological Research.

On my left, of course, is David Kipnis, our distinguished chairman of the Science Board and Professor of Medicine at Washington University.

On his left is Michael Friedman, whose new title is Lead Deputy Commissioner, which means that he's the guy who's really in the hot seat since David Kessler left last week, and is now responsible for various agency actions. So, good luck, Mike.

(Laughter)

On his left is Susan Meadows, who has just returned yesterday from two months sick leave and is ready to function strongly as Executive Secretary of the Science Board.

On her left is Les Benet, professor and Chairman of Biopharmaceutical Science at California, and Ruby Hearn, longtime member of the Science Board and valuable member of the

Science Board, who is here taking valuable time away from the Robert Wood Johnson Foundation.

On her left is Gilbert Leveille, Vice President of Research at Nabisco.

On Dr. Leveille's left is a new member of the Science Board, Dr. Rita Colwell, who we all welcome. She is the President of Maryland Biotechnology Institute, has many other titles, which I won't tell you about, but I know some of them, and we welcome her as a new member of the Science Board.

I should say, there is an additional member of the Science Board who unfortunately could not be present today. That is Charles Sanders. He's accepted membership. He's a former director of Massachusetts General Hospital and president of Glaxo, Inc., so he has a duo background, which I think will be particularly valuable to the Science Board.

On Dr. Colwell's left is a man who doesn't have to be introduced, Richard Setlow, who's an associate director from Brookhaven, and is going to give us a report today on the

Subcommittee's progress.

On my right is Neil Wilcox, whom you all know, who's a special assistant and really the driving force in the Office of Science, Suzie Homire, the lady who does everything so well, who shepherded this subcommittee of the Science Board through very difficult times, as the man on her right can attest to, who is, of course, David Korn, the former Dean of Stanford University Medical School and chairman of the Science Board Subcommittee on FDA research.

On his right, is a member of the Science Board, Bob Langer, and also a member of the Subcommittee on FDA Research.

He's the distinguished and inventive member of MIT's faculty, concerned with biomedical engineering.

On his right was supposed to be Flossie Wong-Staal, whom we haven't seen. Not here. She is the other member of the Science Board who was on the Subcommittee of Research.

Now, I should note we're having one retirement from the Science Board today.

Bill Rutter, who has been here about half the time but hasn't been able to devote the time to the Science Board he had hoped, is stepping down as a member of the Science Board.

I think he's a great person, but it's hard to run a major pharmaceutical company and do many things outside of that in today's world.

So, Bill, thank you very much, and hopefully we'll see you in another venue.

That's all.

CHAIRMAN KIPNIS: We'll initiate, then, our program with the report by Dr. Liebler, Biomaterials Forum Update.

BIOMATERIALS FORUM UPDATE

DR. LIEBLER: Good morning. I titled my report a little more optimistically.

[Overhead]

The truth is, I do think we are making progress. We have a Planning Committee. It's an interesting group because they're very interested people. They're also very busy people.

We've had two meetings which, that in itself, I consider a major accomplishment. Our schedules rarely cross.

We've developed three draft documents, which you should have in your packages: Mission and Goals Statement, Steering Committee Structure, and an outline of a web site.

I think the Missions and Goals and the outline are fairly straightforward. The structure, we need a Steering Committee to run whatever forum we develop.

The document there is intended to be a plan as to how to create the first Steering Committee, for which, we would like input from the Science Board.

Once that first Committee is in place, the goal, from my view, is that it becomes self-supporting. The Science Board really doesn't have to give it any further input, unless it chooses to. However, any recommendations that come out of the Forum would flow through the Steering Committee to the Science Board. We would view the Science

Board as our gateway, so to speak, to the FDA.

I would appreciate any comments. I've tried to go through that document and make it as clear as possible and also make it limit the burden placed on the Science Board in the document. I don't guarantee my own success on things, so I'd appreciate any feedback on that whatsoever.

One problem that we've come across, and I actually have two, and I'm showing this one first, it's the less cosmic one, you might say, is to do a web site, which we see as the best vehicle for inviting comment and discussion, literally, from the world, I have estimates of about $20,000 annual cost for maintaining it.

One of the things that you really need -- is a speaker who's less nearsighted --

(Laughter)

-- what you really need is a moderator.

The moderator or web master, as one chooses to call it, the job of this person is

to actually look at the things that get posted. The strangest things get posted to the strangest locations on the worldwide web.

There's a price for the freedom, and I think it's worth paying the price, but I don't think that we need messages on how to get rich quick or I don't have to work your imaginations on the other messages that we want to eliminate.

So we need somebody to look through these, to decide where they go, how they go, if they go.

Needless to say, that someone has to get paid in some way, be they an independent person who gets paid on contract, or be they somebody who's time is donated by an individual.

So we see a solution of options through paying a full corporate sponsor. That's the more optimistic approach. The more realistic approach is: Have FDA operate the site; in other words, give us a hardware place to put it.

I was just talking to Ed Mueller. It looks like we can have a part of the FDA web site dedicated to a sub-page, a subsection, you might call it, dedicated to the forum. What we'd also like to do is have its own what they call URL or direct address, so that instead of punching in FDA.gov, you would punch in FORUM.ORG, or something like that.

Then find someone who is willing to donate a site design and lay it out and somehow donate that magical person to keep it going.

One of the reasons we're getting creative is that in the middle of our first meeting back in December, I suddenly sat there and came up with this brilliant observation; is that if we keep talking about the Forum as an entity, entities don't have legal standards.

Entities are just things. We were talking about we're getting somebody to donate funds or whatever to run the web site, and it occurred to me that you can't write a check to something that is not a legal entity in the United States.

Notice there's a difference. There's a legal entity and there's an entity. You can exist but you can exist without reality, so to speak.

A good example is global harmonization task force, which is the working on quality assurance and GNP issues internationally. It has no real standing, yet FDA participates, U.S. industry participates.

All the major trading blocks and medical devices participate. The big benefit that it has is it was the brainchild of the European Commission and they pay the bill.

So that it hasn't had trouble continuing itself. It's a little harder to get bills paid here.

It turns out that my initial view is to become a corporation. We've thought about that. Incorporating becomes very difficult. You take on a lot of burdens. You take on tax filing burdens, you take on legal filing burdens.

Somebody has to donate the time and

the effort to collect the money, to disburse the money, to keep the records. We decided that we would go with our Option 2, which is to rely on generosity and make the generosity direct, so that if somebody wants to donate funds to design a web site to go pay a web site designer and just set it up at the FDA site, we can go from there.

So we're looking at, right now, continuing with developing a list of issues for immediate attention. That's our hook. That's how you get people to care. I mean, that's what will draw people in. What problems that you foresee or what problems you have, do you think this will solve.

I volunteered to prepare and distribute a letter soliciting interest and support. We're looking at professional societies, trade associations, academic societies, HIMA members, any other corporate people that we think might be interested.

What we're trying to find out from them is do you care, do you think it's a good

idea? If you think it's a good idea and you care, how much do you care?

Do you care in terms of in-kind contribution? Do you care in terms of dollar contributions.

What it amounts to is really simple, as I think I noted in the report. If nobody cares, let's go home.

We couldn't go out and ask them if they cared until we had enough of a structure to describe. Now that we have that, we have to find out if they want to play.

Assuming they want to play, we will nominate and find a chair and a cochair for the Steering Committee and a secretary. I've got this personal fear about the secretary, but the rest I think I don't have to worry about.

And, now, I'll be glad to answer any questions.

CHAIRMAN KIPNIS: Are there any comments or questions?

DR. LEVEILLE: It strikes me your solution of having this entity is contributed

to the way of handling this is very precarious and you could set it up and it could fall apart very quickly, of course.

Have you explored the option of maybe affiliating with a professional society that could be the entity under which you could operate something like this?

DR. LIEBLER: Yes, we talked about that. But the thing that we're a little concerned about, in fact, we wind up with a couple of things, is that then it becomes viewed as a piece of that organization. HIMA has a web site. I will have a section of our site devoted to the Biomaterials Forum.

But I don't, and I don't think anybody else in our group wants to have the web page or the web site or the Forum itself viewed as a HIMA thing because that puts a different tone on it. You want somehow to freestand if it goes to the Society of Biomaterials.

Every organization has baggage, and the FDA has baggage, we have baggage. Professional societies have baggage. The

baggage gets loaded on the Forum.

In fact, someone pointed out at our last meeting that the Society for Biomaterials magazine is called the Biomaterials Forum.

So before we can call this even formally the Biomaterials Forum, we have to find out from them if that's okay.

I know it's precarious. I just don't know -- I think this has turned out to be a lot more difficult than I think any of us thought.

DR. LEVEILLE: I obviously haven't explored this, but it strikes me that there were a consortia of professional societies. The FACED Group is an example. I don't know whether there's an appropriate consortium that could become the appropriate repository for this kind of a forum.

DR. LIEBLER: I think at this point, we're glad to look at anything that might work. We don't have any set plan that we're trying to do, except make it work, if we can, how ever we can.

Other questions?

CHAIRMAN KIPNIS: Any other members of the Science Committee?

DR. BENET: It wouldn't look to me that the web site would be your major impediment. It seems it's to get the organization with the chair and the membership and start forming.

How far are you to that stage? You list that as your current task?

DR. LIEBLER: Yes. We describe that as if we can get a chair and a cochair and a secretary, since somebody has to write letters, do we structure it that their job would be to put together a slate that the Board would respond to and put the Steering Committee together, which would get that going.

DR. BENET: Would you anticipate that within a time frame?

DR. LIEBLER: I think by fall we might be able to at least have the -- I would hope we can get the chair and the cochair done by then and start working on some other suggestions for

members.

I would like to see that fully in place by the end of the year. I know that sounds like a long time, but the way things have been going, I think it's optimistic.

CHAIRMAN KIPNIS: Other comments? Dr. Langer, do you have any comments?

DR. LANGER: I think that Bernie's done a great job. I think there's a lot of progress. We've started talking about this, whether we can have some kind of effort, and it was actually his vision to begin doing this, and he's been implementing it. I see this as very positive.

CHAIRMAN KIPNIS: I must admit to an element of confusion, in that there are numerous agencies, you've already pointed out, either societies, conglomerate organizations, representing industry, and others, who are interested in this general problem.

Is the function of this group to try and coordinate diverse interests into a cohesive group for information or for policy?

That's one.

The second is: Everybody carries baggage in our society, and that baggage frequently is more perceived than substantive. Unfortunately, it's translated into substantive actions, but the government carries baggage, too. The Science Committee carries baggage.

So I don't understand why baggage is an indication for still yet another organizational entity to be developed. My perception of what you're proposing is to try to bring in to some centralized reporting matter, diverse interests, diverse ideas, diverse innovative approaches.

Why can't that be done from current organizational structures? For example, your own structure. Why can't HIMA do this? Why worry about it baggage?

DR. LIEBLER: I think the biggest problem with baggage is not whether it's substantive, but the whole problem with baggage is always perception.

Whether there's substance behind it or

not makes no difference whatsoever because it's people's perceptions. We did a report on biomaterials, the Aranoff report, and I was very worried when we spent the money and put in the time that it was going to get overlooked because it was an industry paid-for report.

It's a standard response. This was all directed, and I went through great pains not to direct the results. I lucked out. People paid attention.

But it's most common that you just get discounted. It's just the industry being self-serving, if it comes from a certain source. And whether it's true or not is usually not the issue.

I think the idea here was to be able to find some way to bring all these diverse interests into some way to channel their expertise, their knowledge, their opinions, and their modes of operation into one spot to bring the information together.

I always talk about it as trying to create the old potbellied stove in a general

store, but general store is going to be the general store's marketplace, so to speak, and everybody gets together and talks and solves the problems of the world.

And I think that's what we're looking at. There are things that will come down the road that FDA will grapple with in terms of how to regulate, how to deal with it. That's going to affect the industry, it's going to affect academia, it's going to affect medical practice.

We have to get a place for everybody to come in and find some way to get some well-coordinated, well thought out input back to the agency regarding that, with the agency being a player in that discussion.

That is why we called it a Forum, the old Open Forum, the Open Discussion.

CHAIRMAN KIPNIS: Again, this is just one individual's reaction. I'm not naive, to the extent where I recognize that a whole host of environmental circumstances influence receptivity of a report. That's what you're

telling me. I've paraphrased it this morning, with several others.

My old professor used to tell me: What you're telling me is life is hard, and I already know that.

The reality is: How do you get cogent information in a form where then it's presented to an agency, for example, and how do you, in essence, get it, say, straightforward?

You're neglecting a report that has substantive information in it, and I want a response. I recognize that it may not work, but to me this certainly sounds like it's establishing another entity, which carries with it another bureaucracy, which carries with it a support mechanism, highly diffuse and, therefore, not very dependable. That's one of the problems that I see.

On the other hand, what prevents HIMA or anybody else from, within their own organizations, formulating a valid report on any issue they wish related to biomaterials and submitting it to the agency and requesting a

response? And if there is no response criticizing it and then exercising political influence, or if the response is inadequate, pointing out it's inadequate and challenging them.

I don't see how another organization is going to accomplish that.

DR. LIEBLER: Through HIMA, using my own organization as an example, I can get the diverse or the limited diverse opinions of my members, unless I go out and I hire somebody.

That's one slice of life.

What I think we've all been aiming at with the Forum is to try and bring together the various slices that the industry views, the academic views, the clinicians views, and the agency's views, so that whatever comes out, and one function of this group would be tie into professional meetings and other meetings to have workshops where things do result in a report of some sort.

But for that report to reflect that collected wisdom of what you might call the

biomaterials community, not a piece of it, if each piece of it keeps throwing things at FDA, we still have the argument going on.

I think you want to limit the argument, if I can use that word, for the discussion, to something that presents something really cogent that everyone believes is almost like standards, except we're not trying to write standards here.

We're trying to develop approaches to things coming down the pike.

DR. LANGER: May I can also add to that in a slightly different way.

One of the things that I have heard, well before I was on this Committee, whenever you talk to people from industry, let's say, and they talk to the FDA, you almost get this kind of phrase: Well, we sat on one side of the table and the FDA sat on the other side of the table. In other words, not a lot of cooperation and a lot of friction.

I think if you look at even the process that got to this point, as well as, I

guess hope for the future, it's really -- and the question is, what's the right mechanism, but really it's getting them to sit on the same side of the table.

So if you look at actually the way this evolved, you see people like Ed Mueller, who is here from the FDA, working very closely with Bernie to try to put this together and other people, and academic.

So I guess what I saw as a very positive -- you know, sort of anything that's going to happen in the future, what I saw as very positive is, you really see all of these people who classically didn't work together, now working really very close together to try to build something that was different.

So it's hard to know exactly where it goes or what you do from here. I guess that's the intent. But, to me, it was sort of: How do you change that mentality to get people sitting on the same side of the table that classically never did.

DR. LIEBLER: I think, finally, that

one of the tasks is to write a letter to groups that we see is potentially interested, to try and find out if they really are, and if they are to what extent they are.

The end of that is quite simple: If nobody comes to our party, then we stop. If we don't get any kind of response from that that says people really care and really want to do this, then we go home, because I'm not going to build a ball park for players that may show up.

CHAIRMAN KIPNIS: Dr. Friedman.

DR. FRIEDMAN: You're not sure that if you build it they'll come.

(Laughter)

I was going to ask a question that sort of springs directly from what you just said. Granted, you've just defined what will cause this to stop.

I guess I would ask the other question at this moment, which is: Not today and not here, not now, but I think it would be very important to define how you will judge the success of this.

What are the criteria so that a year from now -- it's like setting up an experiment. You say, here's what I'm trying to prove, here's what I hope to see.

Because in the future, depending on resources and conflicting agendas and all sorts of other things, you'll have to ask the question: Has this effort -- and it will be an effort -- has this effort been sufficiently successful.

The way you define it, it's not post-hoc after you've already gathered the data, but you say, if we have so many hits on the network or if we have this or if we have that, you all think about what the proper characteristics of success will be, but spell those out now so that you can look back on this and say: Sure, if nobody submits anything, then you'll close it.

But I have a feeling people probably will submit, and then how will you judge if it's successful or not.

I think that's a hard thing to do, but

I think it's absolutely essential as you start this.

DR. LIEBLER: I think it's also fairly doable.

DR. FRIEDMAN: Oh, no, no. I'm sure it is. I'm just suggesting this is the right time to do it.

DR. LIEBLER: Without overstaying my time, I can give you some ideas, and we probably ought to do it at coffee break.

CHAIRMAN KIPNIS: Thank you very much, Dr. Liebler. I think what we will do is, obviously, discuss this amongst the Board members at some subsequent meeting. But we appreciate the efforts that have gone into this formulation. It is an issue that really deserves further comment and further discussion.

DR. LANGER: Do you need action from us to do anything or not?

CHAIRMAN KIPNIS: No.

DR. LANGER: Okay.

CHAIRMAN KIPNIS: Thank you very much.

We'll go on next to the Subcommittee Report on Toxicology. Dr. Setlow is chair of the Subcommittee.

SUBCOMMITTEE ON TOXICOLOGY REPORT

DR. SETLOW: I will introduce the report and Neil Wilcox will complete after my introduction.

The charge to this subcommittee was to develop strategies to encourage and monitor the progress of the development and the evolution of new toxicity testing methods with an initial emphasis on carcinogenesis testing.

When we met last year, it sort of got itself organized, and this year we had our second meeting on the 12th of February and covered a number of items.

[Overhead]

We are trying to get educated, in a sense, before we start, and so you can see that we started at various workshops.

We've heard from the Centers for Drugs, the Centers for Food Safety on what their assessment devices are and how they do it

and what their problems are.

We heard something from industry. Elkan was concerned about the makeup of the Committee, so we had to consider whether we should change that or not. It's approximately half industry, half academia, and then a sprinkling of others.

We had a lecture from Curt Harris of the National Cancer Institute on one of the things that many people are interested in, namely, the P-53 gene and how this relates to sensitivity and toxicology.

And then a general discussion as to what we should be doing in the future. So let me give you a clue as to the sorts of things that are going on. It starts with something that was introduced before, a home page.

We are fortunate enough to have a home page for the toxicology subcommittee, and many things of interest are on this home page. This was just the last one that came out on the 3rd of March, giving current information, and I put it up for two reasons.

The first is, there's the home page.

And, secondly: There's a list server for this Committee by dialing up this number, FDA.WWW.FDA.GOV. You can send a message to everyone on the Committee, and so the Committee, actually, is doing a lot of its work, not talking to one another but writing one another.

It's a free-floating form of information, and since our last meeting, this is the sort of volume of material that has appeared, giving individual members an opportunity to express their concerns that we're not going fast enough, we're going at the right speed.

Should we be speaking about alternative testing, and what do you mean by alternative? Maybe we should not use the word "alternative," because alternative means that we're doing things which are alternates to animals, and maybe we don't want to do that part.

So there's a lot of discussion back

and forth that's being done on paper, and it's certainly saves a lot of meeting time doing that and actually getting concrete ideas that you can read about it. You don't have to remember, for those of us with short-term memories. So I think the Subcommittee is moving along well,

Neil Wilcox will tell you what we're trying to accomplish in detail.

DR. WILCOX: Thanks, Dr. Setlow.

NEIL WILCOX

DR. WILCOX: I'd thought we'd take just a few minutes this morning to revisit the genesis of the Subcommittee on Toxicology and to kind of walk you through the broad picture, from the beginning, to a more focused picture as to where we are now, possibly where we're going into the future.

Some of the Board members will remember that in February of 1994, after approximately three years of meeting with the Centers in FDA, there was a rather broad recommendation made to the FDA and, in a

nutshell, the recommendation was that the FDA should reevaluate its approach to toxicology and specifically look at biomaterials and carcinogenicity testing.

As a result of that recommendation, there have been several initiatives and quite a bit of action over the last couple of years that have, I think, brought some pretty interesting results and are headed in a good direction.

They include the FDA Information Retrieval Systems, or FIRST. At our last Board meeting, Dr. O'Connor, Anita, reported on the progress of the FIRST and progress continues. We're working with the Information Technology people in FDA, and we continue to develop and hone the system so that it gives relevant information readily available to scientists across the agency from their laptop computers.

As we more specifically find out the needs in the different centers and the initiative continues to develop, we're pretty excited, quite frankly, on where that's headed.

It's the technology from developing the FIRST that we have the expertise in our office to develop this web site that Dr. Setlow alluded to.

One of the spin-offs from that has been marvelous, and that is, doing more with less. In other words, as the responsibilities in, quite frankly, the Office of Science has grown, we have been able to take advantage of this technology and distribute, if you will, materials via the Internet or, if it's on FIRST, it's via the Intranet, so that we no longer have to kill a few thousand trees to send pre-meeting packets to everybody.

Instead, we put it on the web site, send it E-mail, or list their message, and we tell everyone it's there, pull it off, and bring it if you want, and we've saved our office an unbelievable amount of time and resources in putting together and distributing packets of paper for meetings, not to mention the tremendous advantage of the continuing dialogue we have amongst the Committee members.

So we're moving into doing a similar thing from the first web site for agency-wide meetings that we hold on agency committees.

The Biomaterials Forum is another initiative that came out of the recommendations from the Board in 1994, and we heard from Bernie Liebler on that today.

And, finally, the FDA's Subcommittee on Toxicology, which was in the formative stages for several months and, finally, as Dr. Setlow mentioned, had its first organizational meeting in November of '96.

The Subcommittee on Tox at its November organizational meeting has put together a mission statement, a goal statement, has an objective statement. I'm going to show you a couple of this in a second.

But it's our first iteration, but I think still captures the substance that the Committee is trying to do. In the beginning, we are focusing on carcinogenicity.

The subcommittee was put together as a core group of approximately eight people, not

necessarily with specific expertise in carcinogenicity, but instead we're identifying areas that we need to explore and prioritizing them.

Carcinogenicity is first. Once a more focused direction is obtained by the Committee, I envision that one of the mechanisms that we may use is to, in turn, form a working group; a working group on carcinogenicity to start looking at specific tests and their merits for regulatory use.

Reproductive toxicology and neuro-toxicology are two other areas that we've identified as being at the top of the list of things to explore.

Again, this group isn't set out necessarily to get into the specifics of these areas but, instead, to bring people together to do that.

Looking at our first iteration of the draft mission statement, and if you noticed on the web site, it was one of the new icons that the Committee members can access in the web

site, and it's up there for them to send back their recommendations for changing the mission statement.

But, as it stands now, until our next iteration comes about, and I've put it up here to give you an idea of the direction in which we're headed by the current mission statement, first and foremost, is that we have a collaboration or we're forming a consortium between the public and private sector because no one entity or organization has the resources to do what needs to be done alone.

We need to bring together the players and stakeholders, if you will.

We have identified areas. The mission statement specifically, at this point, alludes to identifying areas which improve safety, the generation of safety data, promote methods, research and development that needs to be in place to generate these data.

What new data do we need and how do we generate it?

Encourage recognition and potential

use of emerging test methods.

Dr. Setlow alluded to alternatives. Alternatives in the context of replacing animals is fine but, more importantly, is in the context of methods to augment or be an adjunct to or, if possible, replace current standard methods that focus on more predictive mechanistic data.

That's are we move into we encourage the recognition and explore new methods, and we want these methods to incorporate mechanistically based tests that are more predictive of relevant end points.

What are the relevant end points? We need to identify them. Those are some of the things that need to be done.

Finally, to facilitate a cost-effective product testing model that benefits industry, regulatory and public health needs.

Real quickly: To look at the types of goals that we're thinking of that came out of our first session as we brainstormed this, goals include risk assessment, how do we

improve our current notion of risk assessment;

Promote acceptance to new methods;

Focus on research. What we mean here is directed research. Identify endpoints that need to be measured, and then focus research and develop methods that will generate data to measure these end points. That's kind of where we're going.

Long-term strategy is looking at method development, application, and data interpretation. Once we have these new methods, and they generate data that may specifically target end points that we feel -- "we," being the regulatory community and the private sector in research -- that we feel will give us data that are needed to assess safety, but how do we incorporate these data into regulatory decision-making when we're used to a whole different set of data that come from animal models, say.

That giant leap has to be made, and that's what we need to look at. These are long-term pictures. The good question asked by

Dr. Friedman, well, what are your success measures.

These long-term success measures are going to be methods that come down that are useful to the regulatory community.

What do we do in the interim? We're trying to look at short term, intermediate, and long term measurable objectives. At this point, we're calling some of the ideas or focal points for carcinogenicity. These would be more short-term goals or objectives, measurable outcomes if you will.

They would include looking at the current methods that are available;

Looking at what are the cancer assessment issues;

What does the Agency feel we need to look at that would give them help or assistance in moving forward in doing even a better job of carcinogenicity assessment;

What are the current relevant end points and the mechanisms related to those end points;

What are they now; and,

What are the end points that we would like to measure that we currently can't.

That comes under the rubric of identify knowledge gaps. We've heard Dr. Schwetz talk about knowledge gaps for some time now, and the birth of FIRST was, in the very beginning, an attempt to say, "Look, we have all these preclinical and clinical data," varying files, in rooms of paper, but we can't access them.

Let's develop an electronic retrieval system so that we can take tox data, clinical data, alert them, and explore what tox data were relevant and really answer the questions and did a good job, and what tox data did we look at, or preclinical data, that didn't, quite frankly, do the job, and we found out in clinical testing that the information was not good.

What are the information gaps and how do we fill them?

It comes under the category of

integrated preclinical, clinical and postmarketing data; research to improve methods for identifying the mode or mechanisms. These are all some of the things that we've thought about.

That's kind of in a nutshell of how we got started in this direction. I would invite anything to be added by Dr. Setlow or Dr. Blout or Dr. Schwetz, because they've been, obviously, active on this as well.

CHAIRMAN KIPNIS: Thank you very much.

DR. WILCOX: Any questions?

(No response.)

CHAIRMAN KIPNIS: If not, because we're beginning to run a little bit behind in our schedule, why don't we go on with the next report, on the senior biomedical research services by Dr. Kathy Zoon.

SENIOR BIOMEDICAL RESEARCH SERVICE (SBRS)

DR. ZOON: Good morning. First of all, I'd like to thank everyone for the opportunity to present this on the SBRS today.

It's actually some positive news, and I think that's always a good start to any Science Board meeting.

I've had the honor to be the chair of the SBRS Credentialling Board for the FDA and working with the Office of Personnel at FDA in order to establish and implement the SBRS for the FDA.

In the next 10 minutes, I would like to present to you where we are, what we've done, and what the purpose of this particular program is. I think from a personal perspective, it has been a wonderful opportunity for the FDA, I think, and will continue to be an opportunity for the FDA to attract the very best scientists.

What is the SBRS? That is the Senior Biomedical Research Service. This was established under the Federal Employees Pay Comparability Act. I'll call it FEPCA from now on.

Initially, this was established at 300 positions. That would be used for the

promotion of biomedical research and related activities.

Subsequently, there was the NIH Revitalization Act that was passed, and that number was increased to 500.

Now, this particular service is open to the very best candidates who are physicians, dentists, veterinarians, and Ph.D. levels. I believe that you will see, as I discuss this with you, it had a long gestation period in actually coming to fruition.

While the act was passed in 1990, it actually wasn't allowed to go forth until 1995. There were issues with OMB and various other things that I will not go into depth with, but it actually was able to be implemented in 1995.

The current participants in this program have been primarily the NIH, which is the largest, the FDA and the CDC.

There are other HHS agencies currently also taking place, which is the AHCHPR. This actually is a very small part of the program but has recently been included to take

participation.

Others are interested within HHS, such as SAMHSA, and decisions are still being implemented with respect to that.

The flexibility with this program really resides in the pay scale for these particular individuals, and it's clearly related to the merit of the individual, him or herself. I think this is very important.

We have the opportunity within this program for these experts to get paid between a Government Service level 15 through Executive Level 1, which is 148,400.

It is important to explain how you become eligible for consideration for the SBRS:

One must have a doctorate in a biomedical science. This program is geared toward biomedical research and/or clinical evaluation.

These individuals must be engaged in biomedical research or doing specific clinical product, research evaluation.

This would also cover behavioral

sciences and other epidemiology and other areas of science which are important across HHS. U.S. citizenship is not required for this particular program.

I think that's important because one can use this as a mechanism to bring in experts outside the U.S.

CHAIRMAN KIPNIS: May I ask the question: Do they have to be permanent residents, however?

DR. ZOON: As far as I know, no. They don't need permanent residency. No.

[Overhead]

There are two main categories in the SBRS that I'd like to take an opportunity to describe to you. These are the positions and the definitions currently being used by the FDA.

These definitions have been, in general, accepted by all three of the major organizations participating. That is, NIH, FDA, and CDC.

But within the broader definition, we

have specific criteria and definitional aspects that apply to each agency separately.

There is a Policy Board at the Department level, in which each of the agencies have representatives. There are two from FDA. It's myself and Bob Temple who represent us on the Policy Board at HHS level.

So the two categories of positions in the SBRS are biomedical research. These are individuals that are engaged in peer reviewed original research, and are considered by their peers to be outstanding in their work.

This is very important in both looking at the retention of scientists within the Agency as well as the recruitment of scientists into the Agency.

They must have a high productivity rate in terms of their accomplishments in science, in terms of their publication and stature, not only in number of publications but the quality of those publications and in the journals that those publications are presented.

Secondary criteria include: Major

prizes, visiting professorships, honorary degrees, et cetera;

Their membership on Committees, participation on Editorial Boards and other organizations.

[Overhead]

The second category is the clinical research evaluation. This includes individuals within the FDA in terms of our scope of the definition who are actively engaged in clinical and product research evaluation are considered by their peers outstanding experts in this area.

Again, there are a number of criteria:

Their effects on influence; on public health policy, on policy related to technical areas that have widespread use and leadership.

These have been viewed very important in the Committee that I serve as the chair on, and I will talk to you in addition to.

This has impacts not only at the domestic level but also at the international level.

What is the process that we use for the SBRS? HHS, while they present as a framework to all of the participating agencies, they really left it up to each of the agencies to develop their own process within the laws and guidances established by HHS.

FDA developed an SBRS policy document. All of you should have a packet that includes the FDA instructions and copies of all of these slides that will assist you, and if you have further interest in this, I'll be available at the break for any questions or later on during the course of the discussion.

The FDA, in developing this policy, looked at a variety of different opportunities to develop a system that we thought would retain and recruit the highest quality candidates in both categories of scientists that I have just described.

Input was sought throughout the various organizations within the FDA, at several opportunities during the development process, and I believe has created a system

that is sound.

We've not taken this, though, to the level where we think it's perfect. In fact, we've just recently met, as part of our own Policy Board, to fine tune some of the aspects of the SBR System and to make sure that it can be the very best it can, and we will continue to do that.

The SBRS is, as I said before, very flexible. The appointments are made in the accepted service. That means these are not competitive appointments, and no vacancy announcements are required.

However, I would say that, for recruitment, in particular, we have made special efforts to make sure that these recruits do go out and are advertised as vacancies. I think this is important to get the very best candidates into our organization.

Case documentation is prepared by the Centers, and I will describe a little bit more about the context of that.

[Overhead]

Being the chair of the SBRS Credential Committee, when we get an applicant in either for retention or for recruitment in these cases, I will work with the staff.

We have on our particular Committee, which I will describe to you, a Standing Committee, composed of people at the SBRS level or equivalent to.

We also have an Advisory Board to the Agency which we have established. This Advisory Board is made up of numerous members and experts and scientific disciplines that cover the FDA.

Many of our members have been on our Advisory Board, plus other scientists that we feel have the credentials and the stature in order to review these individuals for their expertise.

Once the package is received from each of the particular centers, the assignments are made.

We have a primary reviewer from the SBRS Board, and we have a secondary reviewer.

We then send it to one or more experts outside of our organization for their evaluation.

The primary reviewer of the candidate then collects all of the information, both his or her own assessment, as well as the others, and presents to the Credential Committee the evaluation of each of the candidates.

After that's performed, the Committee which needs to have a quorum there, needs to have a two-thirds majority in order to have the candidate approved to be credentialled.

If there are questions that come up during the review of that candidate will be deferred for additional information or other, as necessary, be included or not credentialled.

That candidate will then go to the FDA's Executive Resources Board for review. That's headed by Dr. Friedman, and that Committee establishes, finally, whether or not an SBRS slot will be recommended for that position and will decide finally on the pay level.

The Agency head, which is the

Commissioner of the FDA, now Mike Friedman would be acting in that position, would approve the position. The Commissioner is the only one who has the authority to actually put a candidate in that position.

[Overhead]

So where are we and where are we going?

As I mentioned, HHS has authorized 500 slots. Thus far, only a small fraction of those slots have been distributed to NIH, FDA and CDC, and I will give you the numbers. Actually, I probably should show you that now.

[Overhead]

These are the allocations currently distributed to the various participating agencies.

60 for NIH, 40 for CDC, 28 for FDA, and 2 for AHCPR.

Now, as I mentioned, there are a total of 500 slots. We have jointly worked together on a subcommittee to discuss the allocation of those slots, which I chair, and make a

recommendation to Joe Bufford at the Department, who chairs the HHS Policy Board for the SBRS, to distribute the remaining slots in accordance with this particular algorithm, which would be a total of 342 for NIH, 73 each for CDC, and 2 for AHCPR, and 10 in reserve as needed.

At this point in time, we are currently awaiting a response from HHS, and we do not have that as yet, and we will continue go pursue that and encourage them to distribute the remainder of those slots.

[Overhead]

So where is FDA right now?

Well, these slots for the SBRS are to be used ultimately in a 50-50 ratio of retention and recruitment. Like most of the agencies, the first wave of activities were for the retention of our scientists that are currently there.

All the agencies anticipate and will meet the 50-50 ratio by the time they get to their allotment of slots.

FDA's current allotment, as I mentioned, is 28 slots. We have 18 individuals currently appointed in the SBRS. Of those, we now have two recruitments as of yesterday and 17 retentions.

We now have 9 that have been credentialled and are waiting appointment.

We anticipate the bulk of the remaining appointment to really come from the recruitment area. Other individuals that have the appropriate credentials from within the Agency will be presented as candidates and will be considered by the Board, but I think the major influx of those candidates has been with the beginning of the program.

[Overhead]

Some of the activities going on and some of the question remaining is what actually defines recruitment.

Because the Act was passed in 1990 and took so long to get up and running, which I mentioned was 1995, many people were recruited both to the CDC, NIH, and FDA with the

intention that this program was going to get up and running far sooner than it did.

So one of the issues that we are discussing with the Department is what is the date that recruitment actually starts. Some recommendations were being made anywhere from 1992, onward, and we will just have to wait and see what the Department decides.

The other issue is a revision of the definition of recruitment.

NIH particularly would like to use their staff fellows, their tenure track staff fellows, which would be the equivalent to our conversion track staff fellows as a way to get the very best sciences to the SBRS and then be brought into the program as a recruitment.

That is currently still under consideration at the department.

So, at this point in time, I would like to stop. I think that this program has been very positive for our scientists here at FDA in terms of both the retention and the opportunity to recruit.

This process has been an open process. It will continue to be so, and we look for your suggestions, recommendations, comments, and its further implementation.

Thank you.

CHAIRMAN KIPNIS: Thank you very much. Are there any comments from members of the Science Board?

DR. WONG-STAAL: Couple questions.

Does HHS also provide resources for the recruitment packages?

DR. ZOON: No. It's done by the individual agency.

DR. WONG-STAAL: And, also, is there a distribution of the slots to different centers?

DR. ZOON: Yes, actually. Do we have a copy of that, Pat?

DR. WONG-STAAL: It's probably in the packet.

DR. ZOON: Yes, I think it is in your package, but I do have that information here. I can give you that. Just one second. I have those numbers.

Right now, there are -- would you like credentialled or appointed, or both?

DR. WONG-STAAL: What is the process? I mean, is each Center given a quota?

DR. ZOON: No. It's based on the candidate --

DR. WONG-STAAL: The most qualified candidate?

DR. ZOON: Yes.

DR. WONG-STAAL: Okay.

DR. ZOON: So, actually, those candidates who meet the qualifications are looked at as individuals. Currently, the appointees are as follows:

Four for CDRH; two for CFSAN; zero for CVM; three for CDER; five for CBER, and five for NCTR.

DR. WONG-STAAL: Thank you.

CHAIRMAN KIPNIS: Dr. Langer?

DR. LANGER: Yes. I just want to get an idea of the breadth or narrowness of the earned doctorate in biomedical science. Would that, for example, include pharmacy, include

engineering? Or what would it not include?

DR. ZOON: Yes. It would include engineers. It could include pharmacists if they were involved in clinical and product research evaluation. Yes.

I think we're clearly targeted to the biomedical sciences, but can include engineering in its sense over the scope of what we do here at FDA, and we've defined it in the broadest scope.

CHAIRMAN KIPNIS: Dr. Benet.

DR. BENET: Kathy, would you differentiate; where in the administrative structure do people stop being eligible for this? I mean, are Center directors eligible for this also?

DR. ZOON: Yes.

DR. BENET: So it's everyone within the Agency?

DR. ZOON: That's correct. That's correct. You can be an individual scientist just doing bench research and have no administrative or management responsibilities

or you can be a Center director. It really depends on the qualifications of the candidate.

CHAIRMAN KIPNIS: Any other comments?

(No response.)

CHAIRMAN KIPNIS: If not, thank you very, very much, Dr. Zoon.

SUBCOMMITTEE ON FDA RESEARCH

REPORT AND DISCUSSION

CHAIRMAN KIPNIS: We'd like to now go on to what is the major element for the Science Board's consideration today. I'd like to make just a few general comments.

One is that ever since the formation of the Science Board, issues of major concern which were enunciated very early and particularly supported by Dr. Blout was the effort to evaluate and improve the quality as well as spectrum of science in the FDA.

Every presentation made to us from the most senior official, that is, the Commissioner of the FDA, to every Center director and every other administratively responsible person, always introduce the comments to the FDA by

saying this is a science-based regulatory agency.

Implicit in those comments was the importance of science, presumably reflecting both legislative fiat as well as executive recognition of the importance of science quality.

A major effort of this Committee, with the assistance of Dr. Blout has been to evaluate and to encourage any activity which would improve both the quality, the capacity to retain high-quality scientists within the system and recruit high-quality scientists to the system and to, in essence, emphasize the critical importance of science within the agency keeping up with the extraordinary advances of sciences from a broad spectrum of input relevant to the Agency's review and responsibility.

The subcommittee that was formed and given its charge by Dr. Friedman, the Lead Commissioner, which I've never known whether it's the Led Commissioner or the Lead

Commissioner --

(Laughter)

DR. FRIEDMAN: Led. Led.

CHAIRMAN KIPNIS: -- was clearly defined in terms of asking an extraordinarily distinguished group of people to give consideration to the organizational structure, budgetary considerations, the spectrum of science, and how the administration of that science could be more effective in terms of the quality of the product, as well as the impact it has on regulatory decisions.

I'd have to say that that Committee has done really an extraordinary job. It reflected a broad spectrum of input by individuals with considerable governmental experience, academic experience, and industrial experience.

Dr. Korn has done a remarkable job. Knowing the individuals involved, one is dealing with a highly educated, highly sophisticated, highly individualistic group of individuals and to be able to come up in a

finite period of time with a cohesive document, I think is a major accomplishment of leadership.

Of course, I may make an aside, having been dean at Stanford is an excellent precursor training program to accomplish that goal. That may reflect academic competition but it's also a reality. Being a dean at a major teaching medical institution today is great training for how you, in essence, get coagulation of such individual talents into a report.

So we welcome Dr. Korn to present the report to the FDA Science Committee.

DR. KORN: Thank you. Thank you very much, David.

I don't have any slides, so if you don't mind I'll do it from here.

I know that the draft document has been distributed to the members of the Science Board but I am also cognizant of the fact that this is an open meeting and that there are many people in this room who have not seen the documents, so in presenting this report, I'm

going to deal in some detail with at least portions of the document.

The introductory comments that I was going to make have been made elegantly by Dr. David Kipnis. Thank you.

I once heard an interesting definition of a faculty member, which I've always remembered. It is: "A faculty member is someone who things otherwise."

(Laughter)

The Committee that was put together, as Dr. Kipnis has noted, is really an incredibly distinguished and diverse group of individuals, but every one of them is a fiercely independent thinker, and we did, as Dick Setlow indicated, previously, with the group on toxicology, conduct a very large amount of our business through the Internet, through E-mail.

E-mail has a wonderful characteristic. Conversation, I think, is often a reflection of ego modified by super ego. E-mail is ego heavily influenced by it.

(Laughter)

One of the advantages of that is you get to the point pretty quickly. And when people don't agree with something, you don't have to beat around the bush a lot to find out about it.

In any event, we were charged about a year ago with a fairly elaborate set of tasks that are in the report in Attachment D. The roster of the Committee is Attachment A.

In dealing with this task, the subcommittee interpreted its mission very much as Dr. Kipnis has summarized. Namely, how can this agency's regulatory review and decision-making processes continue to be informed at a time of remarkably rapid scientific advancement by the very best and most up to date scientific information available.

The report outlines how the Committee set about its task.

I wish to emphasize one feature of that process, and that was, under a strict pledge of confidentiality, we solicited and put

from everybody at the FDA, and we received about 100 letters from staff across all of the centers and functions which, as a rule, I would say, as a whole, was very, very thoughtful, carefully presented, and all demonstrated a deep passionate commitment to this Agency and a concern for its well being.

The Committee read those letters carefully and paid them close heed.

Now, to the business at hand:

From the very beginnings of this Agency, that is, in its predecessor forms intramural research, scientific research, has always been a feature of the regulatory activities of this agency in accord with its commitment to the principal of science-based regulation.

In Appendix D, there's a kind of a brief summary of some of that history which I was able to develop with the invaluable help of Susan Homire, who has been an invaluable executive administrator, if you will of this process, and the archive service of the Bureau.

But back in 1996, an organization called the Bureau of Chemistry and Department of Agriculture was set up, one of its earliest actions was to create a dedicated food research laboratory.

Now, of course, much of this activity at that time was the safety and purity of foodstuffs so they set up a dedicated food research laboratory and, in addition, encouraged its field analytical laboratories, to mount active research programs and analytical methodologies and to publish the findings of their work, both to enhance the quality of the regulatory program and to advance the state of knowledge of the discipline.

The group discussed at length the role of science in the agency in these times. In these times of scientific advancements and in these times of budgetary stress and to firms unanimously that high quality programs of intramural scientific research are essential components of the FDA science base and are

critical for supporting in a scientifically sound and rigorous fashion the regulatory decisions made by the agency in discharging its mission to promote and protect the public health.

The intimate proximity and interaction of cutting-edge scientific research with review and regulatory activity is probably more important today than ever before given the pace of advancements in all of the foundational scientific disciplines, biomedicine, material science, microelectronics, information technology, and others.

Moreover, these scientific accomplishments are intimately coupled, more than ever before, with equally rapid translation into new and complex materials and technologies for diagnosing, treating, and preventing disease, and promoting health.

We believe that a strong and well managed intramural research program programs the foundation for creating a climate of science and a climate of scientific

communication within the FDA that enhances the ability of the agency to recruit and retain high quality scientific staff to address existing regulatory issues and anticipate future problems and to keep pace with rapidly emerging complex, cutting-edge technology, and respond in a timely, flexible, and competent manner, to new initiatives and regulatory needs.

We think research-based, internal expertise enhances the agency's ability to seek out and critically evaluate external scientific input and it creates a platform from which Agency staff can productively interact with external scientific expertise and especially that from within the regulated industry as respected, knowledgeable, and impartial colleagues.

We considered and debated fairly intensely whether or not the majority of the scientific research needs of the agency might be met in some new scheme from extramural sources in a more cost-effective or efficient

manner that would meet criteria of timeliness, competence, and freedom from conflict of interest, a very, very important consideration, obviously, and decided that that was not a viable argument or a viable approach for the agency.

Now, what about the current state of affairs? The Subcommittee believes that the Food and Drug Administration presently lacks a culture of science and a culture of scientific communication.

That is, an environment that promotes scientific discourse and interchange and makes scientists feel that they are integral and respected members of the agency staff.

Such a culture is essential for nurturing high-quality cutting-edge science.

The existing intramural scientific research programs across the centers are inconsistent in quality and mission relevance, and science management practices are generally poor.

The quality of electronic information

technology in the FDA is uneven, which hinders both intra-agency and extra-agency communication within and among the scientific community.

The extent of scientific communication and the sharing of data and human as well as physical resources within and between centers and with extramural scientists, both in government, academia, and industry, are generally inadequate.

This leads to an inefficient use of resources, duplication of efforts and expertise, and a serious sense of frustration among the scientists and especially, and most worrisome, among the cohort of younger scientists who still retain, I might tell you, a deep passion and enthusiasm for this Agency, which must not be further trammeled.

The Committee believes that the excessive compartmentalization of the Agency is presently structured with relatively autonomously operating centers, is not supportive of first class science and impedes

the creation of a sound environment for science by fostering bureaucracy, internal politics, duplication of effort, and obstruction of communication and of efficient use and sharing of resources.

This organizational structure has not promoted uniformly high-quality science and impedes the implementation of agency-wide policies and procedures necessary to support a consistently high standard of mission-related scientific accomplishment.

In this time of rapidly evolving knowledge and technology, there is a demand for a nimble, responsive organization. Nimble and responsive.

The Agency as presently structured does not meet this criterion.

The decreasing Agency budget is of overarching concern. There is general awareness and, in fact, appreciation of the fact that in times of constrained resources, the Agency must take particular care that its mandated regulated responsibilities are competently

discharged, yet, there is a widely held perception among agency scientists that the research programs do not have strong advocacy at the highest levels of Agency leadership and are, therefore, frontline targets for curtailment or elimination as discretionary resources decline.

The group believes strongly that starving the Agency's base of intramural, scientific expertise, must inevitably, inevitably compromise the quality of review and regulatory activity.

Moreover, times of budgetary constraint demand an even higher quality of scientific management to assure that limited resources are invested in scientific themes of the highest priority and not dribbled across centers and programs in inadequate amounts that only leads to waste, inefficiency and high opportunity costs.

Finally, the Committee recognizes that the FDA cannot possibly encompass internally expertise in all areas of relevant science at a

time of such rapid advancements in science and technology. Moreover, it is illogical to attempt to maintain a large research organization in anticipation of all major issues that may arise.

Consequently, there is a need for the Agency to be creative in supplementing its intramural capabilities with new approaches to interchange with external sources of scientific expertise.

We did not believe, do not believe, that the Agency is currently making the best possible use of such external scientific resources.

Now, I will get to the recommendations.

In thinking about how one might suggest and approach to correcting the deficiencies described in the previous section of the report, the subcommittee was sensitive to the complexity of the Agency's organization and mission and also cognizant of the Agency's dilemma in confronting a continually increasing

burden of challenging regulatory tasks with a budget that is not only constrained but has actually been decreasing in real terms in recent years.

We tried to find an approach that we thought could address the identified problems and significantly improve the environment for science with the least disruption of the Agency's formal organizational structure.

And, although we made no attempt to obtain a cost analysis of the proposal that I'll present momentarily, we did believe that proposed consolidation of management and upgrading of performance of scientific intramural scientific programs, can lead to budget savings from improved deficiencies and from the elimination of existing duplicative center functions and substandard research.

If the Agency, If the Agency were working with an adequate budget base, we believe that the proposals we make could be implemented to a very large extent through a reallocation of existing agency resources.

But, given the reality of an inadequate budget base, incremental funds will likely be necessary.

The approach chosen by the Committee calls for the establishment of a virtual science center, a virtual science center, which I think is appropriate, since we are essentially a virtual committee, to be responsible for the management, coordination, and oversight of all scientific research activities of the Agency.

This "Center", in quotes, would be headed by a newly-appointed chief scientist of the Food and Drug Administration who would be situated within the Office of the Deputy Commissioner for Operations of the FDA.

This proposal is intended to create an Office of the Deputy Commissioner of Operations that would be shared by the Deputy Commissioner and the Chief scientist of the Agency as collegial partners.

The recommendation is deliberate and it's meant to send to FDA and departmental

administration, as well as the intramural and extramural scientific communities, an unambiguous signal of the importance of this high-level administrative positioning to the subcommittee's intent.

The subcommittee believes that the implementation of such a virtual science center can effectuate the desire changes and the scientific climate and create a new scientific ethos by establishing a true community of scientists and of scientific resources across the Agency that, although transparent to Center barriers, will be accessible to all Centers in support of their regulatory responsibilities.

Now, clearly, the success of this proposal rests squarely on the stature and credentials of the person selected to fill the position of chief scientist.

The Committee believes that the appointee must be an outstanding scientist of high national standing to be recruited by an open, competitive national search that actively seeks out candidates from academe, industry,

and government.

Appointee must have exceptional scientific leadership abilities and demonstrated management skills with the vision and capacity to create an intramural scientific enterprise of consistently high quality, respected by and interactive with the external scientific community, and committed to providing dependable, timely, and effective support of the Agency's mission.

The responsibility of the chief scientist is to create a nimble, responsive organization that consistently brings the best possible science to bear on regulatory review and decision making.

The person will be an advocate for science and research at the highest level within the FDA and by delegation from the Commissioner represent FDA in the highest councils of science in the federal government.

The chief scientist will be responsible for developing and implementing policies and procedures to ensure the highest

quality of FDA science in support of the Agency's mission by fostering the cooperative participation of research personnel with review staff and regulatory decision-making and by integrating regulatory review and scientific research staff and functions to the maximum extent possible.

The chief scientists will facilitate and foster scientific communication and cooperation at all levels within and between FDA centers and make special efforts to nuture and improve communication and interaction with the external scientific community.

The chief scientist will be accountable for the consistently high quality of research across the agency through establishing and implementing agency-wide standards, policies, and procedures for recruitment, conversion, and promotion of scientific research personnel, regular external peer review of scientists and scientific research programs, and regular assessment of the management of research in the FDA centers.

Now, for some specific thoughts about implementing this recommendation, let me turn to a few specifics.

One is the chief scientist would oversee recruitment of all scientific research personnel in consultation with the Center directors and, to this end, will establish agency-wide policies and procedures for recruitment by a process that's openly advertised nationwide and scope and competitive for all permanent appointments.

The chief scientist must authorize recruitment and hiring of all scientific research personnel and ensure the commitments of time and resources made as incentives for recruitment are honored.

The chief scientist will establish and monitor mechanisms that ensure that each research scientist regularly participates in reviews and/or serves as a consultant on regulatory and review issues.

We think it's very important. This is not a proposal to establishment and enclave of

science divorced from the day to day regulatory mission and responsibilities of the Agency and am important task of this chief scientist person will be to assure that there is a close, ongoing relationship and interaction and contribution of the science with these regulatory processes.

It's also important for the chief scientist to foster the professional development of research scientists by a variety of mechanisms, including, when appropriate, collaborative programs of education and research with the external scientific community.

I would make a comment about this objective, and that is, while we certainly recognize that scrupulous avoidance of conflict of interest is essential to the integrity of the FDA, some of us at least on the subcommittee are concerned that current interpretations of conflict of interest regulations and policies impede important collaborative interactions between Agency

scientists and colleagues and industry and academia to the detriment of the Agency.

And scientists who cannot adequately communicate with one another are like plants that have neither light nor water. They die.

And this is a very serious issue that -- now, clearly, one is not about to overturn the conflict of interest statutes and regulations of the federal government but there's got to be some attention paid here to find ways within those limits and boundaries to enhance the dialogue between the intramural and extramural scientific communities.

With respect to promotions, the chief scientist will establish, implement, and improve policies and procedures for promotion of all scientific research personnel;

Will approve promotions upon recommendation of a Committee of inter-center and external scientists with endorsement by the Center director.

The chief scientist will participate in regular periodic review of Center directors,

in conjunction with the Commissioner and the Deputy Commissioner for Operations.

The point of this is to make clear that nurturing a climate of science that conforms to Agency policy, procedures, and missions, is the responsibility of every Center director and should be an element in his or her performance evaluation.

Now, of particular importance, we believe that the chief scientist, in consultation with the Deputy Commissioner for Operations and the Center directors, should develop and FDA science and research plan that represents the thinking of the Agency and will provide a mechanism for prioritizing and accomplishing the research needs of the Agency.

The chief scientist, in consultation with the Center directors, is responsible for the conduct of all scientific research program reviews to ensure conformity with Agency-wide policies and procedures, as well as their quality and relatedness to Agency mission.

Such program reviews should take place

at regular intervals and review teams should be composed of intramural researches and reviewers as well as extramural experts.

The chief scientist, in consultation with the Center director, is responsible for ensuring follow-up of program review committee's recommendations.

I want to make reference to one other recommendation in this portion of the report, which I think is important, particularly important.

That is, the chief scientist, in consultation with the Center directors will be responsible for the initiation, continuation, termination, translocation, or consolidation of all scientific research programs within and across Centers, as well as the outsourcing of research programs to extramural research organizations, that is, an authority for make by decisions, where appropriate.

To this end, the chief scientists will determine, in consultation with the Center directors, whether any proposed new scientific

research program should be located intramurally or extramurally and, if intramurally, where, in which Center?

Now, to try to manage this rather daunting task of expectations, the Subcommittee believes that the chief scientist must have broad budgetary oversight authority to empower the position. And, therefore, we recommend that the chief scientist have oversight of the entire scientific research budget of the Agency.

That is, the Centers retain primary responsibility for developing budgets, their budgets, but budget planning and development must involve active participation by working scientists, both researchers and reviewers.

Prior to submitting their proposed budgets to the Commissioner, Center directors must review them with the chief scientist who will have approval authority for all scientific research programs.

This review will focus on quality, mission relatedness, duplication, or redundancy

with other intramural programs, and whether the programmatic objectives could be better met elsewhere in the Agency or extramurally.

There's a brief concluding statement with the report, and I just want to touch on the last piece of it and repeat a comment that I made a short while ago.

The Subcommittee respects the complexity of the Agency and the severe difficulties it faces at a time of increasing demand, regulatory demand, and tightly constrained budgets.

In such times, it is tempting to adopt the seemingly straightforward response of putting more and more resources into review and regulatory activity and progressively diminishing support for intramural scientific research, but at a time of unprecedented advancements in science and technology and in equally unprecedented rapidity at which those advancements are being translated into new medical products that were imaginable a short time ago, the dependence of the Agency on the

very best contemporary science to inform its regulatory activities and decisions is also without precedent.

Accordingly, starvation of the base of intramural research, of intramural scientific expertise, will inevitably compromise the quality of regulatory performance.

The presence in the Agency of a robust high, quality program of scientific research provides the essential foundation for sound regulatory policy and performance and ensures that the Agency will continue to be well positioned to carry out its statutory responsibilities to protect, promote, and enhance the health of the American public.

Sound public policy demands no less.

Thank you, Mr. Chairman.

CHAIRMAN KIPNIS: Dr. Korn, that was a superb report, and I'm sure the Committee is very appreciative of your efforts.

Two members of that Subcommittee are in attendance today, Dr. Robert Langer an Dr. Flossie Wong-Staal, and I wonder if they

had any comments they would like to add to Dr. Korn's presentation before we open the report to the discussion by the Science Committee.

DR. WONG-STAAL: No. I think the report really distills all of our discussions and consensuses, recommendations.

CHAIRMAN KIPNIS: Thank you.

DR. LANGER: I second that. I think a lot of time was spent on it, and I think it covers everything that was discussed quite well.

CHAIRMAN KIPNIS: I would like to open, then, this discussion for the time being for general discussions by the Science Committee, after which we will probably break for lunch and then return to continue discussions and invite public comments at that time, as well as other discussion.

Other members of the Committee?

DR. HEARN: Thank you very much, Dr. Korn. I enjoyed very much reading the report.

I was also interested in the Appendix

that gave the historical perspective and, as you pointed out, the need for scientific leadership at the FDA has been recognized at the FDA for some time. I was interested in the last sentence of the Appendix in which you tried to explain why in the past the recommendations, although they were enthusiastically embraced, were never implemented.

I wonder, you mentioned that you had not, the subcommittee did not cost out this proposal, but you said that you expected that it would require some incremental funding.

I guess what I'm trying to get is is how optimistic should we be that this will be implemented at this time? And do you have a sense of the ball park in terms of the incremental funds? Even though you didn't do the analysis, do you have some idea?

As Elkan pointed out earlier, I've been on the Committee for quite a long time, and I think that we very much would agree, if all of us had been participating in the

subcommittee, we would have come to the same conclusion, so I think we, at least speaking for myself, I'm enthusiastic about the directions that you are recommending, but I'm wondering whether there's something different now that should give us more optimism?

DR. KORN: Ruby, you've put your finger on it very accurately.

I have to tell you that, if we'd had the history before we started --

(Laughter)

-- I'm not sure that the Committee would have had the enthusiasm in putting in the amount of effort and thought that they did. We have not costed it.

We didn't have a way of costing it within the purview of our deliberations, but we do have a sense that there are opportunities of consolidating activities and functions that are now distributed quite widely around the Agency and in all the Centers that could lead to some reallocation of resources and creating this new function.

And we don't call for the creation of a new bureaucracy. I mean, this is supposed to be a lean office that is essentially an integrater or a matrix organization, if you will, rather than some new castle arising on the horizon.

On the other hand, it's very hard to read the newspapers or read science magazines, News and Commentaries sections. The item that was in the magazine probably a month or so ago, about some issues around the PDUFA fees and the threat that that might pose to the CBER group, in particular, without feeling that some strong advocacy and some battling within the administration and the Congress is going to be necessary to mitigate that problem and give this a chance of succeeding.

I mean, we all recognize that the Agency cannot turn its back on mandatory-required activities and say, no, we don't choose to do that because we choose to do something else.

On the other hand, we think that the

objective is important enough that it's worth a fight, but I don't know what the odds are on winning that fight, and that's an honest answer.

CHAIRMAN KIPNIS: Other comments?

Dr. Benet?

DR. BENET: I also enjoyed the report and agree with it. My problem, Dr. Korn, is I was trying to think if I could think of a scientist that would want to take this job.

(Laughter)

Because what you outlined is no science. I mean, this is an administrator dealing with lots of regulatory, trying to get people to work together.

Is there such a person that's going to do this?

Do you think, realistically -- do you envision this chief scientist continuing science? Is he going to have his own laboratory?

DR. KORN: Not necessarily. But, I mean, I think I'm not in this field, as I told

the Subcommittee at our very first meeting.

As a previous investigative pathologist, have never done drugs, so I've had no dealings with the FDA.

There were people, I know, for example, who had come up to industry, who are extraordinarily respected for their ability as managers, a very respectable, very robust scientific programs.

It's a matter of taste. It's a matter of skill and understanding, where the opportunities are and where the talent is, and having the right network so that you can get the best advice you can bring to bear on a problem.

I think that's what building strong scientific organizations require anyway. Most builders are not, themselves, spending a lot of time working in the lab.

CHAIRMAN KIPNIS: I'd like to address the issue that Dr. Benet brought up, in good part, in academia. The problems of many of the major centers has been that for decades people

in the scientific academe have looked down their nose at administrators, only to find that by the time you get to the 2nd and 3rd generation of such devised administrators, you have very parochial views that have impaired the further development of academia.

Now, these are critically important positions, and there are many major directors of major pharmaceutical firms who have had outstanding scientific careers.

Like Roy Vagulo (ph) says, an example of an individual, there are others; George Hitchings, another classic example. But there are also people in academia that have reached the stage of career where they also would like to have an imposition and be able to impress or alter how activities are going on.

There are research centers, institutes; there are a host of people, which means that search committees have to broaden the population they look at for potential attraction to this position, but I think that can be done.

Indeed, there are former deans --

(Laughter)

-- who have done this. By the way, I must point out, David and I have known one another for a long time, and it must have been 20 years ago when he visited as a consultant to Washington University.

I introduced him to my wife at dinner, and she asked him, "What were you before you were dean?" And his response was, "Happy."

(Laughter)

She remembered that, and I brought it to his attention just recently. That was a very distinguished career as an experimental pathologist with a major impact in the evolution and development of institution. So I think that's very important.

I might also address the word "history". The word "baggage" came up earlier in the course, and history is a baggage. Let me express myself in very candid terms.

We have had before this committee major administrators in the FDA who were

unsympathetic to having young investigators go to scientific meetings and would bring up the issue of conflict of interest because the scientific meeting happened to take contributions from industry. I don't know what scientific meetings don't nowadays take that.

There is every trick of the trade that a good administrator and bureaucrat can use to blunt the acceptance of anything. We see that at medical schools, we see that in teaching hospitals.

So I do think that's a baggage that has to be done. That means that the directorship of instituting this kind of activity has to be very strong, has to have a clear view of where he or she is going but, at the same time, has to have a cogent sense of reality that sensitivities inevitably have to be used, but that should not, in essence, divert it.

The Committee has done a fabulous job, I think, in formulating a number of elements that I personally find attractive, and I'd like

to eventually hear public comment on them as well as those from Dr. Friedman and Dr. Blout.

One is the issue of culture. Culture in the FDA presented to this group over the last three years has been a mixture. There are those who are outstanding scientists who feel frustrated and yet are devoted to the regulatory responsibilities of this agency and also to quality science.

Those are people that deserve support. Usually many of them are senior who would like to have a broader involvement, and I think they have to be selected out.

But it addresses the issue of culture. There is a culture in this agency that will use every trick to sustain the status quo. They will use legal terminology.

If you remember our introduction to conflict of interest, I asked the question of the HHS lawyer: "Is conflict of interest defined exclusively in financial terms?" His response was no.

I then said: "Well, let me give you

two hypothetical questions. One is a new genetically-designed see is presented for review.

The official responsible for final action has a spouse that is an organic farmer, an editor of an organic magazine, generates substantial income.

By the way, I kept this gender neutral. I used the word "spouse." Will that official recuse himself or herself from reviewing that product because of conflict of interest?

If you remember the legal response was, "I'm not prepared to answer that question."

The second question was: "If a drug has an adverse reaction, which has political implications, or some other toxic activity, but is clearly defined for use for a different purpose and so specified in labeling.

The official reviewing that has a spouse who is a major individual in pro-life considerations, lectures extensively and,

indeed, is paid for presentation.

Will that individual recuse himself or herself from final review processes? The legal response, you may remember was, I'm not prepared to answer that question. The only thing he was prepared to answer was whether we could take a donut and coffee for less than 12 bucks on a video.

That's what bothers me because there is that context. It's not that conflict of interest is not an important issue, we face that daily in our lives. And in every instance, you may recall, we've always said, public disclosure, honest disclosure, is absolutely right, and some people will say, there's a conflict of interest, others will not, but at least it's publicly disclosed and intelligent people should comment.

I would suggest that one of the impediments to the introduction of this is not that this recommendation, these recommendations, don't really have major, valid considerations, but that it could be lost in

bureaucratic apathy.

I would like, somehow or other, for this report to be not only supported well but enthusiastically supported and disseminated in a fashion which hopefully will, in essence, catch the eyes of many involved in basically formulating policy.

The other aspect of this report that I found very gratifying was the recognition that science and technology is a critical element in decision-making and that those who make decisions don't have the discretion to use science at their will or at their desire but must use science in making decisions, and then acknowledge if decisions are made which are contrary to science, that they so be notified and that there are political expedients as to why a decision is made.

I would wager, in many instances, the political decision won't be made, but it is up to the FDA to involve. It's not that it's the only consideration, but it's a very important one.

The last comment would be that I really appreciated in that report the issue of nurturing. That is, not only nurturing top-notch science but top-notch regulators. It takes years to develop the kinds of skills needed to make complex decisions such as the regulators and the FDA have to make.

It is not easy. They meet all sorts of pressures, from external sources as well as internal sources.

So that nurturing an inquisitive mind, the essential of science, is critically important.

So I've had my say, which makes me feel better, too.

But I would like now to recognize that this discussion is now open for public involvement. I would like, at some point, toward the conclusion, to call upon both Dr. Friedman and Dr. Blout to comment, but maybe we could open up, until lunch hear, discussions from the public, who ever wishes to make the comment.

DR. HEARN: David, while they're getting their hands up, I would like to ask you a question, because it seems to me I opened by looking at the issue of the extent to which funding is an impediment, and you've introduced another set of issues independent of funding.

If they are severe as you're saying, it seems to me that needs to be incorporated here in some way because the implications are very different in terms of what needs to be done.

If it turns out the incremental funding is not that much and easily retrieved from some of the activities that Dr. Korn suggested, then that's not an issue.

It may have been an issue in the past but it's not an issue, and more the environment and the lack of motivation to move ahead might be the issue, and there are different strategies that you'd use to overcome that.

So it's important to understand what the impediments are.

CHAIRMAN KIPNIS: Doctor, my response

is, I think we should, but I don't think that's the responsibility of the Subcommittee's report. I think that's the responsibility of the Science Committee after they've voted to or not to accept the report of the Subcommittee, but then how do we then use that report in an affirmative, effective way.

Not in a pejorative manner, but in an effective way to not allow what has been past history to recur or at least discourage the recurrence of past history.

Would the rest of the Board members agree?

Suppose I start on my right. Please use the microphones to identify yourselves.

PUBLIC COMMENTS

MR. SHERMAN: My name is Glen Sherman. I'm in the Div of Antiviral Drug Products in CDER.

One of the things, since I've been working at FDA, I notice there's two different kinds of models of research. In the Center of Drugs, it's very much a review process where

laboratory is de-emphasized, and in Biologics it's very much research oriented.

I have good friends in Biologics who are spending a great deal of time at the lab bench, and reviews are kind of integrated into the process, whereas my colleagues in Drugs, basically spend almost full time at the computer screen doing reviews.

I'm just kind of curious as to what is considered the best model for a reviewer. What should an FDA reviewer consider as the most appropriate use of time? Is it a mix of these two?

How does one bridge the gap between these two different models? Is there a middle ground that one can achieve?

This is a great debate within the FDA. It's either you're on one side of the fence or the other. Some people think that FDA shouldn't be doing research at all, and others think that, well, we should just be doing research and no review.

I'd just like to have comments of

perhaps Dr. Korn or others regarding this.

CHAIRMAN KIPNIS: Dr. Korn, Dr. Langer, Dr. Flossie.

DR. WONG-STAAL: I think that this is an issue we discussed extensively, too, and I think the overall view is that there should be a balance but integrated between basic type of research and research relating to the regulatory process more directly.

The balance doesn't necessarily have to be on the individual level, it's really at the Agency level that there should be balance. But there also should be communication and integration so that the reviewers can also take advantage of the researchers in terms of information and expertise and so on.

DR. KORN: I think that we did, as Dr. Wong-Staal has said, struggle with that one, because we were aware that there were some rather polar extremes in how this matter is currently being handled.

I think there are some reality tests that have to be put on any answer, and it may

be that having an entire agency replete with mixed research scientists/reviewers, is simply a physically and financially delusory concept.

It may be that having different kinds of integration across the different pieces of the Agency would be a best way of accomplishing the balance, or it might turn out that more of the scientific investment should go into research scientists who spend a serious amount of their time doing science and are available as a team of expertise for interaction with reviewers across an appropriate range of problems that fall within that resource scientist's knowledge and capability.

But we didn't try to write a prescription of one size fits all from the information available to us.

MR. WILSON: Thank you. I'm Jim Wilson. I'm with Resources For the Future, which is a think tank here in Washington.

Let me say that I am here to indulge my interest in this topic of how research is organized and managed and not just speak on

behalf of RFF, which is an independent, not for profit, non-ideological, and broadly supported, non-opinionated, organization.

(Laughter)

What I would like to do is ask your indulgence to share with you a couple of experiences from my time at the Monsanto Company.

About 20 years ago, I managed a process much like this Committee report in which we reviewed the organization and structure of research with Monsanto.

We came up with a number of generalizations, which I think are as true now as they were then that support the findings and conclusions of this Committee.

One of them is that, from the management perspective, if there's information that is necessary to the functioning of the organization and can be generated by research and it can't be obtained less expensively someplace else, that that organization should conduct, should carry out and manage the

research itself.

The implication of that, which was not strictly followed within Monsanto but is largely followed within Monsanto, is that the research is organized at the lowest level in the organization, is managed at the lowest level in the organization that can afford it.

The affording is the second principle that we observe, that there is a critical mass that is required. The critical mass is both one of facilities and equipment and one of intellectual capability.

In my own experience of research, at one time reporting to me, a research group of four people with roughly the equivalent of two others in bits and pieces. That was clearly too small to function on its own. It was combined within a larger research department that numbered about 60 people and functioned quite admirably at that level.

Groups of fewer than about a dozen and a half or two dozen scientists don't function well. So the balance that has to be struck

managerially is having the organization be managed far enough down in a large organization so that it can be responsive to the needs and priorities of the organization to which it's a part but large enough so that the problem of critical size can be attained.

It seems to me that that's wholly consistent with the observations of the report that FDA clearly is big enough and can sustain and needs to sustain a research enterprise that provides information necessary for its functioning, that perhaps the current organization is not appropriate to satisfy either the needs of scale or the needs of responsiveness and attentiveness to the priorities of the organization.

Now, I was interested that the report (unintelligible) organizational structure that is very similar to one that we adopted almost 20 years ago this year, as Monsanto had to face the changing environment of government regulation on environmental safety and health matters.

The senior vice president at that time created a structure very much like the one that is recommended here in this report. He considered himself the head of the environmental network.

That network consisted of a small corporate staff that carried out activities, carried out work that was not, again, cost-effective, for which the scale required was not expected to be done by the individual business unit.

He considered the people who were functionally, administratively, and financially in the individual business unit, to be part of that network.

He did not control their budgets or personnel. He did annually report to the President and the Board of Directors on what those activities were and what the size of that budget was.

Now, I would say that our experience with this network suggests that it's probably not effective to put too much budget authority

in and power in the hands of the scientists;

That his role, at least in our experience, was much more effective when it was one of persuasion, of being close to the source of ultimate authority and, thus, able to influence decisions but not one where the power resided and especially the budgetary power resided in this, the head of the scientific network of the Agency, as you proposed it.

That will probably require some discussion within the Agency, but I would certainly suggest that our experience is very much supportive of the general recommendations that I've heard discussed this morning.

Thank you.

CHAIRMAN KIPNIS: Thank you very much.

DR. WOODCOCK: My name is Janet Woodcock. I'm head of the Drug Center at FDA. I have a couple of general comments I'd like to make.

First of all, I think this is a public meeting, and I think it's important for everybody to recognize that this report focus

on laboratory science. People are talking science and saying FDA needs more science; we don't manage our science adequately, and so on.

I think the report has a lot of merit, however, I think that everyone must recognize that the science is underlying the review and approval of drugs includes statistics, clinical trial, design and analysis, epidemiology, clinical pharmacology, and other sciences that are not basic laboratory sciences.

And that there is a tension; even if the Drug Center were funded to perform research, among how much investment should be put into those sciences versus investment in basic laboratory science.

I think we are, within the Drug Center, a Center of excellence in some of these disciplines now, despite the fact that we don't have ongoing laboratory research programs in them. In fact, some of them can't have ongoing laboratory research programs because they're not laboratory sciences.

I think it's easy to forget this when

you talk about science that it's extremely important for drug evaluation, although not as relevant to discovery work, of course, which involves the basic sciences.

Now, the second thing I want to do is kind of echo what the previous public speaker said. I've spent a number of years when I was in the Biologic Center, in trying to bring together the laboratory reviewers and the other regulatory reviewers who are involved in reviewing applications.

I believe that this is most successful when it's pursued at the local level. It's difficult for me to understand how a chief scientist, how ever well intentioned they might be, especially if they had no regulatory experience, could foster participation of the scientist, the basic scientist, into the regulatory process.

It is true that science requires an inquisitive mind, as you said. Regulation requires a disciplined mind, and regulators must learn, scientists involved in regulation,

must learn to make those balances. This isn't a study section, and it takes a long time for people to learn that.

The only way that I have found that that can be pursued successfully is at a very local level, one on one, the scientists work closely with whatever regulatory group they are assigned to, to have large masses of scientists sort of working autonomously, I think, would be extremely difficult models, although I would certainly be open to it.

I think that has to be considered in your recommendations because the further divorced the groups are locally -- and I think that's the problem now, actually, is that they aren't physically collocated and they aren't intimately involved day to day in one another's activities.

CHAIRMAN KIPNIS: I think those points are well taken. I would just make a few comments, myself.

I never thought of science as being restricted exclusively to lab bench work nor

any other scientific areas, and I agree with you.

That's why I mentioned the fact that to become a first class regulator, it takes years of skill. It may sound easy, but it is a very difficult issue.

The second one, though, I would just deal with; it's very interesting.

The comments before at Monsanto, it turns out that the chief scientist at Monsanto is in the office of the president, very similar to what is now recommended.

Companies that are going to be at the forward edge of science have to have science presented at the forward edge of financial and political decisions.

Actually, if you look at the office of presidents of many companies, many of the big pharmaceutical firms or many of the high-tech firms, you'll find chief scientists now sitting in so-called office of the president, I think to have proximity.

The other point that I would make is

that the vagaries of influence are tremendous in any big organization, and some science centers or some centers within the FDA may have more favorable and progressive attitudes than others.

And, therefore, to a certain degree, a value system has to be institutionalized throughout the entire agency. I don't know the best way of accomplishing that.

I would leave it to the Agency to consider how do you institutionalize it and make it wide.

But to expect it to be made, I think, is critically important.

Any other comments? Any other members of that Committee?

David?

DR. KORN: Yes, thanks.

I wanted to make two comments in response to Dr. Woodcock's points.

One of them is there's an appendix in the report, called Appendix C, which is entitled Definition of Terms, and I didn't read

it. But the appendix basically says that the term "scientific research" is taken to include both laboratory and non-laboratory investigation that addresses questions of immediate applicability of the regulatory problems, or whatever.

Under this definition, scientific research would exclude routine laboratory or non-laboratory testing and analysis using established methodologies but would include the development of new analytical approaches and methodologies.

So it's not just wet laboratory stuff.

DR. WOODCOCK: Did you evaluate, for example, our epidemiologic research program?

DR. KORN: I'm sorry?

DR. WOODCOCK: Did the Subcommittee evaluate CDER's epidemiologic research program as part of its --

DR. KORN: No. Not specifically, it did not.

DR. WOODCOCK: So, although the definition was broad, perhaps the scope of

inquiry of this Committee was basically restricted to laboratory research or not?

CHAIRMAN KIPNIS: My understanding is you invited everyone in the FDA to make comments. I would suggest that the epidemiological group was concerned they should have been comments.

Epidemiology is a tremendous science, more sophisticated than ever, but I would suggest not involved in the Committee is telling you something in your Center that you should pay attention to; namely, if the epidemiology group is concerned, why didn't they send letters or comments, too?

I would tell you that they should understand the definition because Dr. Blout and I have been responsible for reviewing the scientific awards of the FDA. We have brought it to the attention of the FDA administration for three consecutive years, has to be clear in their definitions themselves.

So it is time that the FDA people began to address those people. It came up

three years ago. Superb epidemiologists, mixed with the same thing for laboratory, where there should be two separate ones, I think.

We brought that to your attention, too, and you brought it to the attention of others. So that this is what I meant. It's important that the most senior people in the FDA address these questions and that epidemiology is a science.

How can we exist? I mean, even the laboratory workers, if they're going to have any application in genetics, need first class epidemiological review.

So it is the responsibility of the leadership within the FDA also to bring to the attention of their staff the importance of this. It had nothing to do with definition. That's been an argument for three years.

DR. KORN: Let me just go on for a second with Dr. Woodcock.

Within 100 letters, roughly, maybe a few more, the letters were distributed across the Agency and there were plenty of letters

from CDER personnel.

I don't know, now, at least -- I don't know if I did then, but I don't know now -- which ones of them may have been epidemiologists or other professionals within the CDER organization.

The presence of CDER in the latter file is definite. It was not silent.

The second point I wanted to make is that -- I'm not trying to speak for the group now, but speaking for myself, I don't think there's any doubt in my mind that implementing the interactions of research scientists and reviewers is a local management task not something that happens from way out.

But I think what can happen is that the expectations in terms of job description, in defining positions for research scientists, make clear that this kind of interaction where some rough guide as to time spent in these kind of interactions and activities would be articulated, so there'd be no doubt about it.

But then translating that into

effective activity is absolutely, I agree completely with you, at the level of local management.

MR. EGAN: I am Bill Egan, from the Office of Vaccines in CBER. I certainly wouldn't argue with anything that was said about the report, but I'm curious, with regard to the chief scientist, you are looking at something of a structure like the NIH, with Varmus as head of the NIH, is that the kind of model that you had in mind?

DR. KORN: No, not specifically. We recognize that NIH and FDA are two very, very different organizations, agencies, if that's the right word.

The mission of NIH is to do research. The mission of the Agency is to do a variety of tasks that protect and promote public health. We're very cognizant of that.

So I wouldn't want to say, at least in my mind, that was a specific way to do this, no.

DR. WONG-STAAL: But from my point of

view is that maybe a better model would be the Office of AIDS Research, which coordinates activities related to AIDS, relating to different Institutes, and here you have something that coordinates research relating to different Centers, but it's a centralization and coordination.

MR. EGAN: Okay. And I wondered also about the broad budget responsibilities of that one person, but I think several of the others have commented on that already.

DR. PECK: My name is Carl Peck. I'm Professor of Medicine and Pharmacology at Georgetown University and Director for the Center for Drug Development Science.

I occupied the hot seat that Janet occupies during the years 1987 to 1993. Early in my tenure, being concerned about the quality and relevance of research that was underway for the Center for Drugs, we undertook a zero-based assessment of the quality and relevance of the research, bringing in an outside panel.

We asked Bob Scheplein from the Center

for Food Safety and Nutrition, to head up an outside panel to review the ongoing research. What we found was a mixture of excellence and mediocrity, relevance and lack of relevance.

We took that seriously, made a firm definition of regulatory relevance, research, and redirected the programs.

I want to congratulate Dr. Korn and his Committee for getting it right, in terms of understanding the central role that relevant research plays in the daily regulation and protection of public health at the Agency.

If I can, I'd like to give you a couple of examples of the kind of role that this research capability can play and then end with a comment about the crisis that I think this Agency is facing because of diminishing support for this research.

One Friday afternoon in 1991 I received a telephone call from a colleague of mine at the Naval National Medical Center, Lou Cantilena, describing a young woman who had just recovered from a near fatal arrhythmia in

the emergency room, and they observed that she was taking two medicines, Seldane and ketaconazol.

He wondered whether or not our epidemiological data base had ever seen those two in association with a fatal arrhythmia.

Anyway, I apologize for my articulation. I just got off of a red eye from California, but I thought this was so important, that I should share my views with you despite my sleep deprivation.

We queried the data base that afternoon and discovered 17 cases in which these two drugs were associated with a fatal or a near fatal arhythmia.

Research, using an existing epidemiological data base, was prompted by a clinical observation.

We went over and saw that patient the next morning, the staff from the epidemiology branch, as well as Jerry Collins, who headed up the bio-pharmaceutic research laboratory, and he began work looking at the human drug

metabolism, to see whether or not there was a relationship.

We had existing research contracts at the time to enabled us to ask Lou Cantilena at Uniformed Services University and LuRay Woosley at Georgetown to track down the mechanism of action of this possible drug interaction.

I'm probably telling the choir about this famous story. The Commissioner was on national television within weeks. The CEOs of the relevant companies were in my office, working out the wording for a black box warning, and this episode of ketaconazol, trefenidine, drugs of interaction based upon the inhibition of Sarcum 384 (ph), work that Les Benet pioneered in some of his research work, became a regulatory protective health action, but it was done on short order because we had the resources to do the epidemiological research internally.

We have the resources to task our colleagues in academia to track down the mechanism of action.

The second instance I'd like to cite is the knotty problem, bioequivalence of non-systemically administered drugs.

The '84 amendment charges the Agency with developing bioeffluence standards for systemically available drugs but didn't anticipate with any clarity the problem of topically applied drugs or inhaled drugs.

Research program at the Agency that was subcontracted to the Johns Hopkins University successfully developed a bioequivalence test based upon pharmacodynamic equivalence, which is a significant breakthrough that makes the possibility of availability of these non-systemically available generic drugs.

The third involves an extramural contract that the Agency has had with the University of Maryland -- this is, again, the Center for Drugs -- to improve manufacturing standards so that many fewer regulatory actions have been undertaken on the basis of new science at the manufacturing level that allows

for an improvement of FDA's regulatory function.

I believe there's a crisis now, though, because I understand that the budget available to Janet to undertake this work internally and externally is at least two-third down from what it was when I was there, and that's in 1993 dollars. That's not in 1997 dollars.

Finally, I want to say that I'm aware of several quality scientist reviewers at this Agency because of their perception of a lack of a supportive research environment.

I know of one candidate to head a division at CDER that Janet wanted very badly. I knew of his quality. I talked with him last week, and he has told me that one of the reasons he didn't come was because he understood, under the PDUFA restrictions on his shop, that he would not be allowed time to pursue the research that he was doing in his NIH laboratory.

The American Society for Clinical

Pharmacology and Therapeutics last week, 1700 members, scientists that represent academia, industry, and the Agency -- though there were very few agency people there at this one because of restrictions on travel funds -- but, nevertheless, there was a resolution passed, very strongly supporting the continuation of the research at FDA.

I'm singing to the choir, I can see. I think it's the Congress that needs to be enlightened.

We are aware that there will be hearings this spring in the Senate and the House on reform and on the expenditure of the PDUFA dollars.

I want to strongly urge that Dr. Korn or Dr. Kipnis, or this Committee, be represented in those hearings to advocate the central role that research plays in FDA protection of public health.

If there's anything that distinguishes this Agency from agencies in the rest of the world, that all look up to this agency, is it's

critical review capacity based upon its research quality.

There's no other agency that has this capability. Thank you.

CHAIRMAN KIPNIS: Thank you.

Dr. Zoon.

DR. ZOON: Yes. My name is Katherine Zoon. I'm the Director for the Center for Biologics Research, Evaluation and Research.

I just want to personally thank the Committee, Dr. Korn and the other members of the Subcommittee, for the thoughtful and excellent job they've done in assessing the role of science in the FDA.

This is a difficult challenge. We all understand the financial restrictions currently being placed on the FDA in this area, in our budget as a whole. But I think the ability to do research -- laboratory research, clinical research -- is fundamental in our underpinning of scientific decision-making.

If this is not supported, the ability for the FDA to do its job will be severely

impacted on.

Another point that was made is our nurturing of young investigators. They are our future. If there are no young scientists that wish to come and work at the Agency, we will not have a science-based, decision-making organization in the future.

You will never reconstitute that once it's gone.

So I guess, in my opinion -- I feel very passionately, as you know -- but I highly support your recommendations.

I think the ability to impose a one-model fits all is not appropriate. I think there needs to be diversity in the types and constitution of the research and their integration with the review process, but I would say what is critical is that there be very clear and definite communication between the two and no matter what the model is.

Because you do not take advantage of the scientific expertise if they don't interact intimately and you will lose that advantage and

value.

Now, different models can achieve that. I think we need to be ever present, though, that if the science is to impact on decision-making, that needs to be a key parameter in making sure that happens.

So I'm very supportive of that, but whatever model systems are used, and it may be mixed models, that needs to be integral into that process.

Finally, I think that having somebody at the highest level of the Agency to be a proponent for research and science in our Agency is absolutely essential.

FDA has always, in my opinion, kept its research in the closet, and it really has not really promoted the excellent work that has gone in the Agency that has impacted on major, major decisions, public health decisions, and I think it's time to make that a more definitive argument, and explain to the public and to the Congress the importance of the work that we do.

Thank you.

DR. WOOSLEY: I'm Raymond Woosley. I chair the Pharmacology Department at Georgetown University.

I would like to give you a neighbor's perspective, if I could.

I would start by saying that my perspective is very appreciative of the report that Dr. Korn has put forth, and I think it is a very important message.

I would also repeat what Kathy Zoon is saying. The FDA gets very few opportunities to stand up and blow its own horn. It's kept under a lot of pressure and it's been under tremendous pressure in the last few years of FDA reform.

I came to Georgetown 9 years ago and was very pleased that, at that time, we had one of the FDA reviewers working in one of our laboratories on our PD time. She was there a half a day a week. She came religiously, and she produced data and publications during that time.

Over the last nine years, I've had

interaction, varying interactions, not all at the bench, but interactions with over 50 scientists at the FDA, and they've been productive and they've been rewarding in many respects. Carl mentioned one of those.

I think what I would say is, talking to those people who came from the FDA on their own time and participated in research or participated in discussions about research is that they felt that they were, for the first time, participating in the generation of knowledge, instead of being a recipient of data to review, and simply being there to respond to data.

And their ability to participate in the generation of knowledge gave them a perspective and awareness of potential faults in the data, of knowing what it takes to generate data, you get a sense of how hard it is to generate good data and where there may be flaws in it.

They also gained a prospective on what they could realistically ask of scientists in

industry.

They would say, "I was working, designing protocols that now I know could never be conducted." And that participation, first hand on research, makes them serve industry better.

It makes them serve the public better.

I think for that reason this message to call for support the science at the FDA is absolutely essential and it needs to be voiced in Congress. Because I can tell you, people at the FDA feel very much beat on and underappreciated.

They're afraid to put forth some of the data and knowledge that they're aware of because of repercussions that might come from that data. That's not a healthy environment.

CHAIRMAN KIPNIS: Thank you.

Dr. Benet, you had a question?

DR. BENET: Yes. I'd like to ask Kathy and Janet and Center Directors and Carl, also.

I'm a laboratory that actually trains

people that come into the FDA. In Carl's tenure at CDER, some of my post-docs and graduate students that came out of the lab were able to negotiate certain interactions with NIH Centers, in terms of their time and days.

My more recent people who have come to the Agency haven't been able to do that. Also, they've left after -- even in my mind -- after a relatively short time.

I've just sent a terrific post-doc and a new graduate student who just joined CDER within the last couple of months.

But what I'm concerned with, and I'd like to hear your response to these recommendations, because there is a recommendation here that apparently is being agency-wide for the chief scientists, and I'd like to hear how you're going to interact or you could interact or whether this is the problem.

It seems Janet was indicating it could be a problem in terms of the taking away of some of the authority that you have, and I'd

like you to put that into context of sort of what Carl said: You know, is it now impossible to have these negotiations of bringing people in, that can have a day and a half off a week, and what do you want from us, Janet and Kathy; what do you want the Science Board to do in terms of our interactions and recommendations to implement the help for the Agency in terms of the science area.

Can you address some of those?

DR. WOODCOCK: I don't have a problem with the Subcommittee's recommendations for chief scientists. I don't know that that addresses the fundamental tension that we are actually facing, and I may take a little umbrage in the fact that perhaps I, personally, am against science or would not foster science or something like that. That's not the issue.

As everyone knows, we are under the gun to get our work done. We have had a long history of not getting our work done.

And as the administrator of the Center for Drugs, it has to be my primary objective.

I have to get funded at a level that can get the work done and do the science as well, if I had some model that would include scientific activity, say a day a week, day and a half a week, whatever it might be, that's 20 percent of a level of effort that isn't going into getting the work done.

What I am doing is initiating a lot of efficiencies in the process that I hope will allow us to get the work done in a more efficient manner; but it doesn't help to exhort me to set aside resources for laboratories if we're going to go into a backlog status on our applications.

So my belief is if the agency level, if overall the agency is going to support science, they have to make some hard decisions.

The scientific endeavor is going to have to be smaller for the agency as a whole, and it's going to have to be decided how it is distributed.

And it should be distributed in a way that puts the scientific effort where the

scientific questions are.

Then you raise the question, what are the major scientific questions facing the agency.

Are they epidemiologic, are they clinical pharmacology questions?

Where are the greatest risks for the public?

Where do we need the greatest scientific minds right now? Those are the kind of discussions that have to be engaged in, because there is no free ride here.

DR. ZOON: Yes. To answer your question, I think that the ability for us to give appropriate professional development time is desperately, tried to be incorporated into our programs.

With PDUFA-1, and having research as part of that fundamental structure that was able to enhance that level of interaction, but Janet is absolutely right; there are performance outputs that are demanded by ourselves and the public in order to get our

work done.

But the ability to foster collaborations among institutions and give opportunity for our people is key. Because if you don't have people that are happy in what they're working in and what they're doing, you'll have a very high turnover, you won't have the people with the experience and expertise you need.

So it is a management balance in terms of trying to foster that professional development time with the workload of the agency.

In terms of collaborations with other outside groups, academia, NIH and CDC, we strongly encourage that in CBER; that is a part of our fundamental interactions that I think we actually rate people on when they get reviewed, is their ability to collaborate with people outside our own organization; and I think that is fundamental for doing the very best job we can.

In terms of the Centers' interaction

with the chief science officer personally, I think whatever promotes the highest quality science in this organization I will support.

DR. FRIEDMAN: I don't want to take much time now, but your question raises some budgetary things I just wanted to spend 60 seconds on so that everyone understands the environment in which the Centers and previous leaders of the agency have been operating for the last roughly four or five years.

In one sense the agency has been -- and this is not a plea for more money; this is history. I've Marandized you now.

(Laughter)

In one sense, the agency has been very fortunate in that our apparent budget has been straight-lined.

That is, whereas other governmental agencies have had reductions, we have had a consistent level of funding; and for that of course, we're more grateful than if it had fallen.

However, the real impact of that when

one considers inflation, scientific inflation and mandatory pay raises that are built in, means that there is an actual erosion of the discretionary pot of money that they're talking about for laboratory activities, and for travel and for all sorts of other things, of about $30 million a year.

So that over the past three, three and a half years, we have lost close to $100 million in spending. And you appreciate the magnitude of that impact.

So when people say that they're feeling very stressed because they have regulatory responsibilities with publicly-expressed goals and expectations, they have desires to foster young scientists, they have needs for laboratory investigation or other forms of clinical science, you understand the pressures under which they're operating.

So there has been a very substantial decrease in the discretionary budget for the entire agency that these individuals and their colleagues are operating under.

The second thing is that, as with the rest of government, we are decreasing in size.

So that roughly two and a half percent per year FTEs are falling; and that's been true for the last three or four years and it will continue for at least the next several years.

So the agency is becoming much smaller which, as people talk about increasing demands, you can imagine that's being parsed out to fewer and fewer staff, no matter how qualified.

A very large amount of work. You probably understood that, but I just felt setting that out makes the discussion much clearer.

MR. PERSHEVSKI: I'm Francis Pershevski, and I'm based at the Gillette Medical Evaluation Laboratories here in Gaithersburg, Maryland. This is a division of the Gillette Company.

My comments are twofold; one is to generally support the effort to improve the infrastructure of the FDA to deliver good science.

My primary focus is on commenting on a specific need to relate and to work on good scientific efforts in the area of new emerging technologies. Specifically, we are concerned with new methods for toxicological assessment, as most are in the industry.

The Gillette Company has an interest in personal care products, cosmetics in drugs; and we have internal programs to develop new methodology for tox assessment, and I'm very happy to see that the subcommittee on toxicology is supporting the overall development of mechanistically-based tests.

We support that effort as well, and you can consider the Gillette Company is one interested party willing to work with the agency in developing technologies and understanding the science, and working out good scientific procedures.

We certainly don't stand alone; I think there are many interested parties in the corporate arena that would do the same, but who are not represented here today.

So again I support the efforts to the Subcommittee on Toxicology, and certainly support the effort to do good science with the agency. It's needed, and I think we in the industry are willing to work with you. Thank you.

DR. KRAUSE: My name is Phil Krause, I'm a scientist at CBER. I also do reviews there.

I am also a member of a couple of committees, one of which is called CAFDAS, which represents working-level scientists throughout the FDA, and has representatives from each Center.

I'm also a member of a similarly-constituted committee in CBER to represent CBER scientists, working level scientists, in discussions there.

I'm really speaking mostly for myself, as one who believes strongly in the FDA mission to enhance and protect public health, and also believes very strongly that a high quality science base is critical to doing that.

And who further believes, as a scientist who believes that he has some qualifications, that I'm capable of contributing a great deal towards that end. And in that context, would like to strongly endorse the report from Dr. Korn's subcommittee.

I think I speak for a lot of working level scientists throughout the agency in saying that I think that the subcommittee did an outstanding job identifying problems which scientists are faced with in doing their jobs; and I also think that the proposal of creating a chief scientist will do a lot, is really a very important step towards ameliorating those.

The concern which I have is beginning to be voiced in this forum, I think, which is -- obviously, this ultimate question of "What can one afford?" And obviously, the budget of FDA is controlled by Congress, and despite the best intentions of everybody in FDA, at some point there simply isn't enough money to do an adequate job to protect the

public health and enhance the public health the way that our mission says we are to do.

So when one is faced with these kinds of fiscal problems, it seems to me there are two responses: One of them is to say "Well, we'll continue to do the best job we can based on these problems," and that certainly is a reasonable response which one ought to do; but the other response clearly has to be to make sure that everybody is aware of the consequences of these decreases.

To that end, it strikes me that this report and this committee, especially because the Science Board consists of people who are not themselves within FDA and therefore might not be perceived to have conflicts of interest with regard to what they're saying, can do an awful lot to educate the public, educate the Congress, and really make a push for making sure that FDA really has the resources which it needs to do its job.

That strikes me as the only way that ultimately FDA will succeed in promoting and

enhancing public health.

So I think all of us need to take an active role in educating the public and making sure that whatever can be done to make sure that the FDA budget reflects that need, is done.

CHAIRMAN KIPNIS: Thank you very much.

DR. BURLINGTON: Hi, I'm Bruce Burlington, I'm the Director of the Center for Devices. I used to work in a laboratory until I fell out of that bad habit.

(Laughter)

And like everybody else who has spoken, I want to ride my hobby horse here; and that is that I think running science up the flagpole and saying "Do more, go ask Congress for more money" isn't really addressing the management challenge that Mike, that Janet, that Kathy, that I have to deal with. And that is, within the context of the budget we have, how do you allocate resources among competing activities?

We spend a lot of time and effort in

review work, in compliance surveillance, in enforcement work; and if we really look at functions and we say how do we separate that out, what do we spend out time and effort doing?

We spent some time and effort in generating new information in the laboratory. Hopefully that new information is directed towards solving problems relevant to FDA.

We spend a fair amount of energy setting direction for industry, telling them what they ought to be doing in order to meet the regulatory standards, and then we spend most of our time and energy in assessing conformance, in saying, Did they meet those standards?

In going out and looking and saying, Is the factory producing a quality product because they have quality systems in place?

Is the application meeting the standard of safety and effectiveness? Not how to meet it, but did it meet it.

So when we look among those competing

activities, the developing new information, the assessing conformance and the setting expectations for what people should be doing that we're going to assess conformance against; have we got the wrong mix?

Should we be putting more time and effort into developing the information and setting the expectations, setting the criteria, based on laboratory, based on epidemiologic research, and stop doing so much assessing conformance.

Should we become much, much smaller and implicitly, in doing so, missing some of the items that we now find when we go to assess conformance.

Is that an acceptable tradeoff?

Have we benefitted the American public? have we fulfilled our mission if we put more effort into information development and setting criteria, and less into assessing conformance against those criteria?

That sort of analysis will be very helpful. Now as in any business, when we

assess conformance, there is diminishing returns as you put more and more effort into it.

We probably put five to ten times as much effort into assessing conformance as the British or the Japanese do.

Should we back off and get closer to the level they're at, in order to produce the resources to have a bigger investment in science?

Addressing those sorts of questions I think will be very helpful to those of us who have to deal with the day-to-day management problems.

CHAIRMAN KIPNIS: Can I ask a question?

Is that the role of a science committee, to assess that? Or is that the role of the managers, to assess it. Is that a regulatory issue? -- I recognize these are complex issues, and one influences the other.

DR. BURLINGTON: I think everybody on this Science Committee has had experience with

management responsibilities as well as with developing information in the laboratory. I think that if we were simply saying "Who are the best scientists?" We would have pulled out a peer review group and we would have looked and said -- from non-management scientists and said: "Okay, which people are producing good publications?" But that isn't what I thought that this committee was doing for us.

I thought they were helping us set our science priorities and our review priorities because of your specific backgrounds.

I personally would appreciate your input and recommendation on the issues I just addressed.

But Mike's probably got a finer chart of it.

CHAIRMAN KIPNIS: The other one is, how do you nurture your replacement in ten years? How do you replace yourself?

DR. BURLINGTON: Good question. We all worry about that, it's all part of our program.

Where do you find the people that are going to come in?

We traditionally have drawn on academic folks as well as people that are homegrown within the FDA system. And you do need a critical mass to achieve that; we recognize it.

CHAIRMAN KIPNIS: The level of sophistication as a requirement, takes years to gain the level of sophistication that these top-notch managerial positions.

DR. WOODCOCK: I would say, for example, what Carl was talking about, to answer your question, in the science efforts he made at CDER. He recruited a large number of really qualified people.

They were assigned to us, but they have come up within the organization. They are being groomed now, and I think your concern is, are we still getting that pipeline if in fact we're having a focus right now on primarily regulatory activities. Because of these, our budget is basically sufficient to perform our

review activities, period.

So I don't know what's going to happen. Fortunately, we have this pipeline that Carl set up in better times, but we have to look to the future as well.

DR. PECK: Carl Peck. I just wanted to yield to Les's comment on the issue of review time and research time.

As Janet said, I think there were better times when I was there. I had more discretionary funds, and I had the full support of the commissioner's office, and I didn't have PDUFA.

Now, I don't want to -- probably my income will suffer if I get too explicit --

(Laughter)

-- about the potential evils of PDUFA. It's a terrific legislative incentive, initiative that has enabled the agency to finally meet its own expecations, and the expectations of Congress and the expectations of consumers, sponsors.

And Janet had, and Kathy had done a

terrific job of meeting those expectations.

But the problem is, I believe, that there is such now an overwhelming ethic of "get the work done" under the deadlines and the expectations and the strongly industry-influenced restricted uses of PDUFA funds, that the center directors have less capability to play out their own commitments of work for the research function.

I have no question that Janet supports changing some values for research; she just can't afford as much as I could. And if I were to suggest what the committee can do once again this spring, it is to educate Congress, educate potential candidates that are going to be the next commissioner, on this issue so that we can return appropriate level of emphasis and discretion for the center directors to invest in science again.

CHAIRMAN KIPNIS: Thank you.

We'll have one more report and then we'll break for lunch, and reconvene at 1 o'clock.

MS. ELISBERG: Hi, I'm Rosalie Ellisberg. I'm a laboratory scientist at the bottom of the chain of command. I'd like to thank the committee very much for the report, I think it's excellent, terrific.

You hit on so many points, and as I think has been demonstrated here by the other comments, particularly that there is no real advocate for science. There's no advocacy; we don't have a product that competes with a number of reviews that have to be done per year.

And I mean not just money for research, but an atmosphere that encourages reviewers to go to meetings, to read, have a little time to read, consult with lab scientists, and generally think about the scientific issues.

When we ask the reviewers to even suggest particular scientific issues, they usually can't do it; they're so involved in just getting through the number of reviews on their desk.

So I want to thank you very much.

CHAIRMAN KIPNIS: I think at this time we'll break for lunch, reconvene at 1.

[Whereupon, at 12:06 p.m., the meeting recessed for lunch.]

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

[1:15 p.m.]

CHAIRMAN KIPNIS: I'd like to call to order the Science Committee Meeting for this afternoon's agenda.

The first one I'd like to call upon is Dr. Elkan Blout, to comment on the report of the subcommittee, and make any other additional comments he feels are indicated.

DR. BLOUT: My remarks will be brief and personal.

As most of you know, I've been in this job as Senior Advisor for Science for just five years, and have had my ups and downs in terms of feelings about what the future of the agency would be. At this point, it's one of my ups, because I think this report really lays it on the line as to what should be done with respect to science and research and the overall agency forward-looking activities. I hope we're going

to hear more about what will be done, soon.

I also find that the report emphasizes importantly the role of younger scientists in the agency. They are the lifeblood of the agency, and unfortunately, they aren't always heard. And the report emphasizes that, and I hope it will be heard loud and wide.

The two important areas which I am less certain about are (1) What is the next step? It's a great report, but what is the next step? And maybe my friend Mike Friedman will comment on that.

The second question I would like to raise is how can we, those affiliated or part of the agency, influence positive legislative action? We've been silent for a long time. Can we start to influence positive legislative action?

If we do those two things, then we've made a big step forward. So congratulations, David Korn and your colleagues. Thank you for the report, but it's only the beginning.

CHAIRMAN KIPNIS: Thank you, Dr.

Blout.

I'd like to call on Dr. Friedman, the lead commissioner in the FDA for his comments on the report. I'd be interested in not only his comments in terms of the substantive issues that the report raises, but the various actions that you can take to begin the implementation of some of the major recommendations which the report has proposed.

DR. FRIEDMAN: Following Elkan's lead, my remarks will be somewhat longer, and less personal.

Everyone has a different view of what this agency says with respect to science. My own view is that this is an agency that aspires to be evermore effectively science-based in its methods and its decisions. And while freely admitting that I am not a laboratory investigator, I do care about that goal and these issues very much.

I offered a rather difficult charge to the subcommittee, and the request I made was not an easy one. And so I have to take just a

couple of seconds to echo some things that were said before. I want to personally and in this form thank the members of the subcommittee, especially Dr. Korn, who worked very hard under difficult circumstances, to try and synthesize widely disparate views and to come up with some conclusions that really do lead, I think, to some meaningful suggestions for the future.

I want to thank the whole Science Board. You all sat through what for me at least was one of the most uncomfortable and dissatisfying meetings that I can recall a couple of months ago, and for your attention and your thoughtful review of the draft that's been given to you in your subsequent actions, I very much -appreciated that. I especially appreciate Elkan's role in this, which has been absolutely central, and Dave Kipnis's role.

I want to thank the science staff from within the agency, and Susan has been mentioned on a couple of occasions. I want to just reiterate, her contribution was very substantial. But also Neil and others.

And lastly, I want to appreciate those members of the agency who participated, either by writing or in personal discussions, or in other ways with the committee's actions.

I've already disclosed that I am not a laboratory investigator; I am a physician, and some would say a fairly simple physician; and so I offer you a simple view: This report has, in my way of analyzing problems, three things. It sets out a certain expectation, a certain given, it then tries to make a diagnosis, and it then tries to offer some therapies. If I may, let me walk through each one of those things separately.

The expectation is one that I hardly subscribe to; that science in general and laboratory investigation in particular is a necessary but not sufficient activity for this agency. This report, and the comments that I've heard this morning, underscore the value of high quality scientific thinking and recognize that one very important way of gaining that is to have active laboratory

investigators who are at the very top of their profession.

You've been careful to say that that's not the only way to do it, and you have recognized the breadth of other kinds of intellectual activity and research expertise within the agency, and again I heartily agree with that.

You could have had a different conclusion. I mean, you could have said that this wasn't essential or that there were other ways to do it, or that this might have been a role for the past but not for the future. I am very glad that this independent review has come up with exactly the expectation that I would have asked for.

The second thing deals with what a diagnosis of the current condition is. And here again I think that I agree very much -- perhaps I would differ in some individual, specific circumstances, but I think in many broad ways I agree -- that is, I have the same view of certain obstacles, certain problems

that confront the agency as you do.

There is inconsistent quality, support and planning of our laboratory investigations within the agency. There certainly are pockets of excellence, there certainly are programs of excellence; but these are inconsistently identified, inconsistently supported. And I think that at a time when resources are so dear, that we simply can't afford and couldn't afford this.

You talk very specifically about inadequate cooperation, or less than ideal linkages; and you point out that both within the agency there's not sufficient collaboration. People can define the word culture in different ways, and you talk about culture; to me the ideal culture of science is a collaboration of minds. Different perspectives, either from the same field or from complementary fields, working on problems and coming up with solutions.

I think that we can and must do a much better job of that from within the agency.

You also point out something that's equally important to us, to me, which is that there have to be much better cooperation and communication with scientists and scientific bodies outside the agency. You list that as one of the responsibilities, and I think that's -- I thoroughly agree with that.

We have relied upon traditional laboratory models, and we are in a nontraditional time; and your report -- and again, I understand this is a sort of administrative rashamon: Everyone hears what they want to hear in what you've said. But what I hear you saying, and I'm saying this publicly so if I'm mistaken, you will correct me. What I hear you saying is that there's a very important and timely need for increased efficiency, for increased integration, for increased linkage, for clarity of vision, for more appropriate planning and for following through on commitments that are made.

If in fact that is what you're saying, then again I heartily agree with that.

One thing I thing I particularly like about this report as I've heard it is that I like the fact that it is critical without being blameful; that you make what I consider to be very constructive criticisms without saying that it's any particular person's fault or part of the operational structure of the agency's fault. That's really important to me, and I'll tell you why.

In my mind, everyone bears some of the blame and no one bears all the blame in this; that to the extent that the agency leadership needs to take a much more vigorous role and a much more effective role in this, I completely agree. In the sense that the Center directors can be more effective in focusing on this, I certainly agree. But you also indicate, at least to me, that individual laboratory investigators need to take real ownership of these problems and to take responsibility for the solutions.

To me, if we say that everybody in the agency has this as a priority and then

everybody in the agency has a responsibility for fixing it, that you don't point to someone and say "Well, I can't do it because so-and-so won't let me" if we say that we won't tolerate that sort of excuse-making, then it's everybody's responsibility and I think this model, whatever the model is that we want to achieve, this model that you've described will only be successful if there's a widespread engagement on it.

I think we really need to improve the environment and to change the way people look at this. That's my sense of what your diagnosis is. The patient is healthy, but there is a serious illness that needs to be addressed, and that with proper remedies, true vigor and true health can be restored. That's my interpretation.

In terms of therapy, I think that many of the things that you're proposing are perfectly reasonable, and that my goal in this, my original expectation was that this committee, this subcommittee would formulate a

report, that this committee, this larger committee would deal with that report, it would then be passed to me and that I could then pass it on to the commissioner with my endorsement and support and the offer of my help in implementing it.

Unfortunately, that chain of events has been broken in a way that wasn't anticipated when I first asked Dr. Korn and other members of the committee to begin this exercise. We don't have a permanent commissioner in place right now. My expectation is that such an individual will be identified if not on board within the next six months or so, I hope less, but I understand these things do take sometimes a considerable amount of time.

So some very important parts of this proposal simply can't be implemented at this time. As I've indicated to many of you privately, the idea of having a specific agency spokesman for science in this capacity, in this location, with many of these responsibilities,

this is something that I'm very attracted to and that I'm very supportive of.

The fact is that I can't see recruiting such an individual right now without a commissioner being on board, because I don't think that would be fair to the individual. I don't think it would be fair to the new commissioner, either, but I'm not likely to get the very best person. Any of you who have served in that sort of capacity know that you can't recruit a chief of a division in a medical school when the deanship is open. You need a certain level of support that I would want that individual to have, not from me, because that individual will have it from me, but from the very highest ranking person in the agency.

But does that mean that we should be completely passive about this? My answer is no. I think what I'd like to do is to -- and these are just thoughts and suggestions -- but what I would like to do is if this committee says that this is a report that they wish to

endorse, I would begin drawing up now specific names, getting recommendations of people -- I would begin discussions with people. It can't be a formal recruitment right now, but I would like to have a situation such that when the new commissioner is in place that I could go to that individual with ideas, with names, with suggestions, with plans that should that new commissioner say yes, this is what I would like to do, I could then help that new commissioner achieve this.

I know that's not as satisfactory as many of us would like, but I think it does serve part of the purpose here. The reason I'm saying this out loud and in this venue is that I would like, then, if this committee endorses this report, to then get names and specific suggestions from you, because this will be part of your responsibility to help me in this.

Whether or not this body endorses the report, I still think there are a tremendous number of very good observations in it that have meaning for me, and I think that there are

a lot of ideas for restructuring our activity and improving efficiency that I think we need to move ahead with, anyway. I'm not talking about changing the structure of the agency by coming up with some new part of the organization. I'm very attracted to the idea of cross-center collaborations and what Dr. Korn referred to as virtual science within the agency. Of identifying programs, of identifying areas of expertise, supporting those, beginning the process of a thorough and consistent quality review of this kind of laboratory science within the agency.

I think there are a great many things that we can do in the agency now to move ahead with this. My own belief is that having a vigorous and effective laboratory activity within the agency serves a very important function: it is not enough and it cannot be complete in itself. I think that our scientists also need to be very ingenious and very flexible about identifying new ways to get scientific knowledge within the agency.

Several of you spoke about this earlier; I see that also as a mandate from within this document that collaborations with sister agencies, with academia, with industry, are very important things.

I will be happy to answer any questions that you all have for me. Let me end on just one thing: I've specifically, and I don't want anyone here to assume that anybody speaking on behalf of the agency has said "make a plea for a larger budget." That is something that we are not allowed to do. What your own view of what the budget should be is your own view, and obviously to the extent that you make that known, that's your responsibility in a certain way.

Having said that, though, I also want to underscore that budgetary concerns are at the very heart of this whole activity because as much as we want to do certain things, there are budgetary realities that drive all of our activities. There is a serious commitment on the part of the administration, on the part of

Congress, and a great proportion of our citizenry to reduce the deficit. Government spending is going down. That is something that they are committed to.

So if one wishes to have even the preservation of a budget authority in these times, it takes an extraordinary effort. Our job is to use every dollar that we have in the most effective way that we can, and to show ourselves and our harshest critics and our most dear supporters that each dollar that's invested by the public in the public health is used in the best way that we can. This is a trust, this is entrusted to us, we take this very seriously.

But these kinds of activities; that is, laboratory research activities, are part of the overall spectrum of things. I very much want to improve it; I'm not going to use an excuse that we don't have the money to do it. What I'm saying is, we will do what we can with whatever allotment we can, but the way we're going to do this is by being more innovative

and more flexible, and in that regard, your continued support and your continued input are not just nice or not just something we'd be thankful for -- really are absolutely essential.

Let me stop there; I probably have gone on too long, and I apologize.

CHAIRMAN KIPNIS: Thank you, very much, Dr. Friedman.

Dr. Korn?

DR. KORN: I'd like to make a couple of comments, if I may, and I want to preface them by telling I think for the second time today what I told the subcommittee the very first time we met.

I come to this with as open a slate as anybody could, having never had an interaction with the FDA, having never developed a drug or device or attempted to seek FDA approval of such, or anything else. So you may call unknowledgeable, uninformed, naive, but I'm not biased.

During the course of the last 12

months, I've become totally convinced of the centrality of a quality scientific research effort, using the term broadly as Janet would like, I believe. To both the image and the substance of this agency, to delivering to the American public what I think the American public wants. The agency is a good target at the moment for all kinds of people who want to damage it or curtail it, perhaps.

On the other hand, I don't think the American public wants disasters in their foods, drugs, devices and cosmetics. And I think that if it came to a bottom line question, a simple-minded question to 250 million people about, "Is that what you want to see happen in this country?" The answer would be a resounding "No."

Now having said that, I think that it's a critical time because the budget is so vexing, in that if this board and if some leadership of the agency does believe that the substance of the subcommittee report has merit, that some steps need be taken now to signal

that acceptance or endorsement and to take steps to begin implementing some of the recommendations or moving in steps toward that now.

Recognizing that there's no commissioner and recognizing that it may take a while to do that, I say that because I'm personally convinced, from talking with many, many of the scientists and reading a lot of letters, that there is a morale problem in the agency, and I think that some of the best young people, as Dr. Blout and others have said, are really troubled as to whether there's any future for them in this place. And I don't think that waiting is going to help them. I think that a signal needs to be sent that's very clear and very unambiguous.

I'm not sure of the best ways of doing that. But I'm wondering whether -- and I offer this as again, a naive suggestion, if the Science Board were so moved to suggest to you that some kind of an implementation advisory group be set up from the Science Board or under

the aegis of the Science Board that would have membership on it that would like to try to work with you to initiate those pieces of this direction that you think are tolerable within your overall responsibility, and at least tell the scientific community of the agency "Yes, we really are going to take this seriously, and we really do think there are some opportunities for strengthening these programs even at a time of budget adversity."

Now we can't --

DR. FRIEDMAN: Let me just interrupt you to say, I can't tell you how much I would welcome that, generally, and appreciate your willingness to serve on it, specifically.

DR. KORN: I'm not looking for work.

DR. FRIEDMAN: I know you're not. It's such a good idea, though.

DR. KORN: You know, I've also lived, as you know, in a lot of administrative institutions in my life, and I think there are times when you've got to put some substance on the table behind the words, otherwise the words

tend to drift off and people forget them, and -- look, I also want to say one other thing, Mike, and I think you said it beautifully: That the report is critical, but not blaming. And I don't think anyone on this committee, and I'll say I certainly do not doubt the sincerity and the motivation and the commitment to this agency that every center director has. I mean, I don't know that any of us would want to be a center director in this agency right now, given the strains and stresses that they're under. I think that they do a tremendous job.

We did not, certainly in any way intend in this report to label them as "bad people" or anything; far from it. I don't know that anybody would want to have your job right now, either, as a matter of fact, for the same general reasons.

But even though everybody's a good person, there's something missing. The center directors aren't doing it. You're not doing it, at least to date you haven't be able to, and something does need to be done, I think.

DR. FRIEDMAN: If I may, with the scientists -- I really think this goes throughout the entire agency; and that those concerns -- need to be shared by everybody. And sitting where I do right now, I think ultimately the responsibility and the criticism is mine, unless I make changes and things. And I accept that.

DR. KORN: Criticisms are on your lap, although not directed at you.

DR. FRIEDMAN: Right. It's absolutely appropriate.

DR. KORN: That's the luck of the draw.

DR. FRIEDMAN: Sure. That's the way it should be.

DR. KORN: Thanks, David.

CHAIRMAN KIPNIS: Any other comments?

Members of the Science Board -- well, the members of the committee also are members of the Science Board. Anyone else wish to comment?

DR. LANGER: I guess I might just have

a question -- I'm not sure if anyone can necessarily answer it; but clearly the issue comes up that by and large the consensus that I see is that people think there's a lot of good in the report. The broader issue is how do you get that report implemented, or will ten years from now, if we look in the last appendix, about what's been done over the last 40 years every time this has happened before, nothing has happened.

So I think it somehow seems very, very important that something be done. I don't know if it should just rest on your shoulders; I don't know if there's some publicity that should be given to this, or what the right thing is to do, but it would probably be good to get suggestions from people on the Board or people in the audience, people at the FDA, as to how to make this happen.

DR. FRIEDMAN: Let me deal with that for just a second, because it wasn't just an attempt to be artful that I described a diagnosis and then a therapy.

I think that to the extent that everybody agrees with the diagnosis, action is called for. I could easily imagine a new commissioner coming in looking at this and saying "Yes, I agree with these concerns, but I would solve this an entirely different way." And that would be the prerogative of that new person to do that.

I can't commit to you all and say that absolutely this will be followed through, because that's outside of my control. What I can say, though, and what I'm committed to, as long as I'm sitting in my Deputy for Operations capacity is that there are things that we can do, there are things that we should do, and there are things that I am prepared to do to begin to address these problems.

Now again, if we separate what, the solutions that are proposed in this document from what the problems are, there are a lot of -- I think the activities that are proposed, the solutions that are proposed that we can follow through on, and again I'm perfectly

prepared to do that.

I think there are other things that we can do that are not listed in this report but would get us toward that same goal, where input from both the scientists internally, the leadership internally of the agency, but also some sort of an advisory activity of people who care and are knowledgeable outside the agency would be very useful in doing that.

It would be totally unconvincing for me to say to you, "Rest assured, this will be taken care of." I can't do that. I don't have the budget authority or the administrative authority to do that. What I can do, and I understand that this is a very weak substitute for what I'd really like and what you'd really like, is to say to you that I am personally very committed to this. I initiated this activity, I saw value for this activity. I would not have done that if I weren't prepared to see it through.

There's nothing here that surprises me. There's nothing here that shocks or

dismays me. These are serious problems because we're in a time of scientific subtlety and complexity and budgetary subtlety and complexity, but these are things that we can deal with. I'm prepared to do that, but I can't assure -- you know, your question is going to hang in the question after this meeting is adjourned, and it's the question to ask. How do we know any of this is going to be translated?

DR. LANGER: Let me phrase the question slightly differently. I think it's not a question of, I'm sure you'll do whatever you can and I think that that's great. Let me just give an example of a suggestion that was made before, and maybe there's other suggestions that could be done.

Carl Peck mentioned that for example there's going to be some congressional hearings. In other words, it seems to me that what needs to be done to help you is to get -- and I'm just sort of saying this; maybe people don't agree. Some additional public or

congressional awareness of these issues, so that there will be some support if you do try to do that.

In other words, I don't think it can just necessarily happen from within; that's just my one man's opinion.

DR. FRIEDMAN: I understand. And you understand that if agency people don't comment on that, it's because that's a decision that you all have to make.

We have an obligation to show the Congress and the public and everybody that we are as effective and efficient an organization as we can be. To the extent that the case is made that scientific activity, laboratory, statistical, epidemiologic, whatever it is to the extent that that's a crucial part of our role as a public health promoter and protector, then it's part of the general package.

We are under intense scrutiny, but I am extremely proud and extremely happy with much of what the agency is doing; and that's something for you all and other people to

decide.

CHAIRMAN KIPNIS: Dr. Hearn?

DR. HEARN: I agree with Dr. Korn that it's important at this time that something happened that would be visible and continue the momentum. And in light of the difficulty, as you say, of trying to recruit the kind of person that you would like to.

So I just want to support the notion of the formation of a subcommittee that could be advisory to you, as you think about steps that you can take in the meantime. And I think your suggestion of beginning to pull some names together and informally talking with people about the position would also lend credibility to the notion that we're going to move forward with something substantive. I think that would be very important.

CHAIRMAN KIPNIS: I'd like to make a comment. One is that usually chronic illness has a long history; and people when they're 30, when they're 50 percent overweight can't say that they didn't have warning when they turned

65 and begin to have angina and pain, or arthritic complaints in their knees or other kinds of chronic illness.

So what came about as an analysis by the subcommittee of certain areas of deficiency are not totally attributable to budgetary restraints.

DR. FRIEDMAN: That's right.

CHAIRMAN KIPNIS: They reflect, in essence, certain philosophical approaches. Much of the body politic that evolved that is still present within the agency. Some is not there, some have had renaissance and revelations, but the fact is it's still an agency that has a history and a people. And part of the concerns I think that are being expressed is if the report, not necessarily all of its detailed therapeutic approaches, but if an analysis of the current illness is correct, what signs can we then anticipate that can be introduced to recognize that the agency is going to address these problems; that they will not go away by just maintaining the status quo.

I think that's critically important.

The second issue is that he signs have to be more than just verbal; they have to be associated with actions. You have to see a 50-year old now willing to walk two blocks for three weeks, and then increase it to three blocks, increase it to four blocks, but also that there has been a weight loss associated with that. There has to be some evidence over a period of time that this report is being taken seriously, and not just verbally. I think that's important.

The third is, if the accepts this report in terms of its diagnostic appropriateness, it seems to me highly unlikely that anybody will be recruited to assume the commissioner position who has significant differences in whoever it is' views with at least this element of what the Science committee has dealt with.

If it does, then I think the Science committee can exercise public disclaimer about what's going on. So I think that I appreciate

the restraints under which you and the other elements of the agency have to operate. But I would suggest also that there are clear-cut activities that can be undertaken, which are substantive, and furthermore to send a message to the younger people throughout the system, whether they be the future regulators per se or future lab leaders, et cetera, that there, too, is an acceptance by the agency that their growth and development is critical if the agency is going to be always on time.

I wonder if you'd comment on that.

DR. FRIEDMAN: Absolutely. Several of you have made the point, and I've tried to respond affirmatively, but let me do so in a way that's not mistakable. You're saying that it's very important for us to move to concrete actions that demonstrate a commitment to improving the scientific climate and culture of the agency. I completely agree with that.

Now what those should be, I could think of several, if I were writing up this list by myself, but I think one of the values

of what's been discussed here is that working together, we can come up with things that will be concrete examples, not as mere symbols, but what you start to do is to overcome a certain inertia and move in a certain way. I strongly agree with that, I very much do.

I think it's important not just for a symbol of hope for younger or older or intermediate aged scientists within the agency, it is also a demonstration that business as usual for everybody is not what we're going to do.

Now why do I feel so sure that this can be successful? The reason is, if you look at other processes within the agency, which have traditionally been criticized as being inflexible, outdated, inefficient, and where people publicly said there was no chance they would change, that there have been dramatic changes in other parts of the agency. How we review new products in virtually every one of the centers, how we look at the ways in which we carry out inspections or enforcement

activities. Every other part of the agency has been in the midst of a major revolution, a major re-engineering -- and there are objective facts to point to that.

I'm quite convinced that this agency can do that when it focuses on it; and I think one of the concerns is that this topic, this area has not been of sufficient visibility to be focused on, and that what we're doing, by the subcommittee's activity and by subsequent actions, is to raise that to the same level as some of the other things that the agency wants to do.

I am really very confident that the agency can accomplish that.

CHAIRMAN KIPNIS: Elkan, do you have any other comments?

DR. SCHWETZ: Dr. Kipnis, I'd like to make a couple of comments.

I think the report being approved and accepted by the agency at this time can have an enabling effect. Because there are a number of things in the report that we have been talking

about that this report helps to reinforce, that there's another group of outside people who see the importance of some of these activities, and even in the absence of a new commissioner, the absence of a chief scientist, the absence of a handful of FTEs to throw at this to make it work real easily, there are still a number of things that we've been talking about that are reinforced her that I think the report can have an enabling effect on.

I could give you a couple of examples: The emphasis on the interface between the reviewer and the researcher, the fact that we don't have those connected well enough. We don't talk to each other enough to compare notes on what the real research needs of the agency are. We have researchers doing what researchers think are important and we have reviewers whom we don't talk to enough to know what they would need to have to do the review job better. So we can work on that interface.

We can proceed with efforts to coordinate the research planning and the

cooperation across Centers more thoroughly than we have before. It's clearly reinforced in this report, and I think the comments here will have an enabling effect for some of us to move forward and develop that further. The accountability of the research by the researcher, the accountability of the research by a center director, by the agency in general. I think all of those are things that we can work at now that will not be counterproductive activities today, fearful that a new chief scientist or a new commissioner will change the direction of that.

So I think there are some things that the report will help to enable.

CHAIRMAN KIPNIS: Any other comments by members?

If not, is there a move to accept the report of the subcommittee?

(Moved and seconded.)

CHAIRMAN KIPNIS: Is there any need for further discussion of that issue before we take a vote?

[No response.]

If not, all in favor vote "aye."

[Voice vote]

CHAIRMAN KIPNIS: Let the record show unanimous vote in favor.

Now for a limited period of time, I'd like to bring up for the committee's discussion, this report goes to the FDA; nevertheless, it is a public report. All meetings have been held in accord with the sunshine rule, even when it's not sunshiny outside.

Are there any suggestions that we should consider about, in essence, the distribution of this report to aid its effectiveness and to be of assistance to the FDA's leadership?

There has been comment with respect to the report either being distributed to or sent to key individuals in the legislative group that are involved in FDA issues and consideration; the problem is, first of all people frequently read and determine what they

want to read and determine, even in written paper unless certain explicit comments were made or discussions undertaken.

There have been discussions about appropriate distribution to scientific outlets, and to key science editor outlets for accomplishment. Remember, Dr. Korn clearly made it evident that the issue was not to be identified in terms of being critiques; it was to bring issues of the generic sense that merit consideration and for which there is enthusiasm. But I'd like to hear comments on this so that we can be influenced by what to do.

DR. BLOUT: I'd just like to ask Mike one thing: Is it possible that the agency itself, through its Office of Legislative Affairs and through its public relations group, could undertake, in collaboration with the science board, the distribution of this report promptly, so it would have maximum effect?

DR. FRIEDMAN: Let me answer your question by saying my preference would be

something slightly different. My preference would be that this report, together with an actually concrete implementation plan of actions that can be taken over the next six months makes a much nicer package than simply having the concerns laid out in that regard.

The reason I do that is, exactly the concerns that have been raised here: In the past, the agency has not always been very sensitive to critiques or concerns; and over the last say three, four or five years, increasingly the agency has shown that it does respond in very substantive ways to critiques with objective evidence of improvement.

The basis for every one of those has been a sort of formal plan that's been laid out; time-wise, responsibilities, and what we can do. Recognizing that there are things in this report that can't be done right now, I wouldn't want this to be seen as some sort of vacuous approach -- as Bob or somebody says, it'll be the next line on that list. My concern is that it would merely be seen as that

unless it's linked to -- we say Okay, what will we do? Not What can we do. We can do a lot of things; what will we do over the next six months to positively address and improve the environment.

I think that we can begin to craft that pretty quickly. That's my preference. I understand that people can do other things with it. I just wouldn't want this to be seen as merely the next line on that list of failed opportunities. To the extent that you and I and Bern and the center directors and others who are deeply committed to this, can make this different than that, we're going to do so.

DR. BLOUT: I'd answer you, Mike: I think it would be very good to do it that way, but there's also this time line. And since this now will be a public report, what can we do to help the perception of this report be positive rather than negative?

DR. FRIEDMAN: I'm not sure I know the answer to that, and I'm certainly not trying to manage this. I've heard things today that I

would hope the public would hear. I've heard a deep commitment. After careful analysis, not just a reflex: "Oh, science is good" -- but a very thoughtful examination, a rather probing examination of how different models for doing science within the agency, and then the conclusion after a lot of very careful thought and discussion by this subcommittee, that there was the need for internal science, but it had to be of the very highest quality, it had to be mission-relevant, and so on and so forth.

Restating that, I think, is a very important thing -- not coming from the agency where it might be misperceived as being self-serving; that's not what I intend here; but by very critical outside people who have only a vest interest in what's best for the country. And that's what this board stands for.

There are things that I think have been said in the report, have been said by people in discussion here that lead to a positive set of conclusions, a positive outcome. And granted that these are

unpredictable and difficult times, real commitment that you all continue to want to work collegially with us in coming up with a better model.

DR. WONG-STAAL: First out of curiosity, I don't know if support of science in the agency is even a determinant in the choice of this new commissioner. Isn't it likely that we may even get a new commissioner who doesn't agree with the given or diagnosis, as you put it? And taking some action now, sending a strong message out to the agency or to the Congress or whatever, would that help make an impact on the decision?

DR. FRIEDMAN: I'll try and answer it but I can't, because I can't really full understand the perverseness of how things get decided. Or what the criteria are.

It's not inconceivable that a new commissioner wouldn't agree with this; that's a possibility. And as disappointing as that might be to those of you on the committee, that's a possibility. My own hope is that the

new commissioner would care about science in the agency and he or she might not necessarily agree with the particular remedies that are proposed here, but would have equally good or perhaps even better approaches that they might want to take.

All I can say is, I think there's an awful lot that we have control over in a day-to-day way, and that mu usual belief about this is that when someone comes in and inherits an enterprise that is successful, that they are really loathe to change that. And when somebody inherits something that isn't so good, they look at all different ways to do it.

To the extent that the agency, in every aspect of what we do; science -- regulatory and other things, to the extent that the new commissioner inherits an agency that is somewhat better than the agency that exists now, all of us in the agency will be very happy. And I think it's less likely that that new individual will want to change things.

So what I'm suggesting is that if we

can get started and do some things that are producing better science, or saving money, or that are seen as more efficient and effective, that that person will take ownership of that. That's as it should be.

DR. KORN: I think I understand the difficulty, Mike, that you're in, in a time when the commissioner's job is open, there's a lot of politics out there, and nobody really knows who or how quickly that job will be filled.

I want to make a comment that's a personal comment; but I think that maybe the whole committee might agree with it. I don't think this can be fixed entirely from withinside. And although it may be that over the near term the best that can be done is to work with what you have within the agency to do what you can do, and I certainly applaud that.

I think it would be a terrible mistake and a terrible misreading of the committee's judgment to believe that without some major change of the kind recommended, that

establishes within the agency a very senior and very strong and very respected and articulate advocate for science, with enough power -- using the 'P' word -- enough power to implement or see to it that some of these mechanisms are changed and improved, it will not happen. That's my prediction, and it will be another paragraph in Appendix D, for some future committee.

Now if you look at the history, Mike -- and again, this was an interesting research project for me because I had no idea about any of this before I started. The frequency of these efforts is really -- the frequency is really quite short. It isn't that there was a committee in 1910 and then in 1930 there was another one, and in 1955 -- these things are like a few years apart, which is not a happy sign. It says to me that a well-intentioned, thoughtful effort is made, and very quickly sinks without a trace below the waves, and then a new commissioner is appointed or a new secretary of the Department is appointed and

said "Hey, we've got to look at that again." So there's a kind of a, a very frequent short, short time frame between these things.

That says to me that whatever this disease is, it can move quickly. No, that's not the word. The recommended approach has a short half-life.

DR. FRIEDMAN: It's a sort of administrative winky-bok.

DR. KORN: Well, the recommended approach has a very short half-life. And it either is seized and implemented or addressed early, or it really decays very, very rapidly and sinks; and I think that that's a real danger. And I think that without in any way misreading the difficulties that you have because of the circumstances of the agency that you can't do anything about right now, that if you misread the central fact that an external force is necessary of the sort outlined here, I think you're really making a bad misreading of the entire report.

DR. FRIEDMAN: David, I don't think --

I'm not misreading that. What I'm saying is what's possible now and what's not. The easiest thing would be to say "Oh, I can't implement any of this" because of the current climate. I think that would be -- that's just insupportable right now. So what I'm saying is that given the authorities that I think are appropriate during an interregnum, it would be -- we could do some concrete things, we can begin moving on this. These sorts of solutions certainly have my personal support and backing, but I'm not going to promise something that I can't deliver, not to you and not to the agency.

DR. KORN: If the Science Board accepts a document of this sort, do you distribute it to the members of your agency? Is it accessible?

DR. FRIEDMAN: Yes. I think that this is a document that will have very high interest to really large portions of the agency.

DR. KORN: So it will be made available?

DR. FRIEDMAN: Ye--

DR. KORN: Good. Because again, I think that there's a large cohort of people in the employ of the agency for which the agency should be very thankful, who care deeply about it, including the leadership. I mean, absolutely. I'm not excluding the leadership, but I'm saying at the lower levels of the hierarchy; and I think it would be good for them to see that the committee, this board and you, and your leadership colleagues do know they're there, do appreciate their efforts, do care about them, and do wish to do something to make it --

DR. FRIEDMAN: That's right, but let me just extend that for a tiny step further, which is to say that it will have that effect, and that's good. But the other effect it will have that I think is really far more important, is to say to people: This is a problem, this is a set of problems that we share. It is your responsibility just as it is my responsibility to come up with the innovative solutions, to

break through whatever historic barriers have existed or with whatever limitations have been perceived.

Again, this is very important, I want the agency scientists to take ownership of this; they are not passive victims. We all share a vision -- it might be slightly different. But in large measure, it's a common vision of what sorts of agency science we want to have, and what sorts of expertise and what sorts of skills, and by having this out there, people then will subscribe to being part of the solution.

DR. KORN: Right, but sharing problems between the very powerful and the relatively powerless is tricky.

DR. FRIEDMAN: Being one of the powerless, I completely appreciate what you say.

(Laughter)

DR. BLOUT: David, maybe this is an appropriate time for us to announce that we thought your excellent report would be accepted

by the Science Board; it has now been accepted by the Science Board, and copies of the report are now available to anybody in this room who wants them, as a beginning.

DR. KORN: Whatever your agency process is, I don't know.

DR. BLOUT: We can make it publicly available now.

DR. HEARN: What's not clear, though, from this exchange is whether Mike feels that there are some disadvantages in making it more broadly available.

DR. FRIEDMAN: You mean outside the agency?

DR. HEARN: Yes. It's very clear that one of the problems is, or one of the problems may be a failure of people outside the agency to understand the relevance, the essential nature of having this, improving the science base. In order to carry out the very responsibilities that everybody feels so pressured to carry out.

DR. FRIEDMAN: Thank you. Let me

comment on that.

I frankly do have some concerns because I'm afraid of selective reading of this document, where criticisms will be emboldened and positive statements or potential solutions will be either not mentioned or minimized. And that's the reason why I'm perfectly happy to have this document out there.

I think a better way to have it out would be with a mirror action plan that says "and here's how we're going to do this" so that, as I've said before, it doesn't seem like it's just another footnote in that list of opportunities that have been missed. The agency wants to grasp this, but that's not entirely under my control.

What I'm saying is: How would I optimally like to do it? That's the way I'd optimally like to do it.

DR. HEARN: And how long would it take to prepare a draft of your implementation steps, understanding that you have a preamble that explains the things that you couldn't do

because you don't have permission --

DR. FRIEDMAN: You see, I think it's going to take longer to think about than it is to write it. Because I see this really as something that doesn't have a lot of verbiage: These are the things we're going to do, who's responsible for this, and when we expect to have certain milestones met. I would have it really as an action plan and not some sort of verbose defense of either what's existed or explanations of why we couldn't do something.

I wouldn't waste any time dealing with that. What I would say is: Here's what we're going to do in the next few months. To the extent that I can identify people today who would be willing to serve on that committee, I think we would re-create, Susan with your permission, the virtual mailbox; we'd begin to start doing that and that we would try to fairly quickly come up with some concrete proposals.

I would want to engage more than the subcommittee -- I think that the Center

leadership, the Center directors have a vital role to play. I think Bern, from his particular perspective, has a very important role to play. I think that the agency science groups have a role to play, and that individual scientists have a role to play.

So I would want this to be a very participatory activity, but it would be -- it would be something that would evolve, so it wouldn't be like you'd have to pick only the top six ideas, and everything else is thrown away. What you do is you take the top six ideas or the top 30 ideas, whatever it was, assign people, get started on it, then realize that more could be done, we can add to that. But I'd want to have something out there that says "And here's how we're going to move with this."

DR. HEARN: And how long would that take, do you think, to have something that you'd feel comfortable appending to this report?

DR. FRIEDMAN: Well, I haven't given

it any thought. Let me think about it for a second.

Maybe while I'm thinking about it, let me turn it around: What do you think is realistic?

DR. HEARN: Well, I don't think that the implementation plan has to detail all of the things --

DR. FRIEDMAN: No. No, no, I'm talking about just a general -- but it's got to be real enough so people don't just say so that you're playing with us.

DR. HEARN: Yes. Well, my view is 'shorter is better.' Because I'm concerned about losing some of -- losing the momentum; and I'm also concerned about the credibility within the agency; of what it means when you say a report is accepted.

DR. FRIEDMAN: Sure.

DR. HEARN: So I would be happier to hear that at least -- and everybody understands that, you know, there will be iterations of these things; but that you could put something

together that you'd be comfortable with putting next to the report.

DR. FRIEDMAN: So a first cut in -- what.

DR. HEARN: Because actually, what you're trying to convey to people is that you agree with the findings of the report, and that you see room to move in the direction. So I don't think it has to be a very detailed response to deal with your issue of not wanting it to appear that you're on one side of the table and the report's on the other side of the table.

CHAIRMAN KIPNIS: I'd like to follow up on Dr. Hearn's comment, if I may.

A very wise man once told me that members of a board of directors, such as we might be, should feel free to stick their nose wherever they want as long as they keep their fingers out.

And I think that that's true of a science board. It's not up to us to even sit on a committee that helps you reorganize or

reorient or reeducate. We're available to consult, but as constituent members of that group, that is in essence an intrusion upon what the agency should be primarily responsible for, I believe.

We're all available by E-mail or by telephone to comment whenever asked to comment, but we ought not to be part of an organized activity to see how a plan is implemented. I think that may be setting the wrong precedent for what a committee's function really is.

The second is, to paraphrase my old professor of medicine: what you're telling me is that life is hard, and I already knew that. And that was the comment he would always make when you were up all night and didn't get the blood count done.

It is difficult, but I really think that it's up to the agency to respond now. With all of the administrative problems that the absence of a permanent commissioner introduces, but I do think that they should respond, and in a prompt fashion, because that

committee spent a year talking to lots of those people; and in essence what they recommended and what we as the parent committee have accepted, is the distillation of all of the information and thought processes that went into effect.

So I think that we have a right to expect, or let's say we should have an appropriate expectation that clear evidence of implementation is introduced promptly. The committee may have to take independent actions of its own to see to it that its recommendations are not neglected. That's not a threat, that's a fact. I mean, they didn't stay here working to see something, in essence, put at the bottom of the list.

So may I suggest that what we do is probably we'll be in contact with E-mail with all members of the committee, and by telephone. We've already accepted it, so that's formal. But we ought to give thought to what should the committee's subsequent actions be to in essence reinforce the nature of the report, the

importance of the report; but to undertake activities that don't impede its implementation by the FDA, but can be of assistance to the hierarchical structure and not be an actual operative part of that activity. I think that should be the responsibility of the agency.

DR. FRIEDMAN: Let me say a couple of things, if I may. I think that we can reasonably take a cut of this and have something available in two weeks' time.

I've heard two different proposals made by members of this Board, some of whom have expressed an interest in participating in such an activity, and then Dr. Kipnis saying that he thinks it might be less ideal to do so.

While you all wrestle with that, we will engage internally in the following things: I will ask the senior and the junior science councils to formally consider very specific, concrete things that can be enacted within the next period of time -- by that I mean the next several months, and that it's their responsibility to get this not in a long prose-

filled form, but in an action plan; and the action plan must say what's going to occur, who's responsible for it, what the time line is; that is, when we will achieve certain things, and what the expected outcome is.

So those are the four things that I'm going to ask the senior and the junior science council to do. I'm going to ask each of the Centers which have a chief scientist within each of the centers, to give consideration to exactly the same things. And what I'm asking for here is, "I do not want to hear how we can improve science in an individual center." What I want to hear is, how do we improve science, laboratory science as we're describing it in the agency. And a premium will be placed upon the more innovative and the more creative, and the more promising the approaches.

Those need to be given to Susan Homire, and they need to be given to her by -- what's today, Thursday? I'd like them next Thursday, please. I understand that's a very short time, but it will allow me to make the

two weeks, at least for a first cut that we'll get.

I then charge each person on this committee with E-mailing Susan names, addresses, phone numbers, and two or three sentences about background, of particular individuals that you would feel highly qualified, or particularly appropriate for the chief scientist that we've talked about.

CHAIRMAN KIPNIS: On that positive note --

DR. FRIEDMAN: Well, now wait, I'm not through -- I'm thinking this up as I'm saying it.

And of course the last thing to do is to say --and what else do you all suggest? This will give us a start. I think that I'm going to turn to the Center directors, I'm going to turn to other leadership within the agency for further thoughts.

What we don't want is some hasty, ill-conceived sort of galvanic response here. That's not what I'm after. I've set a time

line and I've asked people to deliver things. If what we get in that time is not an appropriate plan, it will not come out and I will have missed that deadline, but that's the deadline that we will set.

We're not going to do things in a hasty, ill-considered fashion. This problem didn't occur -- David's analogy to a chronically ill patient is the accurate one; you don't take somebody who has had a chronic illness and try and suddenly treat them. That is not good for the patient. We will make a considered approach to this, and we will try and do the things that will have the best impact.

CHAIRMAN KIPNIS: Fair enough.

Is there a motion for adjournment?

(Moved and seconded.)

CHAIRMAN KIPNIS: Thank you.

[Whereupon, at 2:24 p.m., the meeting adjourned.]

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