so enormous. It's got geographical, regional -- as well as all the different things you have to cover. Has that been thought through?

MR. BAKER: We've given quite a bit of thought to trying to scope it down, and we're going to be utilizing our advisory committees to assist with that.

But you're correct. If we looked at everything that we do, first of all it would be hopefully several years in our process, but we want to look at the key elements of what we do. Which is, how our investigations are done, the basic decision-making that goes on from the investigator all the way to the supervisors, the laboratory side.

We want to take a balance, and we can take some things such as this food-borne illness investigation, or perhaps take a look at one of our drug counterfeiting investigations and look how the science played out within those; and take a look at what

worked and what didn't, and when we've had failures, what contributed to the failure?

DR. SCOLNICK: I think one way of restating it is, picking upon Marty's comments is, you're starting a process of reviewing your process and what you've done in order to really make sure that you ensure the highest quality of the whole system.

And that's not a one-time event. Maybe this process is new; I'm not really sure since I've only been on the advisory board here for a couple of meetings. But assuming the process is new for the moment, you're starting a process so you could start it and decide as an agency that you're going to do this continually ever year or every couple of years; and you're going to have some kind of review group that will be partially the same and partially different over time. You're going to update them on what you've done; once the first review occurred, you'll bring new topics to

them on a rolling basis and really institutionalize this review process, which will inevitably bring the quality of it up, of the whole system over time.

MR. BAKER: We hope to get that institutionalized as part of the Quality Management System, though we do have a core group in headquarters that manages and coordinates the QMS, so this would be envisioned as something that would be a component of our QMS.

DR. LANGER: Bern, you wanted to make a comment?

DR. SCHWETZ: Two comments, actually.

Bob Buchanan will remember that when CFSAN was reviewed, there were comments about the ORA support of CFSAN. And I think, Dennis, as we look at how the review of ORA should be done, we ought to look at what we might have learned from the CFSAN peer review about the questions that were raised about the ORA

interaction with CFSAN, because that will give you an indication of where the science or the performance or whatever else may have been questioned.

MR. BAKER: Good point.

DR. SCHWETZ: The other point I wanted to make was coming back to is what happens afterward when the report is written by the peer review team and it's accepted by the Science Board, the Center has seen a draft copy of that by the time it's finally reviewed by the Science Board, and what we expect at that time is that the center director will come and say what they're going to do about it.

That then becomes part of the accountability that the commissioner expects out of the center director, is to keep track of what happened to those recommendations that were made by the peer reviewers to the commissioner through the center.

So there is an accountability that

follows up on that.

DR. SCOLNICK: I would just make the comment I made before. For example, in our laboratory we have a system, and universities do this, but we do it in a slightly different way.

We have an external group that comes in and reviews a variety of our programs three or four days in a row, once a year. A terrific group of people. They write a report, they give a verbal report to the chairman of our company, they come in every year, and we give them follow up on what's happened the year before as we put in a new series of things for them to review.

So over the course of time, it's a continual review process; it's a continuous improvement process with an external group peer reviewing us, even though we are an industrial lab. You're a government organization and you're much more in the public limelight than

we are; you know, we are also in the public limelight.

It's a wonderful system for keeping the quality up over time, because the external committee -- you're forcing yourself to interact with an external peer review group continuously. What you've done based on their recommendations; what you haven't done, why, what you're going to -- et cetera. It's a wonderful process to institutionalize.

DR. LANGER: Cecil?

DR. PICKETT: I'd like to add to Ed's comments, and it's fresh in my mind because I just came from a Board of Scientific Counselors at the NIH. And again, with a new Board of Scientific Counselors, the way the NIH has formatted it over the last couple of years, seems to work well.

Again it's an external peer review group that comes in that reviews the science and the individual laboratories. The results

of those reviews are then given to the intramural director of research, who can review it at a higher level. And it's a continual process that occurs.

And what it does is really institutionalize peer review and hopefully excellence in the laboratories.

So that's another model to take into consideration.

DR. LANGER: Other comments or suggestions?

DR. DOYLE: Just to follow-up with what Bern had to say, I think it would be important to include in the review areas where there may be data gaps in the science as you go about an investigation, and what do you do to fill that hole? And what should you do in the future?

MR. BAKER: Good point, very good point. And that is an issue for us to -- a true issue.

DR. LANGER: Anything else?

Okay, thank you.

I think we'll move the schedule up a little bit. The next topic is *Emerging Science Issue: Tissue and Tissue Engineered Products.*

At the November Science Board meeting each FDA center director and ORA identified key topics and priorities that were confronting them, and we said that these topics would provide the basis for future in-depth discussions at subsequent Science Board meetings, so the emerging science area of tissue engineering will be discussed today by David Feigal and Kathy Zoon. And Bob Nerem actually had some input on this as well.

And that's something we'll probably continue to do, and I think it's actually quite consistent with some of the things that Ed and Cecil were just mentioning, and we'll want to continue that as well as other things that come up here today.

And I was just asked, am I going to let people have a break? The answer to that is yes, right after this.

Emerging Science Issue:

Tissue and Tissue Engineered Products.

DR. ZOON: Thank you. I'm Kathy Zoon from the Center for Biologics, and David and I are going to do a joint presentation today on tissue and tissue engineering, and I will kick off the presentation.

[Slide]

CBER has been involved in the regulation of cells and tissues for a long time; and probably our first interaction with cells and tissues came from our blood program; which has a long history unto its ownself which I will not cover here. And maybe for a future time.

But the scope of the products that I'd like to present to you today covers some of the initiatives that we're currently undertaking in

conventional bank tissues for transplantation, somatic cell therapies, and I'll spend some time on that; gene therapy, which is clearly a major issue and area of involvement of the Center. Some of the activates as they impact on reproductive cells, human reproductive and therapeutic cloning, as was mentioned earlier by Bern, and looking at combination products and some of the challenges in that area, and xenotranspolantation.

[Slide]

Looking at where we had come from, really the issue of combination products, we're first back to a 1991 document published in the Federal Register which really looks at interagency jurisdiction issues. And I would just mention this because this serves as the foundation today where our decisions are made. But clearly, activities and interactions are ongoing in the centers on tissues and tissue engineerings between the CDRH and CBER on a

daily basis.

Probably the first major statement of the Center with respect to cellular therapy, somatic cell therapy and gene therapy, started back in 1993. We have began in 1989 getting submissions in these two product areas, and we wanted to clarify our jurisdiction and expectations in this area.

Also at this time there were a series of tragedies that occurred, with the respect of importation of contaminated tissues that were intended for transplantation that led the FDA at that time to establish an interim final rule of human tissue intended for transplantation. Some material came in from Russia that was contaminated with hepatitis, and was intended for transplantation, and that tissue was confiscated and led to, within three months, a interim final rule to take charge over this, really with the focus on infectious disease testing for both hepatitis and HIV alone; it

did not go beyond that scope.

In 1996 the agency also issued a guidance document on manipulated autologous structural cells for transplantation, and that really dealt with, what's the chemistry, manufacturing and control issues as well as other policy issues surrounding that product area.

We went on, then, in 1996, to work as a Public Health Service team with the National Institutes of Health and the Centers for Disease Control and Prevention and the Department of Health and Human Services to look at xenotranspolantation. We were starting to get a number of products using live cells, tissues and potentially organs for therapeutic applications and the concerns about the transmission of infectious diseases, zoonotic infections, and potentially of a pandemic as a result of this was clearly on the minds of individuals in the PHS.

So this draft guidance was published and served as the framework on which many of our decisions were made in subsequent review of these applications.

In 1997, we published our chemistry manufacturing and control guidance document for somatic cell therapies. We also issued the final rule for human tissue intended for transplantation, and we embarked on a new initiative, which was the reinventing of the regulation of tissue.

There was a lot of concern at this time in Congress about the regulation of tissues, who was going to take over this program. Clearly, some of the impact of the infectious disease risks were on their mind, and also a more global picture of how are we going to integrate all these tissues that the agency was dealing with in cellular therapies to form a logical regulatory approach for these products.

So I will be spending some time describing that to you.

In addition, in 1998 we formally established a Tissue Action Plan; we have continued working on this action plan. CBER has been the lead but we've had participation with CDRH and the Office of Regulatory Affairs and the Office of the Commissioner as we move forward in these initiatives.

So what is this proposed approach? Well, it's a risk-based stratified approach, with the opportunity with those tissues that provided the lowest risk having the least amount of regulation and subsequently as the risks increased, have a higher level of regulation.

These tissues, in terms of the least regulation, were predominantly going to be regulated using the Public Health Service Act, Section 361, which is, primary intent is to prevent transmission of communicable diseases.

And in this case we define those types of tissues as having the following properties: One, that they were minimally manipulated, there wasn't a lot of processing of these tissues, and a lot of growth or extra factors or devices being applied to these tissues; that the labeling or advertising or the intended use of this tissue was homologous, or it was used in the same way that the original tissue was intended to be used.

Next, that it wasn't combined with either a drug, device or biologic, only within certain exceptions, and also that it was not dependent on metabolic activity of those living cells for primary function, and did not have a systemic effect. And there's a few little exceptions to that that I will talk about later. And that there was no premarket review of this. There would be registration, there would be listing, there would be certain expectations to follow certain regulations that

we're in the process of developing now that I'll speak to you about, and an inspectional program, but no premarket review.

[Slide]

What was included in this? Well, it was musculoskeletal tissue, ocular tissue, some particular cellular component such as potentially hematopoietic stem cells, some classes of them, a fair amount of the reproductive tissue, heart valves and dura matter, and skin.

What was not included was vascularized organs, bone, and xenographs, and I'll speak to xenographs as a separate class. They were not included because xenotransplantation had its own set of issues, and we broke that out as a separate action plan. And of course blood was not included and secreted in extracted products.

[Slide]

Well, there was a kick-up phase. And

that meant that if you did not meet the criteria that we established for the Public Health Service Act Section 361, and that there was safety and effectiveness concerns or more than minimally manipulated, or that the labeling extended beyond the original intended use or replacement therapies, then this would be kicked up into a higher level of regulatory oversight. And they would be regulated as drugs, biologics, or devices.

Some of the types of cells in gene therapy that we are dealing with right now in the Center for Biologics include gene therapy; and this can include everything from plasma-derived DNA through looking at the transfection and transduction of cells to put in different vectors in order to express certain properties that we would like, and with the intention of providing a therapy for gene therapy. Much of the ex vivo gene therapy that we now regulate clearly involves a fair amount of manipulation

which is consistent and has a higher level of regulation. All the products here that CBER regulates for the most part are described in this document, are regulated under Section 351 of the Public Health Service Act and would require a biologics license application.

Many of these products pose certain important control factors with respect to not only the infectious disease issue that was raised earlier, but safety and efficacy concerns and how these products would be used, labeled and developed.

The mechanisms would normally be whether or not it were regulated at the Center as a device under a PMA or as a biologic under a BLA, would use either an investigational new drug application or an IDE in the case of a device. And the criteria that would be used would be the same regardless of the mechanism as the baseline, the foundation, the characterization, the cells, the infectious

disease control would all have the same baseline. And we would go from there based on the issues surrounding those products.

With some of these biologics, there is a level of complexity that we have to address; and this is one specific example where you're actually doing self-selection of cord blood and then taking these selected cells and doing transduction with them with a particular factor. Normally, these cells will not grow on their own and you'll have to put a variety of growth factors in there to actually get these cells to replicate; and these include a number of cytokines and growth factors.

Once you get a population of these cells, they are then re-infused into the patients and monitored accordingly.

So there are several levels and what I would call critical control points as well as processing validation issues as one goes through these processes.

Xenotransplantation is another area that I mention, and because of our interrelationship with the Center for Disease Control and the NIH, we have been working as a team and have had several unique issues, some not so unique, because we've used for gene therapy public mechanisms as well, and I'll point those analogies out to you.

We developed an action plan which covered looking at the products themselves, and from the animal sources and the controls and animal husbandry procedures, through the production of the product, through its characterization and then on through the delivery to the patient itself. And then what kind of monitoring of the infectious disease transmission and/or the patients themselves would have with respect to these types of products.

As with gene therapy, there is an issue surrounding the ability to disclose

information to the public; and this is a very sensitive area. The Agency has put a proposed rule out in this area for both products related to xenotransplantation and gene therapy. Historically there has been a free sharing of information to the Recombinant DNA Advisory Committee with respect to gene therapy as well as with xenotransplantation.

So the foundation of this proposed rule has been based on, to a certain degree, the information that's already available in the NIH guidelines, Appendix M, which is used for gene therapy products; as well as the information that has been presented to the FDA Subcommittee on Xenotransplantation, which is a subcommittee to the Biological Response Modifier Advisory Committee.

In addition, because of the nature of the xenotransplantation, there was actually the formation of the Secretary's Advisory Committee, DHHS level, and that first convened

in February of this year, and we are right now getting the group up to speed on the issues surrounding xenotransplantation, and the next meeting will take place later on, early summer.

I mentioned the Burmack committee, subcommittee. There's also, and CBER has the lead on the National Xenotransplantation Registry and Database. This is particularly geared toward looking at infections disease transmission, particularly with recipients of xenotransplanted organs, tissues, and cells.

The nature of this is to be able to have a public health response in case there was an infectious disease transmission, in order for the Public Health Service to be responsive and take action.

There is also a proposal for the Centers for Disease Control to work on a, potentially in the future, a repository for both the animal tissues and the human recipient tissues in order to monitor this process.

Again, this is currently now being directed toward those sponsors who were engaged in this therapy to preserve those samples, and work with the Public Health Service agency in case an event did occur.

To give you a scope of the level of the workload in this area for the Center for Biologics, we currently have, on an annual basis, a large number of somatic cell therapies, which is the red line. Last year alone we received 112 submissions and these submissions continue to increase.

Gene therapy submissions were on the rise. With the death of Jessie Gelsinger there has been what I would call a self-imposed cutback in looking until some of these issues are resolved; so in terms of new submissions into the agency, they have decreased. However, I would say there is an enormous amount of energy being spent in the gene therapy field, looking at internal quality of their products;

and a lot of submissions have been received in the gene therapy area, making improvements to their oversight of clinical trial monitoring plans as well as product improvements in addition.

So last year we had about 1670 gene therapy amendments and about 1300 somatic cell therapy amendments.

[Slide]

One of the big areas, and an area that has a controversial impact as well as routine, what I would say scientific issues, deal with stem cells. The Center currently regulates a wide variety of stem cell products, although we do not have any embryonic stem cell products at this time.

But we are looking at a variety of different stem cells with the intention that these stem cells will be differentiated and used for tissue engineering or tissue replacement.

Some of the types of stem cells that we're looking at, and particularly those with the most interest have been the pluripotent stem cells. While we look at other types of stem cells and in particular one of the areas, certainly looking at stem cells from cord blood and peripheral stem cells. These have been used and are looking at very much based on a standards approach, when they are not more than minimally manipulated.

However, looking at pluripotent stem cells and their ability to differentiate to a variety of types of tissue forms is currently underway.

One of the areas of interest and continue to be both the mazemkimal and blood area in determining different types of tissue that may potentially be useful for therapeutic purposes. Those areas are continuing to grow, and we are looking at a program now in the Center, particularly in light of what I would

call 'developmental biology.'

And this I think is really going to be the area of the future, and we have recruited two or three people in this area because the ability to know and understand this field more in depth and to have a better sense of the critical control points in development is going to be key.

So this is an area that we're looking for good people in and recruiting, based on what we see the future of the science in the Center, and be able to have the expertise. And we'll continue to move in that area.

[Slide]

Obviously the most controversial area is embryonic pluripotent stem cells. Somatic cell nuclear transfer has been the primary mechanism to create these types of stem cells, with looking at the opportunity to cause these stem cells to differentiate into a variety of tissue types ranging from heart, liver, skin,

and a variety of other tissues as replacement therapies.

Clearly, looking at new sources, the report and the literature and in the newspaper recently, I'm looking at the possibility of Pluripotent stem cells in fat -- I'm all for that. I think that would be quite exciting. But there's a lot of controversy.

It's controversy because of the whole issue surrounding the use of fetal issues, it's a political hot potato, and it is one that one has to really work with the various scientific communities, with the National Bioethics Advisory Committee, which we have done in order to get the best advice on how to proceed within the framework of our congressional mandate and jurisdictional responsibilities.

[Slide]

The ultimate, though, is in human cloning. A couple weeks ago I testified for the Agency regarding the use of cloning

technology for cloning a human being.

Our jurisdiction does extend, we believe, over the technologies that would lead to human cloning; however, I would say it is really focused on the scientific issues. And our determination at this point based on the state of the science, and I think it was well reflected during the testimony that we heard at the hearing by a variety of experts, that the scientific issues surrounding the use of somatic cell nuclear cloning are fraught with a great deal of scientific concern, both for the potential offspring as well as for the mother.

And these range from everything with respect to our knowledge of the ability of these types of cells to properly differentiate and to develop into a human being. There are issues with regard to imprinting that we don't understand the science; when genes are turned on, when genes are turned off.

And I think Dr. Yanish from M.I.T.

really had the correct evaluation at this point of the science. Thus far, there has been no normal clone in animals. And looking at, there is always some problem -- whether or not it's obesity, whether or not there are critical control elements that lead to the death of those cells during development, clearly there are problems all along the way. And I think from the issues surrounding this, the FDA took the position that even if someone would submit an IND at this time, we believe the scientific concerns would not warrant that IND going forward.

I believe that this is going to continue to be, while the state of the science of many of the individuals dealing with this issue are not at the level of what I call the most sophisticated, there is enough interest in this by individuals who have experience in assisted reproductive technologies that I think that there clearly will be some folks

interested in proceeding in this.

So the National Bioethics Advisory Committee clearly made their evaluation that they believe the safety issues were paramount not to go forward. They also made statements that there were important societal and ethical issues that needed to be addressed; and right now the Department is engaged in this set of activities, and clearly scientifically there are many unanswered questions. And we will continue to be providing a source of information on this topic and getting more engaged in the oversight of this area which we are now heavily engaged in.

[Slide]

So where are we today and where today, the status of tissue regulations; these are the implementation parameters for our tissue framework that I described to you, and it includes one final rule, which is the establishment and registration and listing;

this lays out our framework for the regulation of tissues, cells, and related products. And that's currently underway; April 6th was the date when this registration and listing has gone into effect, and we're receiving those documentations now.

This particular rule right now only applies to conventional tissues that are currently covered under the existing tissue framework, and does not include reproductive tissues or other tissues that did not fall under 1270, which was our original final rule. These will kick in in two years, so in 2003 those registrations and listing will begin. Although it's voluntary if people wish to do it before then.

What's important to remember in this framework is that it will include reproductive tissue and we are going to work very hard over the next two years if this is to go forward, provided we can get resources for this, to work

with the reproductive medicine societies to look at the appropriate level of oversight for the different types of products.

This would include in vitro fertilization and the more advanced technologies, ICSE and others which are being used to provide new mechanisms for assisted reproductive technologies, and finally up through the use of cloning technology to create a human being.

We also have proposed rules for donor suitability, for tissue and cellular products. This includes infectious disease testing, donor screening, adverse event reporting, good tissue practices -- again, processing of tissues; this proposed rule is out.

We hope as, and our target for implementing all of this if appropriate resources can be obtained, will be two years from the date of the publication of the tissue registration and listing rule.

[Slide]

So I just, in terms of where we are with the final rule, what creates a unified registration system for all human cell tissues, base products, including tissues, biological products and devices, and delineates regulatory categories.

The who, it will be human cell tissue and cellular tissue-based establishments, and here are the exclusions I mentioned already.

The how is a one page form. It will be available electronically in the future. Right now you can get the application form off the web, but our goal here is in the next year or two to be able to register on line; and as I mentioned, it starts April 4th this year, and will go on to other types of tissue products in two years.

[Slide]

We've had a fair amount of oversight in this area; I've just listed it here. If

someone is interested, I'll be happy to discuss it with you; but clearly the IG report would like us to spend more effort in tissues; and part of that is the tissue regulatory scheme I've outlined.

[Slide]

Future actions in this area will be working with the American Association of Tissue Banks, working with the American Society for Reproductive Medicines and other interested groups, holding scientific meetings, public meetings on where we're going in the regulation. Some of the jurisdictional issues and clarifying issues are being discussed by a joint setter tissue reference group, which consists of members of CDRH and CBER; and Ruth Solomon is here.

Ruth, raise your hand. She's one of the cochairs of that group, and has been instrumental in actually writing many of the tissue regs for the Center for Biologics. And

issue guidances on proposed rules, and working with our advisory committees and we're also working with the Department on Assisted Reproductive Technologies.

So I'll end there, and thank you very much; and David, if you would like questions now or we can wait.

DR. FEIGAL: Why don't we wait, because I'll be brief, because you covered so much that it wont take me as long.

[Computer setup]

DR. LANGER: Why don't we ask questions?

DR. FEIGAL: Ask questions for a moment, yes.

DR. LANGER: While we're working on the computer, questions. Bob, yes?

DR. NEREM: There will be other questions after David, but I'm curious as to your own view of change in rules over in the UK which, as I understand it, allow the use of

cells from embryos for research purposes beyond simply reproduction research.

DR. ZOON: I believe they are allowing for therapeutic cloning, somatic cell nuclear transfer of eggs up to 14 days post-nucleation with the, or what I would call an oocyte that contains the genetic material from a somatic cell nuclear egg cell, up until 14 days.

That's a position that they have taken; it's not without controversy. I'm sure that's under discussion by the Congress as to whether or not that's an appropriate pathway for the United States.

This is not an area that I think -- this is more than a scientific issue. Because the issue of when the critical time points are for this go beyond the FDA jurisdiction, and I think are issues that I would hope that the impact, which is the National Bioethics Advisory Council, would weigh in on as well as interested parties.

The Congress will decide, if they proceed with legislation in this area, how they're going to manage. I think it's going to be quite controversial, quite frankly. And several years ago when FDA first established jurisdiction in this area, there was an intention in a number of bills introduced back in early '98 to have a law on cloning with respect to reproductive cloning.

That issue of where that demarcation is for therapeutic cloning and reproductive cloning became quite controversial, and the law was never passed.

So I feel Congress is going to continue to have some important discussions in this area to see if they could come to closure on this issue.

DR. LANGER: Do you want to--?

DR. FEIGAL: Why don't I just go ahead.

DR. LANGER: We'll definitely come

back to you.

DR. FEIGAL: -- complimentary, and then we can both take questions.

[Slide]

This is a slide that actually summarizes many of the things that Kathy was talking about; what I'm going to focus on are the tissues that are more engineered.

This is another way of summarizing, sort of the consumer protections for tissues. Preventing unwitting use of contaminated tissues, preventing improper handling or processing that might contaminate.

But it's in that last category that you find the products that aren't going to be handled in the tissue framework of the non-manipulated tissues. These are the products that are either highly processed; they're used for other than the normal function, are combined with nontissue components, or are used for metabolic purposes.

For example, an artificial pancrease or liver. There are a lot of new technologies in development. This is a picture -- this is purported to be, this is from Wired magazine, of a pediatric heart valve that's been tissue engineered; it's designed to grow with the patient, is the claim; and that's one of the current valves for children, is that you have to replace them as they grow.

But let me show you a product that's actually been approved, and I just picked the most recent tissue-engineered product; there could have not been very much of these; the types of tissue engineered products that we currently evaluate in the Center are the ones that are familiar to the non-tissue engineered products; and one of the products the Center for Devices has are the skin coverings or the artificial skins typically used in burn settings, but this is an example, and this is the press report of the approval of an

artificial skin for a humanitarian device exemption for young patients who suffer from Edipermolysis Bullosa.

This is the start of the label, and it highlights a number of things. One, this is approval under the humanitarian use exemption. This is a part of the device law that's probably more similar to the treatment IND in drugs, if you're familiar with that, than it is with orphans.

But you could see here that the humanitarian device exemption limits the use of the product to fewer than 4,000 patients per year. It's a mechanism for really rare conditions, and it has the same low-level requirement of demonstrating effectiveness that a treatment IND does.

But this is the product description, which kind of shows you what a tissue-engineered product can look like. It's an aseptically processed wound dressing composed

of bovine collagen matrix, under which normal human allergenic skin cells, epidermal keratinocytes and dermal fiberglass are cultured in two layers.

Donor dermal fiberglass are cultured on, and within the porous sponge side of the matrix, and the keratinocytes are cultured on the coded, nonporous side of the collagen matrix. Then it lists some cells that it does not contain.

[Slide]

So what are examples of tissues that need engineering? And bioengineered tissues include artificial skin, we're beginning to see variations of doing things with bone, blood vessels -- as work Dr. Nerem and his laboratories continue to pursue. Products for wound healing, remodeling cartilage, artificial membranes for different uses are examples of some of the structural things.

[Slide]

just illustrated some of the issues, are the live cells safe and effective for their intended use in the product? Certainly you don't want them to be infectious; you want them to be well-manufactured. You want to know what the issues are around allergenicity; whether they achieve the intended function and are necessary for the product.

[Slide]

And then there are all the issues for the engineered structure, the picture on the side happens to be a synthetic polymer that has been proposed to use instead of collagen. So all of the issues on the source of the structural material, if it's a synthetic issue then you have all the biomaterials issues that you have with synthetics, and the toxicology and those types of issues. If it's a tissue and a highly processed tissue, you get into many of the same issues that we had on the last slide about the cell.

[Slide]

So how do we play in this, and how does our science and CBER science and agency science relate in this?

Let me introduce KeeKee Helman, embarrass KeeKee and have her wave and stand.

KeeKee is someone who has been involved with the tissue engineering working groups at FDA and a member of editorial boards of journals in this area involved in workshops and standards development, and this is just a partial list of some of the activities going on.

There's a cross-agency working group on tissue engineering. Standards organizations are beginning to develop standards, and we participate in this process. In fact, this year's president of ASTM is Don Marlow. Don can wave, too. Don is our Director of Science and Technology for the Center for Devices.

Just in the tissue engineering area

there are 43 task groups that have already completed 13 draft standards and three approved standards. And then there's a cross federal agency effort to develop partnerships in this area, and that includes FDA, NIH, NSF, NIST, DoD, DOE, DARPA and NASA. You get an extra point if you know what all of those are -- DARPA is the one that usually gets people.

[Slide]

So the real issue is how do we develop a science-based regulatory framework. This includes not just the previous activities, but also participating in workshops, in conferences. This is an area that I think there's intense interest in, and we'll see continued developments in these areas.

[Slide]

So I'll stop with this slide. This is not the moon over Cincinnati; this is a cross-section of the papillae in the heart with the endocardium down there just below it, for your

contemplation about what you want to have for lunch and things like that.

Kathy, do you want to come back?

DR. LANGER: Questions? I think we'll go down the line this way. Harold.

DR. DAVIS: Kathy; it wasn't clear to me from the presentation what you see as the agency's role in interacting with Congress, from the standpoint of, are you really responding to their questions; are we trying to -- we being the agency -- trying to lay out, based on your perspective, what Congress ought to be deciding?

I see this as such a potential nightmare, where the science is obviously rapidly outstripping what we know about ethics. So I wonder, are we being proactive or, do you sit there with a sense of what the agency thinks Congress ought to be saying around this, or what?

DR. ZOON: The reality is, the agency,

as a science-based agency, will provide technical advice if asked and approved by the administration to the Congress on developing their proposed legislation.

It won't be unique to the FDA; when we had talks on the Hill the last time when we went down and provided technical advice on this issue, we went down with NIH and worked on those issues and talked about the science and some of the scientific questions that were being addressed or potentially were being addressed, where the industry was going in this field, and provided that feedback to the individuals who were responsible for either drafting or preparing some of the legislative proposals.

So that would be the position. Now if the administration decided it wanted to propose a bill, we could draft a bill as part of the administration. At this point in time there has not been a request to do that, but clearly

if the administration wanted to propose something, they might also have FDA and NIH involved in giving their input and possibly CDC as well for a proposal.

So it's not unique to Congress. Whoever in the administration or in Congress, if there's advice and technical information, we could provide we're usually there to help in that respect.

DR. LANGER: Marion?

DR. NESTLE: I also am very impressed by the idea that controversy doesn't even begin to describe what is likely to lie ahead, and I'm wondering whether the FDA has an internal ethics advisory committee within the agency that could work with -- I know it's supposed to be science-based regulation, but let's be real about this. And it seems to me that getting those issues out on the table early on will protect the agency against things that come up that you might not be prepared for.

DR. ZOON: I think a very important part of our business. We've recognized the importance of having on our advisory committee ethicists in a variety of areas. And in fact, in our PHS Blood Safety and Availability Advisory Committee and also on the Xenotranspolantation Advisory Committee.

In fact, on the Xenotranspolantation Advisory Committee, we have an ethicist as the chair. So we're becoming more sensitive to that, and while we don't have our own committee, we often supplement our advisory committees when we talk about subjects that are controversial, having as consultants ethicists join us on our committees.

But your point is a little bit broader, in whether or not there should be a committee. Especially with some of the new scientific areas, a lot of issues related to ethics and their impact. Now our regulatory jurisdiction, as I said, does not deal with the

ethical evaluation by FDA. However, when there are meetings or we're preparing for science based decisions, we always want to either listen or participate and understand the more global issues with respect to our science-based decision in the broader environment.

I guess there probably are pros and cons to doing such an ethical advisory committee, but I think it's a really interesting proposal that should be analyzed carefully to look at, how that could be used in the future to help the agency, or whether we're better positioned to use other outside advisory committees for advice so we're not so linked to ethical decisions. And that's something I think, that's a challenge we'll need to face.

DR. LANGER: Bob?

DR. NEREM: I guess first I want to add a comment to what Marion said. I'm thinking about what I'm probably going to call the, Ed's "David Letterman top ten list." But

if one asked the question, you know, what is going to bring the most controversial decision-making to FDA in the next ten years, they're probably all going to be related to ethical issues.

So I think we would be well-advised to more and more take that into account.

I first really want to ask for an informational answer. Last night the word 'bioengineered' was used, and I was more or less told that "Well, yeah, it's genetic engineering," but then David you used 'bioengineered' and I know it wasn't genetic engineering.

So what is the definition, by FDA, of the word bioengineered? And is there an answer to that question; and if not, I believe there should be. Not today, but I think FDA more than probably any other agency needs to be careful as to how terminology is used.

DR. FEIGAL: I take your point. The

examples I was giving were not meant to be all encompassing of all bioengineering, but as an example of the kind. So I think thinking of what's included under bioengineering, what should be described by other terms, is a point well taken.

DR. NEREM: I'll let you people come up with a definition. Unless you have one.

Do you have a definition?

DR. ZOON: There are many. But I think if you're asking do you have one agency definition -- bioengineer covers a spectrum of activities, and in terms of how we apply technology to biological systems.

And my sense is, depending what the question is, almost every Center is involved in some sort of bioengineering process across the FDA with respect to whether it be foods, devices, traditional biological products; or even in the case where things may be used with drugs.

So my sense is, and the term had a broad implication; but as most things, the devil is in the details as you start drilling down into the definition.

DR. NEREM: Well, you weren't at the dinner last night, but there it was more or less being used to mean genetic engineered, but they didn't want to use the term.

But I think it is in the details, and there's times when a more general term is appropriate. But when you're getting down to more controversial issues, I think one needs to be more specific.

I want to ask a different type of question, and I don't know which one of you is going to answer that; but it really comes from your presentation, David; which doesn't mean that you're the one that should answer it. At some point maybe the answer will shift from you to Katherine.

A lot of these tissue engineered

products will be what I call hybrid technologies. In fact, the reason I wanted this on the agenda was not so much to focus on tissue engineering in and of itself, but as an example of the kind of hybrid technology we're going to see more and more of it FDA. And quite frankly, I really don't know if FDA is organized optimally to really review these kinds of products.

But just to help me understand a little bit, as you mentioned I'm interested in blood vessel substitutes. Now I know if it's purely PTFE, that's a device, right?

DR. FEIGAL: PTFE, --

DR. NEREM: A graft.

DR. FEIGAL: Yes.

DR. NEREM: If I put in an endothelial inner lining, is it still a device?

DR. FEIGAL: Probably currently we would still make it a device, because the definition of a device is its primary use, and

the primary use of the blood vessel is still structural, not metabolic. Even though that endothelium is metabolically active.

DR. NEREM: Okay, now we'll go one step further. I'm actually not going to have any synthetic material there; I'm going to have a natural biological scaffold in which I seed smooth muscle cells, and then I put in an endothelial lining.

Now it's totally biologic but its primary function is still delivery of blood flow; so is it a device or is it a biologic?

DR. ZOON: You know, we've had a number of discussions, and I think your point is well taken about the complexity of the field and its interfacing.

The Centers, I think, really, Dr. Nerem, do work well together. Can it be improved? Yes. But I think it would be fair to say there are issues in terms of structural devices that CDRH has an engineering background

in that I don't see a need to replicate in the Center.

In contrast, though, I think the issues as you go into biological systems, and talking about cells and the issues of cells, clearly the issue of a biologic -- I mean, if you ever had to define a biologic, a cell and a tissue is as biologic as it gets. So in terms of both the complexity and the scientific issues, we need to address and have been able to focus biologics over the years.

In the Center, we have the opportunity to look at different mechanisms by which biological products are reviewed. And as you heard earlier, our Center has the ability to use more complex tissue the biologics license applications. We can also use PMAs, which are the device mechanisms, or we can look at them as tissues if they're in their simplest form.

Really, the amount of regulation and the type of regulation is very much impacted on

what the biological material is, and as it is intended to be used, as well as what are the issues surrounding that tissue.

David and I have discussions, we continue to have discussions, because sometimes, as you asked, the question becomes very pointed; and what are the lines of demarcation. I think for every time you draw a line in the sand there'll be another question that's raised that you have to address.

So I think this will be a continuing ongoing process that the agency will evaluate and look at mechanisms and scientific issues and work together, and I think that's something that's really important; and your attention to that issue is really I think important to the agency and to both centers.

So we take your interest really in the good spirit of trying to really focus our attention on that. And I think it has, and we will have discussions be the two centers on

trying to make those lines as clear as possible, but recognizing cooperation between the two centers is going to be critical to maximizing the effectiveness of our resources and doing a good job.

DR. LANGER: Rita and then Harold.

DR. COLWELL: I think you're going to have to establish a taxonomy of these systems, because I do agree with Bob that you will find that you're impeded in some very fundamental areas that are of great value such as synthetic tissues and so forth which really don't involve the germ cell line.

And if there is a way to develop this categorization, this taxonomy, it will be very, very helpful to you especially in being able to triage those issues that really ought to go to the ethics committee and those that you should be able to address and be able to deal with as your routine processes and business.

DR. DAVIS: Kathy, you mentioned that there might be pros and cons of how we used ethicists or brought in the base of using ethicists. I'm just reminded of the comments that were just made about this firestorm that's coming. But also the article that was sent out about the use of consumer advocates as a part of review panel, advisory boards.

I think back some years ago probably most of us would have thought that that was maybe not a good thing or, you know, we're so science-based how are they going to play a role, et cetera? And yet it's a natural thing now, nobody thinks too much of it, especially in the negative sense, and I think the use of ethicists is going to probably be in the same light, that this firestorm is coming; I don't think we can even begin yet to imagine how big or bad it's going to be.

And I think one day we're going to look back and say it makes perfectly good sense

to use these ethicists. So I would like to make sure that we're very proactive with that; and that's probably going to be a natural thing one of these days.

DR. LANGER: Other questions? Bob.

DR. NEREM: I just wanted to make one more comment. I do realize that there's been this task force, which I think dates back to '94 or something, and I give FDA a lot of credit, both for all the thought that's gone into the tissue engineering area and the leadership they provided to ASTM, and to other organizations.

Having said that, I still am concerned, not so much about tissue engineering but about the broader spectrum of products. Everybody else in the world is trying to reform FDA, and we have a new administration and there may be efforts now to some way change FDA. And I think it's appropriate for FDA to think itself about how they may want to, how you as

an organization may want to reinvent yourself for the 21st Century.

Don't be reactive to whatever goes on in Congress, but be proactive in the context of what you think is really needed to get the job done.

DR. LANGER: Any other comments?

Let me suggest this: Why don't we take a 10 minute break, and then --

DR. NEREM: Go to lunch?

(Laughter)

DR. LANGER: No, no. And then we'll come back and do at least the first part of Susan Wood's presentation, and then we'll do lunch. But you'll get your break.

[Coffee break.]

DR. LANGER: If people could have their seats.

The next presentation is going to be on the Office of Women's Health.

Susan is the new Director of the

Office of Women's Health, and she's going to be presenting an update on how the Office of Women's Health modified its scientific program based upon comments and recommendations from the Board at the April 2000 meeting.

And some of the questions that came up then are, how do you focus the selection and evaluation of products, how do you ensure peer review and objectivity in selecting these projects, how many of the seed projects funded by OWH went on to be funded by the agency or NIH or other sources, like what's the percentage outgrowth of this program, and then finally research in the area of dietary supplements.

Office of Women's Health

Research Program Update

DR. WOOD: Thank you for inviting me to come to speak to the Board, and to hopefully try and review and bring you up to date on what we've been doing with the science program

within the Office of Women's Health.

Last year, Peggy Miller, who's sitting over there, who is the manager of the science programs, presented to you. So we're going to try and update you on where we are right now. Some of the revisions and changes that have occurred in the program in the last year and to see if there are any other questions or comments that you guys can bring to bear on this.

And I will call on Peggy for assistance if some of the questions relate to some detail, since I did arrive in November, at the end of November, and still consider myself very new to FDA and new to the office. So I'll call on Peggy who really knows what she's talking about.

[Slide]

I do want to take a few minutes to tell you that I have a bit of a checkered history in that I started out as a basic

science with my Ph.D. in biology but looking at the biochemistry of invertebrate phototransduction; and that seems a long way away from women's health policy.

I made that transition by working, after doing, actually doing further work, postdoc at Hopkins on the biochemistry of olfaction. Took a AAAS fellowship onto the Hill and worked for five years with the womens caucus working on womens health legislation and policy. And it was a way of trying to see whether at that point an exploratory move of whether taking science and applying it to policy, even though it was something wildly different from what I had done in the lab was a good way to go.

And obviously I stuck with that; in '95 I moved to the Department of Health and Human Services with the Secretary's Office on Women's Health, and worked department-wide. And I think that plays into how the office

works now here at FDA where I am trying to focus on the agency's missions and its activities.

So we were moving with the Womens Health Office at FDA -- and I wanted to give you just a little bit of background on the office so you have a feel of sort of how it fits in with the agency.

And that's to tell you that our role is really to serve as the advocate for women's health across the agency, and to look at the FDA product line that it does regulate, and make sure that it's safe and effective for women. That we in the process of either clinical trials or other evaluation, that the needs of women are assessed. Not only are women included in clinical trials, which was sort of the hot issue ten years ago, but at FDA it is not really an issue in terms of participation of women in clinical trials.

But then to take a look at the second

level question: Is this data evaluated and analyzed for gender differences and can we get useful or relevant information from that? And I think sometimes the answer is yes and sometimes the answer is no.

We also want to look at how women use the products that are regulated by FDA, and that gets played into looking at the risk-benefit decision; because when you look at whether women use more prescription drugs or whether they are more at risk due to pregnancy for food safety, or whether they're high consumers of dietary supplements, these are all questions we need to take into consideration as we look at FDA's actions and thought processes.

And finally that we take a look at how a product use is communicated. In the labeling process, for example, this can relate to pregnancy labeling where we're working with CDER on how to revise pregnancy labeling. It can also be involved with other aspects of

product labeling that may not be related to pregnancy, but may reflect either the differential use or differential physiology of women in using a product.

So in monitoring the inclusion of women in clinical trials, I've talked about that, that we look at the biological differences and whether there are different periods of susceptibility or vulnerability, or whether there are exposure differences. These are the types of questions that not only in the research projects that we fund but also in looking at the activities of the centers are relevant as well.

[Slide]

Now in talking about the science program, and I know the issue came up last year in talking about how do you balance the short and long term projects, and we do have sort of a mix of these going on now. And I think they sort of cover the range.

One new type of project we're doing is with the Department's Centers of Excellence in Women's Health. These are 15 academic medical centers that have been designated as Centers of Excellence across a wide variety of aspects, be it clinical care, education and training, but also in their research portfolios.

We've tagged onto that project particularly in the area of dietary supplements, which I'll talk about in a minute; but by going to the centers of excellence -- it's a group that's already been identified by the Department and then being able to solicit research projects in particular areas through a contract mechanism. We're able to get at some targeted questions that are relevant to FDA's mission with a relatively straightforward mechanism.

The second area, which is a more long term program; we've started working with NCTR to develop a Women's Health Initiative -- and

I'll talk a bit about that in a minute.

But we have continued also the intramural research program, and are funding that this as well. I'll give a little detail in a minute.

[Slide]

To make sure that we're addressing some of the questions of how the peer review is done, this year for the Centers of Excellence program and for the NCTR projects, we have convened review panels from the product Centers involved in the topic and used them to review all of the proposals.

With the intramural program we have continued to this point with using both internal and external experts, although we did go, we revised the protocol so that we identified people with expertise in the field independent of the PIs, if you will.

So going back to first program that we're finding, the Centers of Excellence; the

topic areas that we identified for this previous year that have been funded is in the area of dietary supplements and drug interactions as well as safety and effectiveness for use in women, because we do know that a lot of these products are very heavily used by women, and particularly related to reproductive health and menopause and so on.

[Slide]

I can't go through them all and I do have a listing of them if you're interested in seeing the ones that we funded; but I want to talk briefly about a couple of them to give you an example of the projects. This is one that Dr. Steven Hall at University of Indiana is doing, and he's looking at cytochrome p450s functioning and its interaction between St. John's wort, which affects the metabolism by cytochrome p450s and how it interacts with the circulating levels of oral contraceptives, which is a sort of known interaction and it's

used for doing some quantitative evaluation of those effects.

Another one we're doing, which is at the University of Washington by Gail Anderson, is looking at soy products, and it's looking at again how the responsiveness differs between Asians and Caucasians in response to soy; and again the interactions between photoestrogens as well as drugs for women who are taking soy products.

[Slide]

The NCTR program that we're funding is a 5 year program, and it's really trying to address long term activity in women's health research; and to do it sort of in a proactive way.

So we're working with folks down there to develop in vitro model systems that can be used to explore drug-drug and diet and drug and dietary supplement interactions; and we're hoping to develop some targeted genomics and

proteomic screens to address some gender differences in medical products.

So we hope that this will evolve into something that's really functional; but at this point we're still in early stages and still in development with the folks at NCTR.

[Slide]

Another issue that apparently was raised last year was how do we focus what we fund and what are our priorities, and make sure that it ties in with FDA's needs and mission. And I think that's an important point, and it relates to also what were the outcomes of the research that's already been funded?

We did develop this -- and unfortunately I only have one copy; we're updating it as we speak -- but last year at the time I believe of the meeting, this was being developed and it was finalized and I believe sent to you for the meeting six months ago. So hopefully you all have it in your files, and

I'm sure you've read it in detail. There will be a quiz.

It identifies the outcome both in terms of papers that have come out, papers that have been submitted, and to some degree sort of where the funding has led -- we provide seed funding, and there has been additional funding. I think part of the difficulty of getting that information is when we send out a query to those we had funded and said "How much funding have you received from outside sources?" We heard back from a number of people and they all said "We got great funding."

And I think there are some good examples of that, where, for example, Ray Woosely's group at Georgetown has been able to more fully develop the work on QT prolongation and torsades-deplant arrhythmia, based on some initial funding that we gave them, and there are some other examples like that.

But of course we didn't hear back from

a lot of people, and we can't say that that's because it was a dead end or because they didn't send us an e-mail back, at that point. We did not have it built into our granting process, if you will, that they had to give us back this information. So it has been rather tricky to really get a full assessment of sort of what is the outgrowth funding from seed funding.

But we will continue to try and monitor that with funding as we go forward.

So if we're looking at where we're going, we did really want to focus again on research projects that had significance to the FDA mission and its regulatory authority; but we did also want to give a big more direction to the centers on the priorities of the office; and so for the FY2001 projects, we sent out the request for proposals and targeted an area of gender differences in product safety or effectiveness, as well as on questions of

safety and effectiveness of products used by women as they age.

So I think in previous years there had been sort of an open call to the Centers, or there had been discussions with the center leadership to sort of say what are projects that you would like to see us fund? This time we did try to put a bit of a shape onto the call for proposals, and then went through a similar process of evaluating the projects and going to review.

And we have just recently awarded funding for four proposals, which again if you're interested, I can get you copies of at least the titles of what those projects are.

[Slide]

Another question came up regarding how do we distinguish, if you will, between the type of work that FDA does and the type of work that NIH does; and I think I've answered that in part in terms of trying to look at the

projects and questions that are of interest to FDA's mission.

For example, we are looking at, for later this year, doing some funding in the area of studies on medication use in pregnancy. Actually funding some PK-PD studies to try and demonstrate, develop a proof of concept, if you will, of how do you carry out ethically and sort of with scientific validity and rigor, some studies on pregnant women who already have a particular condition and who are already on a particular medication for their own health needs, and then try and capture that data to make it useful for labeling purposes as well as to aid in diagnosis and appropriate treatment.

And so that's one way we sort of take a cut, if you will, given the limited research we can fund, to how we put it towards FDA's mission. But also there are other ways where this office works sort of internally within FDA but then also links back to the Department and

to the Public Health Service Coordinating Committee to try and find out what, other agencies that are funding research or carrying out research, how do we have synergy and not really draw a hard line and say this is NIH's and this is FDA's and this is CDC's, but rather, where is there the overlap and where can we either not duplicate but rather work together and develop programs that address both of ours or multiple agencies' needs? Because ultimately we're all working towards the same goals.

And there are a couple of examples, and both of these are related actually to medications and pregnancy where we're working on one side with NIH trying to take a look at some of these questions around the pharmacology of pregnant women, and they're interested in it from some of their aspects and questions; we're interested in it from largely the pregnancy labeling type of interest, and we're trying to

develop some joint projects that we can do together.

Similarly, CDC has just gotten a chunk of money appropriated in the area of, for safe motherhood. This is primarily, their interest is mainly in surveillance and in preventive services; how do you monitor women in prenatal care, how do you actually measure pregnancy outcomes and so on with regard to the women's health. They've got other people looking at children's health, but obviously there's a link there.

And we're bringing into that picture, which is something I don't think CDC had really thought about, the fact that the women that they are most concerned about, the women with high morbidity or high mortality or at risk for that, are women who are likely to have a chronic condition, they are women who are likely to be taking medications, that may or may not have very good information on its

effectiveness or appropriate dosing or potential side effects for the woman or the fetus as women who become pregnant try to go off all of their meds to protect the fetus, they may be creating more problems than they're avoiding, but unfortunately the database for that is very limited.

So we're trying to work with CDC to say part of what safe motherhood is is bringing together that information about the pharmacology of pregnant women, what do we know about medications and labeling for medications for pregnancy, and how can that ultimately mesh with CDC's goal of reducing the numbers that they are responsible for surveillance and prevention on.

So it's that kind of meshing together that I think our research agenda, along with other parts of what the office does, is important to keep in mind. And I don't think there is a real hard and fast line that can be

drawn.

In looking to the future in terms of how do we establish ongoing priorities and future priorities; for example, next week the Office of Womens Health is hosting what we're calling a women's health dialogue, and we're bringing together Center directors, Dr. Schwetz will be there, and groups that are either womens groups, health professional groups, the industry, research organizations, to try and have a two-way conversation on both what FDA can do in this area, but also listen to their ideas and try to develop some strategies for actually either moving forward in the area of either policies and regulations or research, but also in moving forward and being able to get the resources that we need to actually follow through on what needs to be done.

Similarly, we'll continue working with the Coordinating Committee on Womens Health at the Department level so that we can stay in

touch with what the rest of the Department is doing in this area; and then the central way that we work is by collaborating with the product centers to identify issues that are critical to them and trying to add value to the work that they do with, in this case talking about the research side of the office, funding projects that are relevant to their missions and their particular activities.

And I think that's it for now. After lunch --

DR. LANGER: We'll maybe take time for some questions. I'm sure people can wait for a few minutes for lunch.

DR. WOOD: I'm sure, yes.

DR. DAVIS: Thank you for the presentation and welcome to the agency.

One question I do have though. I noticed in one of the examples that you gave, the one where someone had applied for funds to look at the differences around soy for

response that they were seeing in Asian women.

So that was a project that they had; and we provided supplemental funds to do some further investigations to see if they could characterize what enzymes were being turned on differently in Caucasians and in Asian women. So they had already presented some data with biomarkers to show that they were responding differently, and we were just adding some supplemental funds there to see if we could determine the mechanism.

DR. WOOD: I think this is a very preliminary project. And were it to come forward and say Right here are some particular pathways which are affected and affected differently, in two populations, let's now move it forward to a broader population, take a look at it in various groups.

And I think the Asian population again, because this is in Seattle where I think this is probably, they're using at the cultural

and the usual diet of women and not modifying diet; so it's probably to some degree a -- I wouldn't call it a sample of convenience, because it's a sample of relevance. It's relevant to that population, moreso at this point in dietary habits than other populations.

DR. LANGER: Cecil and then Bob.

DR. PICKETT: I was interested in some of the work being done on dietary supplements and drug interactions. And I'm wondering really how the agency views really how to use the data once obtained in the context of perhaps policy decisions on dietary supplements.

DR. WOOD: I think that's a very good question.

I think in many of these cases, particularly in the area of dietary supplements --and at least this is my take on it and I'll look to other folks at the agency to say in terms of how CFSAN could take it in the context

of the authority or limited authority or lack of authority that FDA has in the area of dietary supplements; but I think a large part of the problem is the lack of information that exists in these areas on how, when are there safety issues that need to be raised? That rise to the level that the agency should or could take action on it. Or could at least build a cogent argument that there needs to be a variation or modification of the authority?

And at this point, our interest for the area of women's health is to take some of these very specific questions, because we do know women are taking these products and that they may have very specific interactions. The example of oral contraceptives is very relevant to women and it's probably not just St. John's wort we're talking about; so we're trying to develop a database that can be useful. Granted it could be useful to a lot of people and is not necessarily just specific to FDA's

regulatory authority, but I think it's at this point still trying to build the database.

DR. PICKETT: One more question, in that context.

The laboratories that you choose to do this work I assume have come out of some peer review process, and I would assume that the data that's collected are collected using validated assays, et cetera; and which-- because it's really that data that you're going to start building a database to make policy decisions, I assume.

DR. WOOD: Yes. I'll have to defer to Peggy about the specifics of their assays; I will make that assumption as well, but I do know that the Centers of Excellence themselves did come -- these are all the institutions and the project directors of the Centers of Excellence have gone through; it's been through a peer review selection of these centers and their site visited more often than they'd like

and so on and so on.

When we get down to the specific projects, we're not -- you know you don't give a grant to a -- I mean technically you do, but you're giving it to a particular lab and a particular group of investigators. And in the process that we use for the evaluation of these proposals, we did set up a review panel, although it was an internal review panel if I'm correct, from actually multiple places, and used them to review all of these proposals before award.

And these are very small awards. We actually felt that because of the fact that they were doing existing projects in this area and were getting some funding by virtue of being a center of excellence, that they were able to do a whole lot more -- we're getting a lot more research than you would normally expect from say an NIH grant of this magnitude, because it's a very small grant.

DR. LANGER: Bob?

DR. NEREM: I guess I want to come back to Harold's question. If I understand the question, understood the answers, I understood that this Caucasian-Asian soy project, it originated someplace else and then you provided some additional funding to do some additional things, which I guess raises a question in my mind, Bob, certainly if anything FDA should have more money to do research; I think we would all agreed to that. But I do -- this just triggered my mind -- I do wonder about the organization of the research; whether the agency is best served by having pockets in different centers or whether a more integrated, interdisciplinary research center is appropriate.

I know industry goes through this all the time; you know, should we have central research laboratories or should we have research laboratories out in the business

units? There's arguments both ways.

DR. LANGER: Bern, maybe we'd be interested in your --

DR. SCHWETZ: You raise a good point, Bob, and I would encourage that we would continue to have this discussion as we talk about the FDA University, because that could be a mechanism where whether it's funding for orphan products or whether it's for women's health projects or other programs where we would put food safety initiative. That's at least a place where these kinds of things can be brought into one focus.

And some of the priorities of the Agency can be imposed at that level. The mechanism by which the money would go out, whether it's cooperative agreements or contracts or grants or whatever it would be can be looked at from the FDA standpoint under the FDA University.

I would come recommend we come back to

that discussion because you raise a point that is particularly pertinent to that.

DR. WOOD: I would ask also, and I'm trying to make sure that I'm hearing what you said correctly, and I may be misunderstanding; were you suggesting that we were supplementing something else that FDA was already funding? I mean, I think their base project was probably NIH-funded, and then we supplemented the NIH program.

DR. NEREM: I missed that point. Thanks for the clarification.

DR. LANGER: Liz wanted to add to that and then I want to add one comment.

DR. L. JACOBSON: As we do have that discussion, especially the guys at the FDA University, I just wanted to say that in FDA we've done the experiment both ways because we do have our consolidated research program at NCTR in the toxicology area, and we also have research programs in each of the product

regulatory centers. So we actually have -- I mean, it is a continuing discussion, and I know industry has the same discussion, but it's kind of interesting that we've done it both ways here.

DR. LANGER: Ed.

DR. SCOLNICK: It's a complicated statement. I think that your talk and the subjects have actually been very interesting. I never really thought about this issue before, and it has stirred me to think.

The first thought is I heard this list of questions that Bob put forth that we asked, and I heard your talk, and I'm not sure they connected.

DR. L. JACOBSON: Probably not.

DR. SCOLNICK: Yes. So --

DR. L. JACOBSON: I tried.

(Laughter)

DR. SCOLNICK: No, I couldn't remember all the questions.

The other thing is in thinking it through now for really the first time, clearly the FDA deals with food safety, and I guess supplements come under food safety, and then drugs and devices.

And I've really never thought about it before what the most important issues are in women's health that truly falls under FDA aegis.

Because I haven't thought about that and I don't know what those are, I can't really relate your comments to the kind of what the imperative really is. Somehow I feel now that you've stirred me to think, I'd like to understand that in a better way.

I don't know how to do that, but those are my comments.

DR. ~~COLWELL~~ Wood: So you're trying to understand sort of why is women's health a priority at FDA?

DR. SCOLNICK: No, not at all.

DR. COLWELL: No.

DR. SCOLNICK: I accept that it should be a priority at FDA.

DR. COLWELL: Okay.

DR. SCOLNICK: What I'm really saying is I don't really know within the domain of women's health in the categories that FDA regulates, what the most important issues are and what the most important medical problems are that you face that you have to deal with where there is inadequate information, and what it is that you need to fund in order to help you make those decisions.

I don't know that, and so my ignorance gets in the way of my understanding the context for this.

DR. COLWELL: Well, I don't know that there's a "this is it" kind of answer. There's not a simple answer. It was a complicated question. Because I think there's a -- I mean, it's sort of like asking what is FDA's -- on

any topic area, what is its biggest problem or what is its biggest challenge, or what is its single-most important thing that it does.

And I think because it's got such a broad mission, all of those things come up, and there are within each question, and I just tried to hit on just a couple of them here, ranging from looking -- and this is why I think a year ago when Peggy came here to the Board to say how do we think about what are the best research questions that will be most useful to FDA, but also most relevant to women's health, and sometimes those things are together and sometimes they're not.

How do we identify the priorities? And we've tried to do that by creating a mix. We've created a mix of funding mechanisms in terms of the internal and external. We also have some sort of short-term gap funding that if somebody comes to us with a high priority project we'll put in a little bit of money for

that or whatever we think is appropriate and that we have, which is not much.

I mean, our total budget for the office is on the order of $2 million, and we put about 1 million of that into the research program.

So we've done it by trying to create a mix of mechanisms, but we've also done it by creating a mix of topic areas, and by working with the individual centers to let them identify with us where they think it's important and where they need some help getting through research and data analysis.

The pregnancy, dietary supplements, just looking at gender analysis of data, be it at CDER or CBER, we have funded some projects to go in and analyze the NDAs and INDs of those centers to try and understand what is there and what is not there in terms of understanding gender differences and responses.

When you get to foods, they're sort of

all over the map. With devices and biologics, with biologics, for example, we work with them in the area of assisted reproductive technologies, because when you look at tissue regulation and so on, there are other parts of HHS that are involved in that as well, and our office helps make that link with HHS on assisted reproductive technology.

So we end up being pulled in about 20 different directions, and that's okay, you know, because I think that's appropriate that we get involved in sort of the broad spectrum, but there isn't an answer like, you know, we don't want to be at the point where we only have enough money to do one thing, but we've tried to focus it down as much as we can, as I mentioned, with the priority for 2001 being gender differences and aging.

And maybe next year we'll shift to a different set to try and get a different slice at some of the issues.

DR. LANGER: We've got a bunch.

Harold, Bob.

DR. DAVIS: I'd like to add.

Your comments started -- made me thinking about something -- your comments about whether or not the Agency -- whose authority it was to respond to dietary supplements, or how much authority that there was.

It might not have been what you intended me to think about, but following up on what Cecil and Bob said.

You know, Cecil asked the question about are these validated assays, et cetera, et cetera, and I think part of the line of reasoning behind that, Cecil, was that this data will be used or applied in some fashion.

Your comment about who has the authority to do what with the data, it seems to me the FDA needs to be very careful doing research generating data that will be used in some fashion.

We ought to be asking the question at the same time, what are we going to do with the data. You know, we're going to fund it, but what are we going to do with it? It's horrible in my business to get data that you really haven't anticipated or questioned how it's going to be used.

And so Bob asked the question about central versus decentralization of research funds. When you have a decentral funding source, it's easy for one group to set off on a tangent and generate data that the whole organization hasn't thought about it, and I'm not arguing one way is better than the other way, but it just came to my mind.

DR. WOOD: I do think the development of doing research in dietary supplements was done very closely in consultation with CFSAN, who is the place at FDA that is -- I don't know what their authorized, actually; their authorization is somewhat limited in the

area -- but whose interest area and who identified it as a priority area for getting information on dietary supplements.

So I think -- I mean, I wouldn't want you to think we were all saying, hmmm, this isn't important to us. It is, but it's also of importance to CFSAN.

DR. DAVIS: No, no, no. Understand I'm not being critical of this project at all.

DR. WOOD: No, I understand.

DR. DAVIS: It just caused me to think that the comments that in a larger Agency prospective, because data generated in CFSAN, once that data's out there, will be used to regulate other areas as well, et cetera. So I'm not saying what you did was wrong. I'm not arguing for centralized versus decentralized. I just think the question needs to be looked at perhaps under this University concept that as the FDA funds things, it will be hard for a reviewer in any of the groups to not look at

that data generated by the FDA or where the FDA dollars is having some regulatory weight behind it.

And so, one, we ought to make sure that the data comes from labs, and I believe that's probably the case.

DR. WOOD: Yes.

DR. DAVIS: But we ought to make sure that we have a sense of what are we going to do with the data when we get it. And that's not a criticism --

DR. WOOD: No.

DR. DAVIS: -- of this project but just as a general comment.

MS. MILLER: With the St John's Wort and the OCs, we had the CDER, actually, was the main group that wanted to have us conduct that study. They had already put a warning on low dose estrogen, oral contraception, but they didn't feel very comfortable with that warning, based on the data that they had. And they