Third Meeting of the
Secretary's Advisory Committee on Xenotransplantation

Transcript

Open Session: FDA Overviews and Plenary Discussion

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Sheraton Columbia Hotel
10207 Wincopin Circle
Columbia, Maryland 21044

Reported By:

L.A.D. Reporting Company
1684 East Gude Drive
Suite 201
Rockville, Maryland 20850
(301) 762-8282

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P R O C E E D I N G S
8:35 A.M.

Agenda Item: Opening Remarks

DR. GROESCH: Good morning. I think we should get started. We've got a very full schedule today, and we want to be able to end on time because people are traveling. I have a couple of housekeeping announcements. First of all, the members at the table have a pink form in front of them. This is that confidentiality form that we talked about. If you could sign it, and we'll collect them. And then members of the audience, the federal employees who are planning to stay for the closed session, you should have a packet of the information, and there's the form on the back, and we'll ask you to sign that, and we'll collect that before the start of the closed session as well.

The other thing is that we have so much to do today that during the closed session we're going to be having a working lunch. We have boxed lunches that are coming in, and we've ordered enough for the SACX members, and if there are any federal employees that are staying for the closed session and you didn't order a boxed lunch and you want to, if you'll raise your hand, we'll try and get that taken care of. So anybody that wants one that didn't order? Okay. Terry will talk to you. Okay. Harold has a quick remark, and then I'll do an intro.

DR. VANDERPOOL: I want to accent vis-a-vis a brief discussion with Marian Michaels that our reports of the two working groups, informed consent and science and safety issues, will be issued by the whole committee. And so anyone on the committee who has concerns about either report will have opportunities to express those, and they will be indeed taken into consideration. Marian, for example, posed questions about the notion that this committee would speak as if we should require or in some way force lifelong monitoring, and she's opposed to that for good reasons. So the point is that although our committee has not made up its mind at all on that issue, and we'll have to think that out over time, the point is that everyone on this committee will have a say about what the reports contain, including the informed consent people for science and safety and vice versa.

One of the things I mentioned very briefly yesterday was the suggestion that I initially received from David Cooper that we might seriously think about issuing our reports as draft statements which call for commentary. And I had a brief, but very informative, conversation with Lily Engstrom, whom we're very happy to have with us today. Also I would welcome Mike Swindle. Mike virtually found all sort of ingenious ways to finally get here late last night. Mike, thanks for coming and for being with us. So Lily, I think you have a comment or so about the question of thinking through the possibility of issuing our reports as drafts rather than as final statements.

MS. ENGSTROM: Basically when Harold and I were talking about this and he mentioned that his working group on informed consent had entertained the notion of having their recommendations or report containing recommendations vetted through public comment, I was very much in favor of that, and the model that has been used in the past quite successfully is one that's adopted by the committee that I consider sort of a sister committee to this one. There is also a Secretary's Advisory Committee on Genetic Testing, and they have been around for, I think, a year or two longer than SACX itself, and what they've done and done very, very successfully is in fact developed their recommendations, and then they've posted not only on the website itself, but also offered it for public comment through the Federal Register. And this allows, I think, the public and all interested parties an opportunity to really review those recommendations and reports and basically provide their perspective and their views. And all of that actually has resulted in a really well-crafted and well-brought report that contains very sound recommendations. And it's really important, I think, that all state holders, you know, that are involved in any particular issue have a chance to have that kind of input, and I think that any kind of report coming out of SACX will only benefit from that kind of public process, and I highly endorse that.

DR. VANDERPOOL: Thanks so much for those very informative comments about the experience of other DHHS committees, particularly, of course, the one on genetic testing. Okay. Mary, without further ado, we have an exciting agenda before us today.

DR. GROESCH: I'd like to take two minutes to give some background for today's presentations and also give

you a heads up about an upcoming modification to the committee's charter. In developing the charter for this committee, the PHS entities represented on the committee; NIH, FDA, CDC, HRSA and Office of the Secretary, have very carefully considered the wording so that it would accurately convey the intended function of the committee, and I think we largely succeeded, but we want to clarify one of the charges since questions have come up in our previous SACX meetings and also during public presentations about the committee.

When we delineated the charge to the committee to review current and proposed xenotransplantation clinical trials, identify and discuss medical, scientific, ethical, legal and/or socioeconomic issues raised by these clinical trials, we had discussed amongst ourselves what we did and didn't intend with the use of the word review. We did intend that the SACX would deal with the broad scientific, safety, ethical and policy issues that arise from the xenotransplantation clinical trials. These issues are likely to be germane to either a class of xeno clinical trials or to the entire field, and in order to identify and address these issues, the committee has to be informed about the range of past and current clinical trials as well as those that are likely to be initiated in the future. And that's really why we're here today for today's sessions, to hear from the FDA about these studies. It's why we've had presentations from investigators and sponsors at previous meetings and why internally we're working out a process by which this committee will be informed about future studies. And in this sense the SACX is reviewing xenotransplantation clinical trials for the purposes of identifying the salient issues for its attention, but we really didn't intend that the committee would be carrying out technical reviews of the research. While it might be useful to discuss a specific clinical trial as a springboard for a broader issue-based discussion, it wouldn't be for the purpose of a detailed technical review.

So to clarify and underscore this, we'll be modifying the charge to simply say, "to identify and discuss the medical, scientific, ethical, legal and/or socioeconomic issues raised by xeno clinical trials."

And with respect to informing the committee about the xenotransplantation clinical research, many FDA staff have been working for many weeks in order to prepare for today's sessions, and I think it's safe to say that we're really looking forward to these presentations and that we really appreciate the tremendous effort that has gone into them.

DR. VANDERPOOL: I want to register my opposition to this change. I'm surprised it's being almost imposed on us as a committee. I never took the word review to be that we would perform any of the invaluable and sustained functions of the FDA because it has its own charges, and I always took review in the spirit of the way Mary just described it. The sentence that follows has "identify and discuss the medical issues raised by these clinical trials. " If we're not able to be informed about what these clinical trials are, we will lose part of our teeth. And so I don't know whether we need to discuss this further. I think we have a full agenda. But to me the word review is not an alarming word. It does not give us powers beyond what I've assumed this committee should have. But if the committee is unable to be able to be informed about the kind of trials that we will be informed about today, then we lose our ability to really know what's going on and make the judgments we need to be able to make.

DR. BLOOM: I think basically you're both saying the same thing. You are going to be, and it's important that you be informed about clinical trials that are ongoing and that will happen, and that's what we've started to do, as Mary had said, by inviting companies to discuss them and what we're going to do for you today in closed session. The term review in FDA language, if you will, does have very specific meaning. We have reviewers who do reviews, who write reviews and who submit those reviews to files. We have FOI requests about reviews, and so to us that language is quite specific. And FDA does not ask our FDA advisory committees to do such reviews. What we generally do is we will update committees on the status of various clinical trials as they relate to that particular committee's purview, and we have some people here that have been involved in that type of activity with other advisory committees. An exception you might point to would be the RAC, Recombinant DNA Advisory Committee.

DR. VANDERPOOL: Two quick comments. Eda, I appreciate your comments. First of all, this is a Department of Health and Human Services committee, and I understand the connotations of the word review for the FDA, but this is a DHHS committee for which review could mean something quite different, namely, to be able to be thoroughly informed. So I don't know whether the puzzle is just to delete the first sentence of our charter, which is the proposal which I would oppose, and instead, replace it with some kind of different wording,

if not keep "review, " at least say, "become thoroughly informed about current and proposed xenotransplant clinical trials. " We have to be informed about these trials or we're guessing like members of the public who don't know what these trials really are. So if that first sentence is deleted as proposed, then I think we lose our ability to be able to make the decisions and understand what's going on as well as we should.

DR. MENDEZ: Excuse me. Mary, can you reiterate just that one specific change for us, please.

DR. GROESCH: Yeah. It was to remove the sentence that says, "review current and proposed xeno clinical trials. " It will continue as is with "identify and discuss the medical, scientific, ethical, legal and/or socioeconomic issues raised by these clinical trials. "

DR. MENDEZ: That implies that we will not review the clinical trials that are ongoing or proposed?

DR. GROESCH: Not review for the purpose of critiquing the design of them or giving advice to FDA about whether they should authorize an IND. It was to look at the issues presented in them, and we would be informing the group about what the studies are about, what their product is about, the trial, the description and who's in it, but not to provide specific technical details and get technical critique of it.

DR. MENDEZ: But we would be given --

DR. GROESCH: Would still be informed about it.

DR. MENDEZ: -- information about them?

DR. GROESCH: Yeah. There has been misunderstanding about the connotations in the word review.

DR. VANDERPOOL: My point, Bob, is that if the word review connotes a critique and ability to decide to intervene in some way with the FDA, well, then we perhaps need to change that word, but I think the idea that we shouldn't be able to be thoroughly informed about proposed xenotransplantation clinical trials or something to that effect, then we lose our ability to be able to understand what we need to understand in order to be a cutting edge committee. We can always be a committee that operates after the fact of finding out in some way or another what the clinical trials are.

MS. SHAPIRO: Harold, how about "be thoroughly informed about current and proposed xenotransplantation clinical trials so as to be able to identify and discuss the medical, scientific, ethical, legal and/or socioeconomic issued raised by these clinical trials? "

DR. VANDERPOOL: What does the committee think about that wording?

DR. SCHECKLER: I was just going to suggest "be apprised of. " I don't want to lose the idea of that sentence, which is to make sure that we know what's going on, and I think if we remove the sentence, we don't have it explicit enough. So whatever the words are to get rid of "review, " I understand the problem with that, but keep the rest of the sentence.

DR. VANDERPOOL: Other comments from committee members on this issue?

DR. BLOOM: I understand the concern. I don't think that we have a problem with "be apprised of, " for example, or "be informed about. "

DR. VANDERPOOL: Great. Could we have a vote on the committee that is in keeping with the proposal of Robyn Shapiro and Bill's comments about keeping the sentence, but changing the wording? All those in favor of the proposal by Robyn and voiced by Bill raise your hand. Okay. Let it be noted in the minutes that by unanimous vote that's the belief of this committee. Thanks.

DR. GROESCH: Okay. Our first speaker today is Dr. Eda Bloom, who we heard from yesterday. Eda is with CBER of the FDA, and she will be providing an overview of xenotransplantation INDs.

Agenda Item: Xenotransplantation IND Overview

DR. BLOOM: Good morning again for the second morning. You get to start off with me. I don't know that I'll be as amusing as I was yesterday. Hopefully not. Okay. So what I'm going to discuss is an overview intended for public presentation on what xenotransplantation INDs the agency currently has or has seen.

To reiterate, FDA regulates xenotransplantation, and any clinical investigation in xenotransplantation requires FDA oversight. There are a number of mechanisms by which we can review xenotransplantation clinical trials. Generally we use the IND mechanism. That's the investigational new drug application mechanism, which is used for drugs and biologic drugs. However, under some circumstances xenotransplantation products may be reviewed as devices. The IND mechanism is primarily used by the Center for Biologics Evaluation and Research and the device mechanisms by the Center for Devices and Radiological Health.

Now, on the bottom bullet on this slide I'm saying that FDA confidentiality regulations apply as set forth in 21 CFR 601.50. I know that sounds pretty bureaucratic, but what I mean by that is there may be questions that will be asked in open session that I cannot answer. For example, we may not even disclose the existence of an IND in public if the company or sponsor has not already done so. So we are very restricted, as you know you are now, from discussing INDs.

For the INDs that exist for the use of xenotransplantation products, to date a total of 40 have been received. The first xeno IND was actually received in 1992, and for those of you with really good memories for detail, I have told you before that the first IND was received in 1994. That IND was the first IND that was received with the intention of being xenotransplantation. In fact, in 1992, which was well before the development of any xenotransplantation policy by FDA, we began to receive gene therapy INDs in which the vector producing cells are implanted directly into the patient, and those vector producing cells are, guess what, mouse. And so in retrospect, these are also xenotransplantation INDs. Fortunately, the review of the vector producing cells, which virtually all of them, if not all of them, produce retroviral vectors. The review of those INDs, the testing of the products, the carefulness with which we asked the sponsors to look for recombinant replication competent retroviruses and other viruses is very similar to that with which we review xenotransplantation INDs. So we're confident that the review of those INDs was appropriate. But I just want to bring to your attention that a very significant number of xenotransplantation INDs are also gene therapy INDs.

As far as the INDs received by year, those are shown in this bar graph, and as you can see, we had a big surge in 1995, followed by a lull. We've had a few received this year. This bar graph shows you which of those are gene therapy INDs so that you can see the vector producing cell implantations seem to have been a fad. Now, to put this number of INDs in perspective, I said that there are about 40 xenotransplantation INDs. There are about ten times that number of gene therapy INDs. When you look at therapeutic proteins or cytokines, a specific kind of therapeutic protein, there are many, many more, so this is not an overwhelmingly large number of INDs.

I guess I'd also like to mention that for reasons not directly related -- in fact, not related at all to this committee -- our Office of Manufacturers Affairs made an estimate of the number of pages that an IND holds, and that number was 7, 000 pages per IND. The reason it's an estimate is because an IND comes in to the agency. The reviewer reviews it. One of these just came in two weeks ago. It came in in a crate that is the size of photocopy paper, and a reviewer at FDA has to review that -- notice the word review -- within 30 days. And actually just to let you know, the 30 days is significantly shorter than 30 days because by the time we get it at our desk, it's been logged in and delivered, it's shorter. But that would fall at the upper end of the volume of an IND. We can get an IND that comes in like this. Those are often more work because they don't contain the information that we need to know, and we have to get back to the company and say, "What about this, this, this and this? " And then the papers start to come in. So I just wanted to give you a feeling for what an IND actually looks like.

This pie chart summarizes the types of xenotransplantation product exposure that we have under IND. As you know, the definition of xenotransplantation includes -- and I thought I was going to have it in this set of slides, but obviously I don't, but you'll be hearing it again from future speakers, and you've heard it numerous times -- it includes nonhuman animal cells, tissues or organs that are implanted, infused or transplanted into a patient, or it

includes human cells that have had ex vivo contact with nonhuman living cells, tissues or organs. And so the ex vivo contact are the ones you see on top. We have seven of those. We have seven in which there is extracorporeal hemoperfusion. That's another kind of ex vivo contact, of course. We have 21 INDs which describe direct implantation of nonhuman cells, et cetera. And we have five in which the xenotransplantation product is contained within a barrier of some kind.

The kinds of animals that are sources of xenotransplantation product is shown on this slide. At your first meeting you heard about one of the fruit fly studies in which the Drosophila cells were used as antigen-presenting cells so that they were co-cultured with the patient's own lymphocytes, and then those lymphocytes were given back to the patient. As you can see, we have INDs from mammals as well or using mammal parts as well.

The type of status of INDs that we now have -- and I'll try to explain what I mean by each of these -- the pending on top are still under review. At this point in time we don't know whether they will be allowed to proceed or whether they will be put on clinical hold. And it's not to say they will or they won't. It's just that we don't know yet. The review is not complete. One of them is that big box. Ten INDs have been withdrawn by the sponsor. Of those, four were never in effect. We have 13 that are currently in effect. That means they may enroll and accrue patients. And you can see that's 13 out of 40. Nine of them are on clinical hold, which means that they may not enroll patients until they have satisfied whatever concerns FDA has told them we have. And of those, seven have never been in effect. So what that means is there are two that were in effect that were then put on clinical hold and have not come off of it to date. That doesn't mean necessarily, by the way, that those two had ever accrued patients. Two are on partial hold. What that means is they have more than one clinical trial described in their application. And at least one of those is on hold. We don't necessarily put a whole IND on hold. If it's possible that two of the three clinical trials, for example, have satisfied our concerns, if there's only one that hasn't, well, then that one will remain on hold. In such a case it's unlikely to be a product issue because the same product would be used for all the trials, so the hold issue in such a case would likely be something else than product issues. In a phase 1 clinical trial, as you probably know, the reason for putting the trial on hold has to do with safety, whether the information is incomplete for us to judge safety or whether we judge it not to be safe. Four INDs are inactive. That means that they have not been withdrawn, but that the sponsor wants to keep them active, meaning that at some point they may choose to reactivate and send a new clinical trial.

By clinical indication, xenotransplantation INDs include cancer as the largest group. And again the cancer treatment may be some, for example, of the Drosophila cells and that sort of treatment. Neurologic disorders or injuries. And you heard from one sponsor in the first meeting regarding treatment. You hear about one every day. Liver failure is another common indication for xenotransplantation, diabetes, and then small others. I didn't want to make a bunch of single pie segments.

In summary, the majority of xenotransplantation INDs describe the direct implantation of nonhuman cells. More than three-quarters of the source animals are either pigs or mice. Approximately only one-third of the INDs are currently active and in effect. Suggested clinical indications are cancer, liver failure, diabetes and neurologic disorders.

Now I'd like to talk to you a little bit about the actual recipients that have been treated under these INDs. This is the same bar graph that you've seen before except you can see which or how many or where the INDs have fallen that have never been in effect, and you can also see in the light blue color which have been in effect, but have not treated patients. And so the number that have actually treated patients is about half or a little less of the total INDs that we've received. Of the patients that have been treated, 60 percent of them have been treated with xenotransplantation products, 40 percent have been treated with gene therapy products that are also xenotransplantation products, which would be largely the vector producing cells.

The kinds of exposures that the patients have had -- now, this is different than the INDs. This is the actual patients -- half of them have had direct implantation, 12 percent the ex vivo contact, about a third have had extracorporeal hemoperfusion, and six percent have had xenotransplantation products encased in a barrier implanted.

The source animals that have been used include almost 90 percent of them being pig or mouse, which goes along with the INDs, and the fruit flies and cows show up. And the one percent that's nonhuman primate were treated prior to the FDA guidance saying that we had concerns about the use of nonhuman primate xenotransplantation products. One of them, of course, you heard about yesterday, and you're well aware of, is the baboon bone marrow.

In summary, there have been approximately 470 patients total treated under the IND mechanism. Under some of the INDs there have been no patients treated. 40 percent or so have been treated under gene therapy protocols. Most of the recipients have received implanted products or undergone hemoperfusion, and most recipients have received products involving porcine or murine cells. I'll take questions now before I go to my last slide.

DR. LUBINIECKI: Eda, could you distinguish between how many of these deal with organs and how many of them deal with cells as the transplanted article?

DR. BLOOM: I can distinguish between that to say we currently have under IND no organ transplants. However, in these data are contained two published xenotransplantation product recipients that received in the early '90s whole liver xenografts. That was again before a xenotransplantation policy developed and was in fact part of the impetus for the development. So the rest of them are all cells or tissues or the ex vivo contact.

DR. MICHAELS: Of the 470 patients treated under the IND where it has the slide on the xeno IND showing the number of patients, is it 470 that are permitted to be treated under the IND or 470 who have been treated?

DR. BLOOM: Have been.

DR. MENDEZ: Eda, of those that are on hold, are they on hold because of a policy decision of the FDA or because of incompleteness of the submission? What percentage would you say are what other factors?

DR. BLOOM: In phase 1 we have two reasons that we can put an IND on hold, and both of them are related to safety. I actually have the reg book, but we have the director of our division on clinical trial design, and she could answer that more completely than I, but they are on hold for safety reasons as judged by FDA reviewers. Very often it's because they haven't submitted information, which is where we get these little INDs, and we say, "Whoa, you need to send us all these other bits of information. " There was another hold that Dr. Wilson will discuss, when she gives her talk, when PERV was identified, and we already had a number of INDs using porcine tissue, and now we're finding out that porcine cells contain a virus that can infect human cells, so we put those INDs on clinical hold until the sponsors could show us data to support their development of appropriate tests to monitor the patients and to test the product.

DR. MENDEZ: And there is a hold now on pig products because of the PERV viruses?

DR. BLOOM: No, there's not a blanket hold at all. Once sponsors were able to develop such tests and to follow such patients, they were then allowed to proceed again. And you'll get a rather complete presentation on the results of those tests.

DR. SCHECKLER: Question.

DR. VANDERPOOL: Dr. Scheckler?

DR. SCHECKLER: So the pie chart you have with 46 percent mouse as source animals, these are basically all gene therapy protocols or virtually all gene therapy protocols. And we had a discussion in our scientific session yesterday about growing things on mouse cells or with mouse cells and recognize that that's considered by the FDA as xenotransplantation, but I suspect most of the scientists that do xenotransplantation hadn't thought about it that way. It's interesting that that makes for much larger numbers. Am I correct?

DR. BLOOM: You're correct on virtually everything you've said. Most of those patients were treated under gene therapy protocols that received mouse. However, there are patients included in that that were treated with

human cells that have had ex vivo contact with mouse cells. And you're right that probably most investigators are not aware of that. When we identify those procedures, we tell them to visit our website and to visit the SACX website and that, "Guess what? This is a xenotransplantation product. Here is where it's been published. " We're going to have a nice relationship now.

DR. SCHECKLER: But the way you're looking at that then, this all comes under our sort of -- informed consent and our review of the science and so forth would all relate to this batch of products as well?

DR. BLOOM: It's important that you remember that, that not all products may pose the same risk. A few of you were on the FDA subcommittee on xenotransplantation and attended meetings where FDA tried to get the committee to give an answer to the question, Is an organ transplant more risky than a cellular transplant? Does the length of exposure, if it's just a short extracorporeal exposure, make it less risky than if it's an implanted intended for life? Are cells exposed ex vivo less risky than an implantation? The committee was unwilling to make a call on that. And not just the notes, but the transcripts of those meetings are on the FDA xenotransplantation website or can be accessed from it. The only exceptions were when the ex vivo contact was with a well-characterized cell line. You will hear, after my talk, about a product in which the contact is ex vivo, and the contact is with a well-characterized mouse cell line. We presented that product to our advisory committee, and you'll hear about the results of that.

MS. SHAPIRO: Being a proud co-resident of Wisconsin with Bill and Jamie Thompson, the news tells us that the embryonic stem cell lines that are available for federal funding some day were grown on mouse feeder cells. So is it the FDA's position that all of this applies to any research that might be done with them?

DR. BLOOM: They would be considered xenotransplantation products if they are put into people. Any xenotransplantation product that comes to our door we will review.

DR. VANDERPOOL: Dr. Bloom, going back to one comment from Dr. Mendez, is it true that there's still protocols on hold that stem from the hold the FDA placed on all xenotransplantation protocols until assays were developed and used? Have some companies just not done those assays? Are they sort of in limbo from 1995?

DR. BLOOM: Those were not all xenotransplantation protocols. Those were porcine xenotransplantation protocols. And the letter was October of 1997. And yes.

Okay. My last slide is -- I've already blown my cover here, but another xenotransplantation product is a human skin replacement produced by co-culture with mouse feeder layer cells, and the product is known as Epicel. This was discussed previously. It is regulated by the Center for Devices and Radiological Health. As I've said, advice was received from our subcommittee in January of last year, and Dr. Peter Hudson from CDRH is here to give you a summary of that meeting and the product.

DR. GROESCH: Okay. As Eda said, our next speaker is Dr. Peter Hudson. Peter is a reviewer and biologist in the Division of General Neurological and Restorative Devices that's within the Office of Device Evaluations within CDRH, the Center for Devices and Radiological Health, of FDA.

Agenda Item: An Example of a Xenotransplantation Product Involving Ex Vivo Contact With a Well-Characterized Cell Line

DR. HUDSON: Good morning. I'm Peter Hudson, and I'm a reviewer, as Mary's just said, of medical devices at the Center for Devices and Radiological Health. Today I'm going to discuss a medical device that, due to its composition and manufacturing process, is considered to be a xenotransplantation product.

At the Center for Devices and Radiological Health we review Investigational Device Exemption, or IDE, applications and Premarket Approval, or PMA, applications for a number of skin and dermis replacement products. Most of the products reviewed do not raise concerns regarding xenotransplantation since most do not involve manufacturing processes that include ex vivo contact with live, nonhuman cells. However, the manufacturing processes of some of the products do involve the co-culture of human and nonhuman cells. One of these products, Epicel, was presented to the Biological Response Modifiers Advisory Committee's

subcommittee on xenotransplantation in January 2000 to discuss the xenotransplantation-related issues of the product. FDA has established guidelines concerning animal sourcing, product, preclinical and clinical issues for manufacturers of xenotransplantation products. Epicel was presented to the committee for the purpose of determining how the guidelines recommended by FDA should be applied to Epicel. Today I will describe the product and summarize the subcommittee's opinions for implementing FDA's recommendations for xenotransplantations such as Epicel.

Epicel is manufactured by Genzyme Tissue Repair and is intended for the treatment of patients who have sustained a deep dermal or full thickness burn covering 30 percent or more of their total body surface area. It is manufactured from autologous keratinocytes that are harvested from healthy skin and expanded in co-culture with murine, lethally-irradiated 3T3 fibroblasts to form proliferative sheets of keratinocytes. Each graft is backed by a moisture-retaining, petrolatum- impregnated gauze dressing. The prepared grafts are available 15 to 21 days later.

Cellular products similar to Epicel have been approved by FDA for use on chronic wounds and acute wounds such as burns. The products, with the exception of Epicel, are composed of live human allogeneic cells or human cellularly-derived allogeneic material. The indications for use of products approved for acute wounds are surgical excision sites, including full thickness and split thickness donor sites on burn patients. The indications for use of products approved for chronic wounds are diabetic and venous stasis ulcers and wounds and donor sites created after the surgical release of hand contractures due to recessive dystrophic epidermolysis bullosa. These other produces are used, with the exception of the product approved as a temporary wound covering for burn patients, under a more elective clinical setting than Epicel. Epicel is an autologous, permanent treatment for extensive burn wounds. The Epicel grafts are required to be prepared within a very short time frame. The short time frame is the reason for the inclusion of the xenogeneic component in the Epicel product.

To understand where Epicel fits in the list of treatments burn surgeons have at their disposal, I'll briefly go over burn wound treatment alternatives. The conventional treatment for burn wound closure today is placement of a split thickness autologous skin graft. A split thickness skin graft is harvested from an area of the individual's unburned skin. This donor skin is placed upon the freshly excised burn wound, and closure ensues. Limited availability of autograft, especially in large burns, can be life-threatening. In a larger burn the donor skin can be meshed and expanded in an attempt to cover a larger surface area with a smaller amount of available skin. If the patient does not have enough donor skin to cover the wound, the physician needs to consider alternative means of wound closure in order to save the patient's life, such as temporary coverings or cultured epidermal autografts, such as Epicel.

Now I'd like to provide a brief summary of how cultured epidermal autografts were developed as a burn wound treatment option and why they require a xenogeneic component. Cultured epidermal autografts became an option for the burn surgeon in the mid to late 1970s. An answer to the problem of limited autograft availability in massive burns was provided by the development of a new biotechnology that permitted rapid propagation of human keratinocytes in cell culture to form epithelial sheets suitable for grafting. Although the idea of using cultured epidermal cells as skin grafts was not new, prior investigations were severely hampered by methodological limitations. By 1975, however, techniques allowing serial cultivation of disaggregated human epidermal cells had been developed by Rheinwald and Green. The method of cultivation proposed by Rheinwald and Green that overcame the in vitro cell expansion limitations involved the use of a feeder layer of cells. The investigators co-cultivated human keratinocytes with lethally-irradiated murine 3T3 cells. The cytokines secreted by the cells enhanced the in vitro colony formation of keratinocytes so that within a limited period of time investigators could rapidly expand the number of cells to the extent that they could cover large burn areas. I have no hard number estimates for the extent of use of skin substitutes manufactured by the Rheinwald and Green methodology. However, the methodology is employed worldwide, and the burn clinical literature cites the methodology often.

Here's the definition Eda was referring to that you probably have already seen. The xenotransplantation subcommittee referred to the PHS guideline on infectious disease issues in xenotransplantation when the committee discussed Epicel in January of 2000. The definition of xenotransplantation as put forth in the guideline includes any procedure that involves transplantation, implantation or infusion into a human recipient of either live cells, tissues or organs from a nonhuman animal source, or human body fluids, cells, tissues or

organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs. Although the 3T3 murine cells in the Epicel product have been lethally irradiated, they are still viable nonhuman cells which could harbor infectious disease, therefore making Epicel a xenotransplantation product.

The recommendations contained in the PHS guideline regarding measures used to address the risks of transmission of infectious disease by xenotransplantation products were presented to the xenotransplantation subcommittee. The information presented was discussed with attention paid to the concerns associated with a product such as Epicel. FDA sought guidance from the committee for interpretation of the PHS recommendations in consideration that the product is manufactured with a well-characterized murine cell line and, therefore, is a special type of xenotransplantation product. The committee was briefly informed of the PHS guideline recommendations regarding animal herd and colony surveillance and source animal documentation, preclinical studies intended for characterization of the potential for microbial agents contained in the product for causing pathogenic effects in the recipient, screening assays and validation procedures for detecting the presence of microbial agents, patient informed consent of their xenotransplantation status and its implications with respect to the potential risk of transmitting unknown xenogeneic infectious agents to others, product and patient archiving and establishment of a patient database, patient follow-up procedures and blood donation deferral.

Now I'll go over each of the PHS guideline recommendations discussed by the subcommittee, followed by FDA's recommendation with specific consideration of Epicel, and then I'll summarize the subcommittee's opinion. FDA guidance recommends that information regarding animal husbandry, including housing, feeding, veterinary care and drug and biologic treatment of the animals that are the source of cells, tissues or organs to be used, be supplied for evaluation. In the case of Epicel, FDA believed that these safeguards were not applicable. The xenotransplantation subcommittee agreed.

FDA recommends that xenogeneic cell lines be characterized as to the potential for microbial agents contained in the product for causing pathogenic effects in the recipient. The 3T3 cell line used in the Epicel product has been characterized by the sponsor with respect to identity, sterility, and has been extensively evaluated for viral contamination. Murine, bovine, adventitious and inapparent viruses and retroviruses have been screened for. In addition, the transforming capability of the cells was assessed via soft agar and nude mice assays. The cells were negative for viral contamination and did not demonstrate a transformed character. The xenotransplantation subcommittee agreed that the testing conducted by the sponsor was extensive and that the testing characterized the cell line well. They did recommend that newer methods for analysis and methods of assessing noncultivatable bacteria, for example, should be considered in the future. The committee also advised FDA to ask the sponsor to quantitate the number of murine cells present in the final product.

The committee discussed whether patients receiving Epicel should be informed of the xenogeneic nature of the product. The PHS guideline recommends that the informed consent should counsel patients that they are accepting that some risk of infection cannot be eliminated and that this risk extends to intimate contacts and may have implications in considering future child bearing. FDA recommended that Epicel recipients be informed that they had received a xenotransplantation product. The committee, when asked their opinion, was split with six members voting yes, six no, with two members abstaining.

The PHS guideline recommends that samples from xenotransplantation products and patient tissue and serum samples of xenotransplantation recipients be archived. In the case of Epicel, FDA recommended that baseline patient samples and final product samples be archived. The xenotransplantation subcommittee believed that the recommendations were appropriate.

The guideline also recommends specific, timed follow-up evaluations of individuals receiving xenotransplantation products. FDA had no specific recommendations for Epicel recipients. The committee discussed whether patients receiving Epicel should be actively monitored, that is, that they should have a specific follow-up examination schedule or whether a passive monitoring follow-up schedule is appropriate. The committee discussed the difficulties with obtaining active follow-up information and decided that for Epicel patients active monitoring was not necessary, but that periodic reviews of the passive monitoring of patient data would be advisable. The committee voted 13 to 1 that passive monitoring should be conducted. For example, the committee agreed that if an Epicel patient went to their physician with a suspicious type of infection, there should be a recording of this event in the database.

With respect to blood donation deferral, the guideline recommends that recipients of xenotransplantation products and their intimate contacts defer from donating blood. In the case of Epicel, FDA recommended that recipients defer, but that deferral was not necessary for intimate contacts or hospital caregivers. The committee voted six yes and ten no that future recipients of Epicel should be deferred indefinitely from blood donation. The committee believed that withdrawal of blood or plasma products based on past donations by recipients of Epicel was not necessary and that deferral of blood donations by recipients of Epicel in the future did not need to extend to the intimate contacts of these recipients.

So in summary, Epicel is considered a xenotransplantation product because during product manufacture human keratinocytes are co-cultured with viable murine fibroblasts. With respect to the FDA recommendations regarding xenotransplantation products, the xenotransplantation subcommittee of the Biological Response Modifiers Advisory Committee recommended that the animal sourcing recommendations were not applicable, the cell line was well-characterized, but the number of murine cells in the final product should be determined. The panel was mixed with respect to whether they thought Epicel recipients should be informed of the xenogeneic nature of the product. Patient and final product samples should be archived for possible future testing. Passive monitoring with periodic review of the patient database should be conducted. The panel voted six yes and ten no as to whether Epicel recipients should defer from blood donation. The panel did not believe that intimate contacts of Epicel recipients should defer from donating blood. This concludes my talk. I guess the next speaker is Dr. Carolyn Wilson.

DR. VANDERPOOL: Could we have a couple of minutes for any questions that might stem from the group? Dr. Bill Scheckler.

DR. SCHECKLER: Thank you. In the well-characterized cell lines, such as you've described, I'm assuming that in the manufacturing processes of putting the autologous skin on the cell line, that there's also controls so that the cell line doesn't become infected somehow or other. I'm assuming, generally from what I know, most cells, when they get infected, die. So that's one safety mechanism. But what's the mechanism to be sure that the cell line that's being used for a specific patient is also free of any kind of extraneous infection?

DR. HUDSON: Right. There are standard operating procedures for handling the tissue specimen, and the tissue that's prepared is checked prior to release for sterility and infection of microplasma. There are two different stages in the development of the product where it's checked prior to release.

DR. SCHECKLER: You mentioned something about it being lightly irradiated. What does that mean?

DR. HUDSON: I'm sorry. I kind of spoke quickly. Lethally irradiated. It's a process where the cells are exposed to radiation. It renders the cell nonproliferative, so the cells are viable, they attach to the substrate of the flask and are able to provide cytokines for the cells and kind of that undefined entity that allows keratinocytes to form more colonies and therefore allows the product to be grown quicker.

DR. SCHECKLER: Fascinating.

DR. SYKES: You said that the investigators had to demonstrate that there were no murine cells contaminating the final product. At what level of sensitivity did they need to demonstrate that? With what sort of assay was it measured?

DR. HUDSON: That's a good question. It wasn't that we required them to demonstrate that there were no cells there, but we wanted to determine how many cells there were. I mean you might think that there might not be any cells that got transferred with the product. The level of sensitivity, that's something that's under current review, and we're looking at it with different methodologies.

MS. SHAPIRO: I'm interested, if you know, the why behind certain of the votes on the committee. For example, the informed consent, why would half of them not want to tell the recipients? And also with respect to the deferral, why that the recipients should defer, but the close contacts shouldn't?

DR. HUDSON: Yeah. Good questions again. I was there. I read the transcripts. I can't pretend to know how their thought processes went, but those were simply the results. I mean I think your point is that if you vote that they should defer, then why not intimate contacts? That's a good question.

DR. BLOOM: I think that the committee was presented with a product that FDA felt might pose less of a risk than some other xenotransplantation products because of the characterization that was possible of the mouse cell line, and I think they considered that in their decision about blood deferral. For example, the vote being split on the recipient, the contacts would be once removed from the recipient, and the likelihood of an infectious disease being present was perhaps -- again like Peter, I can't say what was in their brains, but perhaps considered less. The issues of blood deferral are quite contentious and complicated. It was not only discussed at our Epicel advisory committee from our BRMAC, it was discussed at the BPAC, the Blood Products Advisory Committee, not specifically Epicel, but the general policy that FDA is trying to develop about donor deferral in xenotransplantation products. And we published in, I think it was at the end of 1999, December of 1999, a draft guidance that again is on our website that makes recommendations about deferral from blood donation for recipients and their contacts. That was after public comment. Lots of public comment was received on that, a lot of it from the blood professional organizations. And the draft guidance is being revised and will be issued again in the probably not too distant future -- but I've said that before -- as another draft for more public comment because of the contentiousness of the proposals.

What you have to remember is that when a person donates plasma, for example, blood for plasma, it goes into a pool, and it becomes a pool of, golly, I don't know, a thousand or however many patient samples go into a blood product. If something like that has to be withdrawn, it's a big, big deal, and it makes a major impact on supply of blood products. If you start to defer, if you consider that there have been, what, a thousand patients or so perhaps that have been treated with Epicel over the course -- because those weren't included under my INDs. This is a not-under-IND. But if you think that there are a thousand patients that have been treated with Epicel, and maybe each of them has several intimate contacts -- intimate contacts will be defined in our next guidance document -- you could end up with 5, 000 people being deferred. If Epicel then continues to grow in usage, you could end up with a severe problem in the blood supply. And so the idea was to weigh that problem versus the risk, and that's what the committee was trying to do.

DR. VANDERPOOL: Dr. Bloom, thank you for that survey overview. That was a very extensive discussion. The FDA had to struggle with that. It affects how much blood will be collected. There's already a long list of identifiable factors as people walk in to give blood, and this was going to be yet another paragraph to a lengthy list. I think our questioners first are, as I saw the lights, Lily Engstrom and then Jon Allan.

MS. ENGSTROM: I share Robyn's curiosity about the fact that BRMAC voted in large numbers not to actually inform the patients that they were getting a xeno product. I assume, of course, part of it is not to create undue alarm since it was a well-characterized cell line, but on the other hand it seems to me that in the spirit of informed consent, I think that the recipients probably should have been told that. Of course, Peter, I'm not asking you to try to read their minds at the time they were voting on it, but it is a curious thing. I can't quite get over the fact that usually these kinds of committees are more for divulging and for disclosure to patients than they are against it, and it's sort of counterintuitive for me that they decided not to.

DR. HUDSON: And just in response, FDA has recommended that the informed consent be explicit with respect to that.

DR. ALLAN: I'm one of the people who was on the committee, and I have a really bad memory, but I think the issue, again which was already alluded to, was that the Epicel thing had been going on for years, so it wasn't that this was a new thing, and we had to deal with it. It was that Epicel had been around for such a long time and had been used relatively routinely to treat burn patients. So in light of the fact that it was probably the least infectious disease risk scenario, and I think that's one of the reasons it was presented, because it was like this is one that had the least amount of risk. I mean the mouse feeder layer cells are still viable, as he said, and they can transmit viruses, but they are well-characterized cell lines. So I think one of the questions was, do you go back? It was very difficult. I mean the committee didn't really know what to do for several of these questions. And so I think that's why you saw the breakout because there was confusion in terms of what people should do and how they should do it. So I think what you saw in the voting was essentially confusion in terms of how you

deal with some of these things. I mean the blood product thing, since you had so many people that were already out there that had already donated blood and had received these products, do you make recalls? We really got into sort of a morass in terms of what to do with people that had already been treated. But from what I understand, the people who do get treated now are deferred from donating blood, and I think that's appropriate. And the other thing, which is a question I have, is that typically the assays that were used to detect viruses that could have been transmitted were mostly old assays. So the committee had suggested that more modern molecular approaches be instituted to screen for some of these murine viruses, and I don't know whether that's been addressed or not.

DR. HUDSON: We're in the process of review and currently working with a sponsor along those lines.

DR. CHAPMAN: Just two comments. One, which Jon basically already said, but just to reiterate, I was present at that committee meeting, and my perception, my memory of it, is that the split in the vote on whether to inform patients reflected not so much the members' convictions about the importance or the absence of importance of informed consent. It reflected more their perception of the degree of risk and that there were members who felt that the degree of risk was so trivial that you in fact were more likely to do harm to people by raising the specter of risk that wasn't there by informing them it was a xeno transplant product than you were to do harm by not saying that those were the six who voted no, the six who voted "yes, inform them, " when the ones who said, "well, yes, it's a very low risk, but the balance comes on the other side, and we should inform them. " I think the key thing is that all FDA subcommittee transcripts are available on the website, right? The ones that are not directly xeno related, like the BPAC, the Blood Products Advisory Committee, is maybe a little more cumbersome for you to track through to because you can't just get it from the xeno site, but I would encourage you to go back and read those discussions of the xeno subcommittee and of the Blood Products Advisory Committee for yourself. You don't get the full sense without being able to see, but you could at least see the discussion as it occurred and get more of a sense of what the reasoning was.

DR. HUDSON: I think that's right. If you go to the transcripts, risk and informed consent are intermixed. So it wasn't like they clearly voted on one versus the other. It was kind of put together.

DR. VANDERPOOL: Dick Kaslow?

DR. KASLOW: One brief comment or question, I guess, Louisa, since you were there, one thing that might have come up is whether by not informing the patients, you might have prevented what was proposed in the way of passive surveillance. If the patient doesn't know they've received a xeno, then they can't let their physician know that in a case where an unusual event occurs. So we might want to link those two things at some level in the future as we get to thinking about surveillance and what the implications of that are.

DR. HUDSON: By definition, these patients are more than 30 percent burned, so they have a lot of interaction with the treating physician.

DR. VANDERPOOL: Dr. Bloom?

DR. BLOOM: And as Peter has said, the FDA has made the cut to ask for the insertion of that in the informed consent.

DR. VANDERPOOL: One comment on informed consent. As Robyn Shapiro and others here know, one does informed consent not just because harms are at risk, but because people deserve to have the information that they wish to make regardless of whether there are harms and risks that can occur.

DR. LUBINIECKI: Are there any plans by any of the federal agencies or the company to conduct long-term surveillance and to make these data publicly available?

DR. HUDSON: Well, the company is developing a database for following these patients. About revealing that to the public, that would be something Eda might know.

DR. BLOOM: When the database that we discussed yesterday is up and running, we will also include those

data in that, and then reports will be available.

DR. VANDERPOOL: We need to move on to the next session. Thanks so much, Dr. Hudson. As Jon Allan says, these are extremely complex issues as they are discussed, and we saw some mirror of those complexities as we witnessed our own exchange.

DR. GROESCH: Our next speaker is Dr. Carolyn Wilson, who will be giving us an overview of the processes for and experiences with screening for retrovirus in xenotransplantation. Carolyn is a senior investigator in the Division of Cellular and Gene Therapies that's within CBER, the Center for Biologics Evaluation and Research, within the FDA.

Agenda Item: Screening for Retrovirus in Xenotransplantation: Overview of Processes and Experiences

DR. WILSON: Thank you, Mary. As has already been said, I'm going to be discussing data that's been submitted by sponsors in response to questions about screening for xenotransplantation products, retrovirus expression in those products, as well as in subjects who are treated with xenotransplantation products. To just familiarize everybody a little bit more with retroviruses, I think probably everybody in the room is familiar with the virus that causes AIDS. That's the human immunodeficiency virus which, in the grand scheme of the family of retroviridae, would be found here in the genus lentivirus. There are other members of the genus lentivirus that would be found in xenotransplantation products, for example, from nonhuman primates and cows. And what I've done here is just show you all the different genre found in the retroviridae family and the various source animals that have either been considered or used in xenotransplantation clinical trials. For the purpose of this talk, I'm going to focus only on those retroviruses present in pigs and mice because, as Dr. Bloom mentioned, nearly 90 percent of the patients treated to date have been treated with this class of products. And the only infectious retrovirus that's known to be present in these animals is a member of the genus gammaretrovirus.

So to just tell you a little bit more about gammaretroviruses, in mice it's been known for many years that murine retroviruses can cause a variety of different disorders in mice, most of which are fatal, from hind limb paralysis, leukemia, thymoma, hematopoietic disorders, such as anemia and splenomegaly. In terms of nonhuman primate data, there's one piece of information that was actually -- this was an experiment that wasn't really a deliberate experiment to address the question of murine retroviral disease in nonhuman primates, but inadvertently, a preclinical study was done in immune-suppressed monkeys that were infused with bone marrow cells that were transduced with a retroviral vector. This vector was contaminated with a replication competent murine retrovirus. Subsequent to treatment three of ten of these animals developed lymphomas and died. And although this study doesn't definitively demonstrate a causal association, there were retroviral sequences that were present from the retroviral vector producer cells that were found in the tumor tissues of those animals.

So the murine and porcine xenotransplantation products that I'll be discussing today include, in the murine class, those that involve ex vivo contact of human cells or body fluids with murine cells, as we've already heard from Dr. Hudson, for example, the Epicel type of product, and then direct implantation of murine retroviral vector producer cells. This was a whole group of clinical trials that also Dr. Bloom mentioned this morning where retroviral vector producer cells are actually directly implanted as part of gene transfer clinical trials. In the porcine xenotransplantation products, these will include those that have ex vivo contact of human body fluids with primary porcine cells and direct implantation of primary porcine cells.

Now, murine and porcine cells carry a type of retrovirus which is endogenous, and for those who aren't familiar with what that means, I want to just take a few minutes to emphasize what the significance is of an endogenous retrovirus as opposed to exogenous retroviruses or exogenous viruses. Most importantly, these viruses are integrated into the genome of every cell of the animal. They're present in the germ line, and therefore, they're vertically transmitted from mother to offspring. And although most loci of endogenous retroviruses -- and this is true in murine and porcine genomes -- encode defective viruses or viruses that aren't expressed, in some cases some of these loci are capable of encoding infectious retrovirus and become activated under certain circumstances. And the final point is that the co-evolution of the host and its endogenous retrovirus may provide pressure for this virus to be noninfectious or nonpathogenic. Obviously if you have an endogenous retrovirus that's fatal, you're not going to survive very long as a species. So again just to emphasize the point,

endogenous retroviruses differ from exogenous viruses by being integrated, heritable genetic elements. This means that you can't screen a source herd for xenotransplantation and say it's free of these viruses. That will never happen.

So now to concentrate a little bit on the murine xenotransplantation products and the retroviruses that are present in those, there are three different types that really are distinguished by their host range; ecotropic, able to infect mouse and rat, xenotropic can't infect murine cells, but in fact, a variety of other mammalian species, and dualtropic can infect murine and other mammalian species. And the only reason I go to this level of detail is just to mention that because of the differences in tropism of these viruses, it means that you have to usually use multiple different detection methods in order to identify any of these murine retroviruses that may be present in a particular cell. So these are the types of assays that are typically used. Sometimes direct analysis of the cells, for example, using a very specific and very sensitive assay for a virally encoded enzyme reverse transcriptase has been used, as well as direct PCR detection of viral RNA or DNA.

So in terms of the results of murine xenotransplantation products, the retroviral vector producer cells that have been analyzed, that have been used clinically, have been free of RCR prior to clinical use. I want to just make the caveat, though, that this doesn't mean that all retroviral vector producer cells in all cases have always tested negative for RCR. In fact, there are cases of certain retroviral vector producer cells that have given positive results. Importantly, those are excluded for clinical use. So I just wanted to make that clear.

Then in terms of ex vivo contact, for example, the type of cell line that was used in the Epicel product, when you have an established cell line, you can develop what we call a master cell bank, which is usually a large bank of cryopreserved cells that you generate. It should be large enough to be able to support manufacture of product for that clinical trial, and you take one or two vials or several vials of that master cell bank, and you can do a whole battery of tests. And using the battery of tests that I mentioned on the previous slide, no RCR was detected in any of those infectivity assays, and analysis of even the irradiated cells was also negative for any replication competent retrovirus. So the irradiation conditions didn't induce expression of these viruses.

In terms of subject screening for murine xenotransplantation products, we refer to our guidance for gene transfer clinical protocols. This was issued in October of 2000. The title is shown at the bottom of the slide, although I don't know if everybody can read it, Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vectors Based Gene Therapy Products During Follow-up of Patients in Clinical Trials Using Retroviral Vectors. It's a really catchy title. I came up with it myself. At any rate, in that guidance we refer that you can use one of two methods to assay subjects for evidence of retroviral infection. One is to look for RCR-specific antibodies, and the other is to look at the subject's PBMCs by PCR for the RCR-specific sequences. In either case if a positive result was obtained, then the sponsor's advice was to do direct culture assays of appropriate specimens from the subject and look to see whether or not you can isolate and characterize infection virus. And the assay choice should consider, for example, the mode of vector administration and the immune status of the patient.

Now, in 1996 we had an FDA NIH gene therapy forum where we had sponsors from representative data that had been accumulated at that point from over 400 subjects in gene transfer clinical trials. Not all of these are xenotransplantation. The direct injection of the retroviral vector and the ex vivo transduction protocols are not considered xenotransplantation, but I just include them here for completeness. And at that point there was no evidence in any of the analyses that there had been infection by a replication competent retrovirus.

I want to, just for a moment, expand upon this one, which is a xenotransplantation product where it was included in intracerebral injection of vector producer cells. A total of 128 subjects were treated. The results of this study have actually been published in 1998. I'm just summarizing them here. But after analysis of multiple time points from each of these subjects, there was no evidence by PCR analysis for any replication competent retrovirus or by culture assay. However, there was a subset of subjects who developed an antibody response to the core protein of the retrovirus, and importantly, this core protein is also present in the retroviral vector as well as in retroviral vector producer cells. These subjects who developed that antibody response were always the group that had multiple administrations of vector producer cells. So the fact that they developed antibodies in the absence of having any PCR positivity or ever being able to isolate infectious virus from these patients suggested that in fact this was an antibody response most likely to the vector producer cells as opposed to an

indicator of an authentic retroviral infection.

So now in the second half of my talk I'd like to turn to the results from porcine xenotransplantation products, of screening for the product, as well as the subjects. As many of you remember, Dr. Salomon already presented very nicely at the last meeting of this committee a summary of all the published data on this topic, so for the sake of time, I'm not going to reiterate that here. I'm going to confine my talk only to data that's been submitted under IND because that's not necessarily, although some of it may be, in the published domain.

As has already been discussed by Dr. Bloom this morning, in response to the publication from Robin Weiss' laboratory that porcine endogenous retroviruses were capable of infecting human cells in vitro, as well as data from our own CBER laboratories, we did issue a letter in October of 1997 placing all INDs using porcine xenotransplantations on clinical hold. And this was so that we could gather more data in order to assess the potential safety impact of this novel finding. In particular, we wanted a sponsor to develop assays for detection of infectious PERV in the xenotransplantation product and to submit the data from those assays for review. We wanted them to go back and look at all subjects who had previously been treated as well as, of course, prospectively any new patients treated for detection of evidence of infection of PERV, and again submitting that information for review, and develop contingency plans if evidence of PERV infection in subjects is found, as well as revising the informed consent documents in order to acknowledge potential risks presented by the potential infection by PERV.

What I'll be reviewing for you today is the data that's really been submitted by sponsors in response to these first two bullet points. So to just briefly review the porcine endogenous retroviruses, there are three different classes. A and B infect porcine and human cells in vitro. Class C infects essentially only porcine cells in vitro. So again like the murine situation because they're viruses with different tropisms, you need to take a complementary approach of assaying by different methods. And sponsors have done this by different ways. Most commonly what's been done is taking the porcine cells which are a component of the xenotransplantation product, co-culturing those with cells that are permissive for all three types. So for example, most commonly is a human cell line called 293, which can be used to detect PERV-A and B, or a swine cell line called ST that's used for detection of PERV-C. Then these co-cultures are then assessed for evidence of infection by just looking directly for the viral enzyme reverse transcriptase or doing DNA PCR or RT-PCR for PERV nucleotide sequences. Some have also answered the question whether or not PERV-C is present or expressed in these cells by just doing direct RT-PCR for that particular envelope.

So to summarize the data that's been submitted, I'm grouping together here all of the information that's been submitted regarding hepatocytes. This is a cumulative data set from four different sponsors. So we have a number of different methods that have been used, direct RT assay, co-culture with both human and porcine cells. There was one sponsor that even looked directly in their perfusion device whether or not there was evidence for transmission of the virus and again looking directly for the PERV envelope. And really in all cases the results have been negative, so at least the data so far suggests that porcine hepatocytes in vitro do not express any infectious retrovirus. Fetal neuronal cells have also been examined by co-culture assay with permissive human and pig cells, and those results have also been negative. And one sponsor submitted information from porcine PBMCs activated with PHA and IL-2, which was also negative.

I just want to point out that there are reports in the published literature of other porcine tissues that do clearly in vitro express infectious retroviruses. So there may be differences, either breed-specific differences, tissue-specific differences and so on, not to say that this data is going to be representative of any and all porcine tissues.

So in terms of subject screening, the type of assays that have been used primarily is to look directly by DNA PCR for PERV sequences in the PBMCs, and those sequences have usually been to the regions of the retroviral genome known as gag and pol. These are the most conserved regions, so the idea is if you design primers in this area, they'll be able to detect any of the PERV strains that have been identified to date. The most problematic issue with taking this approach to patient screening, especially when direct implantation of cells is involved, is the issue of microchimerism. Porcine cells, of course, will be positive by DNA PCR. So most investigators have devised methods, such as looking for pig specific sequences, like mitochondrial genes, as a way of getting at this problem so that if you see a signal for the PERV sequences and you see a signal for, for example, pig

mitochondrial DNA, that that would suggest that you're really just seeing pig cells circulating in the patient. And you also kind of get at that question by looking to see whether or not that signal goes away over time. In addition, some investigators have developed serologic methods, such as western blot or ELISA assay, and in a few cases we also have some data looking for plasma viremia by RT-PCR for PERV sequences.

So to give you an overview of the subject data, I'll be reviewing data that's from four different clinical trials, two of which using hepatocytes ex vivo, but with a barrier between the patient's perfused plasma and the hepatocytes, one ex vivo liver perfusion, and one implanted neuronal tissue. As you can see, the number of subjects treated varies widely. And the analysis, as I mentioned, has always been, at a minimum, DNA PCR, and then in some cases, additional analyses as well. And the other point I wanted to make is that multiple time points are assessed, and these are some typical time points shown here at the bottom of the slide.

So for simplicity, I'm just dividing up the hepatocytes into A and B. In this first, hepatocytes A, five subjects have been treated, and the data that's been submitted to date is just information from PBMCs that were collected, of course, prior to treatment and six hours immediately after each treatment. And in all cases the results have been negative for reverse transcriptase activity, which is just the direct assay, as well as for PCR for PERV sequences.

In the second trial, hepatocytes B, this was a much larger group of patients, 107 treated subjects. At the time we had issued the letter in October of '97, 29 subjects had already been treated, so this analysis was done retrospectively on subjects that were treated anywhere from one to five years post-treatment. In addition to that, since that time an additional 78 subjects have been analyzed, so this has been prospective, and the time points that have been used for assessment of evidence of PERV infection are shown here on this time line at the bottom. And the distribution of these numbers below the line are the number of subjects who have DNA PCR analysis done. These are the latest time points where they would be. So in other words, 26 subjects would have data from not just the 12-month time period, but the nine, six, three and so on. So this gives you an idea of the spread and the volume of data that's been collected so far. And I apologize to the sponsor because this is a huge amount of data, and I have to boil it down quite a lot. So hopefully I'm giving it due justice. At any rate the DNA PCR analysis for the retrospective analysis of 29 patients was all negative. The prospective analysis, 74 of the 78 subjects have had all negative results at all time points tested. Four of those have been positive, but when additional analysis by DNA PCR was done for the pig mitochondrial DNA, those were also all positive. So the interpretation is that this was most likely microchimerism. Also importantly, those positive results were only found in the samples taken immediately post-treatment and in subjects that were treated from three to seven times by this perfusion through the hepatocytes. So it's not too surprising that there would be some level of microchimerism given the exposure. Additional analysis by RT-PCR for the serum viremia was negative, and additional time points by DNA PCR have also been negative. So it's very clear that this seems to be just really pig cell contamination.

In the western blot analysis for antibodies to PERV, 63 of the 78 subjects have tested negative, and I want to just go through a little bit more detail, of the 15 subjects where a band was detected in the western blot, what the significance of that result means. Seven of those subjects had a positive western blot at the pretreatment time point. This is not that unusual in that it's known that there's always a subset of human subjects, for example, who have circulating antibodies to murine retroviruses. There are just some cross-reactive epitopes that are out there. So this isn't too surprising. Of the other eight, what the band that was present in the western blot was was labeled as nonspecific reactivity, and what that meant was that it was of the incorrect size. It wasn't a size corresponding to that you would expect for a viral protein. And it was also found in the uninfected cell lysates so that it's pretty clear that that's really not a specific reaction. And importantly, of four subjects who gave a positive band in the western blot, later time points were all negative by western blot, and of those four, RT-PCR for PERV sequences was also negative. So importantly then, the overall conclusion from these 15 is that they are negative for PERV-specific antibodies.

Okay. Now, the next trial I wanted to review is that of an ex vivo liver perfusion. Five subjects were enrolled, one of which died prior to treatment. An additional two have died subsequent to treatment. So a total of three out of five originally enrolled have died. The sponsor obtained spleen samples upon autopsy, performed DNA PCR, and it was negative for PERV sequences. Excuse me. There's a mistake here. I meant to correct this. Two out of four subjects actually are still negative at both 36 and now actually 48 months post-treatment. I

apologize. I meant to correct that slide. That's by DNA PCR as well as ELISA for antibodies to PERV.

I wanted to just spend a moment on one particular adverse event that came up in this trial where a subject was diagnosed with inflammatory bowel disease versus ulcerative colitis. To rule out that this wasn't due to some xenozoonotic infection and that PERV wasn't involved in particular, when a biopsy was performed, DNA PCR analysis on that colon section was negative for PERV. RT-PCR analysis of the serum was negative for PERV. And then additional analysis for potentially xenozoonotic infections that would be a likely cause of this type of syndrome were also negative, so ruling out a potential infectious etiology for this particular situation.

Then the final trial I wanted to discuss were those group of trials really that involve exposure of subjects to porcine neuronal tissue. A total of 44 subjects have been treated in these trials, and I'm lumping together actually five different phase 1 studies and a phase 2 study just for simplicity really. And again I've shown the distribution of sample analysis by DNA PCR by the time points that have been examined so you can see that there's a variety of places in terms of follow-up. Of the 44, 43 have been tested by DNA PCR and been shown to be negative. The last one is still under analysis. ELISA assay for PERV antibodies, 12 of 33 that have been tested so far were what are called above the normal range. For those people who are familiar with this technology, ELISA assays always have -- you establish sort of a baseline background reactivity that you know with all negative samples will always give some kind of background level, and anything that goes above that cutoff you call a positive. So in this case it's called above normal range. Additional analysis of these 12 above normal range samples showed that, again like the other set, six of those 12 were positive pretreatment, and then all 12 were negative when looked at by a western blot to confirm whether or not that was specific reactivity. So again like the other data set, this is negative for any PERV-specific antibody response.

So for those of you who have gone glazy-eyed by now -- and I wouldn't blame you -- now is a good time to wake up because you get the take on the lesson. Basically the experience to date is that all murine and porcine xenotransplantation products that have been tested in vitro have been shown to be negative for evidence of replicating retrovirusus. Similarly, all subjects of trials that use murine or porcine xenotransplantations, all of that analysis has shown no evidence of infection by retroviruses.

So finally I'd like to just speculate what do the results that we've accumulated to date mean in terms of the future. And I think that it's still probably too soon to be able to definitively say that in vitro analysis of porcine tissue will always be predictive of the in vivo situation. While certainly that's true to date, so far all tissues that have been negative in vitro haven't shown any evidence for infection in vivo, I think that as xenotransplantation becomes more successful in the clinic and you would have longer term survival of implanted cells, that this may in fact change that scenario. And in addition to that, one consideration that hasn't been used clinically are transgenicly modified pigs, for example, that may contain complement inhibitory factors and the effect that may have on transmission of PERV. On a more positive note there's actually a recent paper that came out in the December issue of Journal of Virology showing that at least in one particular herd of animals, that there were some members of that herd that had very limited numbers of loci that appeared to encode infectious retrovirus. So this gives some optimism towards the approach of identifying through selective breeding strategies, combined with knockout cloning technologies, some PERV-free pigs.

And I would finally like to just thank all the sponsors who provided all the information and answered my many questions to make sure I had the story accurate for presenting here today. And I'd be happy to take your questions.

DR. VANDERPOOL: Dr. Wilson, thank you so much for this very sophisticated analysis. Let's do take questions from the committee. I said at our first meeting that we had a steep learning curve. I think your discussion now shows that the lay members of the committee have Mount Matterhorn to also ascend. It's a very challenging set of data for the lay persons.

DR. WILSON: I'm sorry.

DR. VANDERPOOL: No. We've got to learn how to understand some of this level of information. But if the lay members have -- nonscientific members I should say, not lay -- if the nonscientific members have questions for clarification, great. Obviously the scientific members will want to have further questions and details.

DR. SCHECKLER: Two questions. For me and the lay members could you define a little bit more what microchimerism means, which seems to be a benign thing rather than a bad thing. And number two, are there any kinds of assays or tests that are done -- we heard about micro arrays and other kinds of things -- to look for a prion-type viral particle in these pig cells?

DR. WILSON: To answer your second one first, to date there's been no evidence of prions naturally occurring in any pig, so we don't ask sponsors to do that analysis for that reason. As you probably know also, to do that analysis it's very difficult to assay for infectious prions. The bioassays usually take many years. So that's not a trivial request. So in the absence of any evidence that they exist, we felt that that would be an undue burden. To answer your first question, microchimerism really just means that there's an existence of a small number of porcine cells in the recipient after treatment with a porcine xenotransplantation product. And the reason it's significant in the setting is because porcine cells, of course, will score positive for porcine endogenous retrovirus. So when you get a positive result by DNA PCR, when you're looking for those sequences, you need to be able to distinguish whether or not that's actually a human cell that's become infected with that retrovirus or is that just a circulating porcine cell that's still around after treatment. Does that help clarify or is it still confusing?

DR. SCHECKLER: I'm just thinking of the porcine cells in my colleague here, Jim, and what microchimerism would mean for him five years after his transplant.

DR. WILSON: Well, to date there actually hasn't been evidence looking in PBMCs, which is peripheral blood compartment, of any circulating porcine cells in those subjects who were treated with porcine neuronal tissue.

DR. SCHECKLER: But he might have an antibody to a protein?

DR. WILSON: Right.

DR. SCHECKLER: But that's benign?

DR. WILSON: No. I mean if there was an antibody result that was definitively really positive and specific for pig retrovirus, then we would ask for additional analysis culturing in an attempt to culture the virus and so on to try to figure out what is the significance of that antibody result.

DR. SYKES: We heard yesterday from Jay Fishman about his perceived need to standardize the PERV assays that are used. Could you tell us a bit more about your requirements for sensitivity and what controls are required of your investigation?

DR. WILSON: We don't have a standardized requirement, but we review very carefully all of the protocols and all of the data for those very parameters. What is the sensitivity of the assay, what are the positive controls, what are the negative controls and so on? And you have to realize also that in 1997 none of these assays were available. You know, everything since 1977 has been research grade, and really investigators have really done a very good job at sort of stepping up to the plate and developing these assays in a relatively short time. I would say that it's not a static process, that these assays are still under development and are being refined, and we are increasing the sensitivity and so on. So I think that rather than commenting that we asked for this specific level, I think I'd like to just say that it's an iterative process that we're still trying to improve and work on these assays with sponsors individually.

DR. MICHAELS: That was a wonderful distillation of a ton of information. I was wondering if you could speculate at all on the several patients -- I believe there were seven patients that were positive by western blot prior to transplant and another six, I guess, in the neuronal one. And while that obviously had nothing to do with that procedure, it may in the future raise issues, so if we find a positive, that there might be another route. Any speculation on those patients or why?

DR. WILSON: You mean that rather than it just being a cross-reactive antibody, that it's actually from some other exposure?

DR. MICHAELS: Yes. Or if it is cross-reacting, what is it cross-reacting to? Because at some point as these procedures become more common, we might have patients that are going to fall into that category, but be misinterpreted as caused by the xeno.

DR. WILSON: That's a very good point. I think that that probably highlights an area of a need for further assay development, whether or not we can increase the specificity of these assays choosing a different antigen to react to and such, so that we can have less of that background level so to speak. I know that, for example, there was a report many years ago -- goes back probably 15, 20 years ago -- where there was antibodies to a gibbon ape leukemia virus GP70, and there was great excitement about this that there was some analogous retrovirus in humans, because this virus is a nonhuman primate virus, and it's an ape virus, and it causes myeloid leukemias as well as lymphocytic leukemias in gibbon apes. And so everybody got excited because everybody wants a retrovirus that causes cancer in humans, and it turns out that it was a cross-reactive integral membrane protein present on human cells that these patients were having an antibody response to. It took about another ten years for people to track that down. And I would guess we're seeing something similar in terms of the PERV antibodies and the murine antibodies, but I think that we probably can work with just fine tuning the assays to try to rule out those kind of cross-reactivities.

DR. MICHAELS: Just as a follow-up, I think it was Mayo was going to do it, but there were going to be some studies done looking for the ELISA and for PERV in the pig workers.

DR. WILSON: I agree there's been a lot of discussion of doing those studies, and I think that they've been done or are in progress, but I haven't seen any published results. Louisa, do you know any more about that?

DR. CHAPMAN: I know there was a study that was completed. My knowledge of it is because the investigators had approached us about initially doing confirmatory -- I mean they wanted to sort of ice the product by having serologic testing in another lab. We had complications getting IRB approval, and by the time we were in a position to do that testing, the key investigators had both left Mayo, they were both taking on new jobs, so they had the paper virtually written up, and they were no longer interested in putting everything on hold. So I don't know what's happened since then. The key investigators in that were Jonathan Hibbs and Dave Percy, and you could check with them. I suspect what happened is that they both left, went to different locations, took on new responsibilities, and the product simply hasn't come out yet. But you could inquire from them more directly.

DR. WILSON: And actually while she was doing that, I remembered there is one published study from Joachim Denner's laboratory that came out this summer that did an analysis of people who worked in cider houses, and there was some antibody reactivity in that population. His interpretation of that was that the rate of reactivity in that population was not greater than the rate in the general supposedly negative control population, although the sample sets in that study were relatively small, and there was no statistical analysis, so I don't really know how definitive that was.

DR. VANDERPOOL: Dr. Allan?

DR. ALLAN: That was a good talk. I appreciated it.

DR. WILSON: Thank you.

DR. ALLAN: The thing that usually keeps coming up is the issue of how do you screen people who are dead? Because you're only able to get PBMCs, and if the PERV virus doesn't replicate in the PBMCs or is found in tissues, or in the case of neuronal implants, may be contained within the site, but could potentially be in human cells as well, so it becomes very difficult. So the antibody-based assays tend to be most definitive in cases where the virus either replicates only for a very short time and then goes latent, which many retroviruses do, so that if you don't find the virus or viral DNA sequences, if you get an antibody response, that's going to give you much greater confidence that you have some infectious process that has either happened or is ongoing. But the antibody-based assays are very difficult to control because what you don't have is you don't have appropriate positive control samples, so you're sort of in the dark. So when you set your cutoff for ELISAs or even for

western blot, you're still in the dark because you really don't know what you're looking for. So you have these what you think might be cross-reactive antibodies, but it's very difficult to sort out because what you really need to have is like, with HIV infection, what you usually use in an ELISA is an HIV-positive person because they have a certain profile of antibody responses to different antigens. In pigs they don't make antibodies to PERV, so you don't have a positive control. When you're doing the western blots, you're primarily looking at P30 I think; is that correct?

DR. WILSON: The western blots are typically done taking infected 293 lysates, so you actually are looking for all the potential reactivity to any of the viral proteins. But then you have 293 human proteins on there too, and that's why I think we see this nonspecific reactivity where you get a band at a different size and so on.

DR. VANDERPOOL: Due to our time constraints, we need to bring our questions to a close. Dr. Chapman, did you have one other comment or question?

DR. CHAPMAN: I have one quick question, but so the answer will be meaningful to the nonscientific people on the committee, I needed to make a comment. Jon touched on this. When we talk about serologic testing with western blot, what you're talking about doing is checking the antibodies present in the person against a series of individual proteins that are present on the infectious agent you're looking for. And with western blot testing for HIV, what's required to call it positive is a specific pattern of reaction to three separate proteins on the HIV virus because historically when they were developing the tests, they found if you used one reaction to one protein or even any combination of two reactions to two proteins, it was too nonspecific, and you often got false positives. You told people they were infected when they weren't. So it requires a pattern of three.

My question for Carolyn is in these new PERV testing, how many positive bands to PERV proteins are required? When they say it's a positive result, are they calling that on the basis of one reaction, a pattern of two reactions or a pattern of three reactions?

DR. WILSON: It's a good question. I think with the western blot that hasn't really been sorted out. I think mostly people would be looking to see a P30 reactivity, which is the core protein.

DR. CHAPMAN: So it's just one positive.

DR. WILSON: But since we haven't had an authentic positive result yet, I don't know that that has really been very well discussed.

DR. CHAPMAN: In the published papers out of, for example, our labs and other labs when they talk about positive serology, they're talking about one positive reaction of the patient's antibody to a porcine protein, not something more definitive, like a pattern of three that's defined as we use in HIV.

DR. WILSON: Right.

DR. CHAPMAN: So there's more room for error.

DR. VANDERPOOL: Dr. Mendez has something.

DR. MENDEZ: Just one quick question. Has there been any retro studies on patients in ex vivo therapies with hepatocytes or with porcine livers prior to 1997 who were previously alive, mainly those that I know of in England and in Europe? Have there been these studies done?

DR. WILSON: Yes, they have. And those are the subject of the published reports that I didn't review here, but if you go back to Dr. Salomon's presentation at the last advisory committee. But there's a Nature Medicine paper from Robin Weiss' laboratory where they looked at extracorporeal perfusion of hepatocytes. And then as you probably remember, there's also that large Novartis retrospective analysis of a number of different subjects that had been treated, and the majority of those patients were through extracorporeal splenic perfusion, but there were some other treatments as well. So there is some published information about the retrospective analysis of those subjects.

DR. VANDERPOOL: Thank you, Dr. Wilson. I want to express on behalf of the committee my very great appreciation for all of these presentations by Drs. Bloom, Hudson and Wilson. These take a great deal of time out of schedules that we can tell are very busy. At points you work under time constraints that are very great, and we truly appreciate your doing this and your also setting up the discussions that will follow in closed session.

We'll take a very brief break after we do one other thing as we prepare the room for the closed session, and that is we need to think about what we want to focus on next time. I don't think we have time really to discuss this, but maybe what we should do is have Dr. Groesch send us out a list of possibilities and have us e-mail back and forth and vote on what we think think we should focus on. I think out of the meetings thus far that I've heard, some of our main possibilities for our March meeting would be to certainly further focus and secure the content and completion of our two working group reports, to think seriously about dealing with the pressing international guidelines and regulations vis-a-vis what we've heard has been termed a xeno tourism, to perhaps deal with issues and questions related to the birth of the knockout pig, to think about ways to inform and educate the public, we at least can discuss that because these working reports are hopefully coming out before too long, and we want to do what we can there about educating the public, and we appreciate those who are members of the public here and hope that some of what our deliberations do gets into news and journals, issues related to patient confidentiality vis-a-vis the database and specimen storage, and finally an issue that has been mentioned a time or two by several members of the committee, that is, the xeno issues related to stem cell research. Given what Dr. Wilson said about murine xeno screening and some of the antibody responses that have been determined, the question is, should we think about some of the xenotransplantation issues behind stem cell research? So those are some of my candidates.

Do we have a moment for other comments from the committe members?

DR. GROESCH: Yes, we do.

DR. VANDERPOOL: Let's take a little bit of time to discuss what some of your preferences are to prepare us for this e-mail exchange that hopefully sets the stage for the meetings to come.

DR. SYKES: I would like to comment that our subcommittee, our working group, has come up with a list of probably between 10 and 15 speakers that we would like to have a day to hear from next time in order to complete the work of our working group.

DR. VANDERPOOL: That's excellent. I'm sorry. Sometimes I do have memory lapses occasionally, such as 1995 instead of October 1997, but I also sometimes am given to too much humor beyond what I should do. I said our group didn't need specialists. Well, actually we do need specialists in the law and other issues pertaining to informed consent. And so one real candidate, Megan, is for us to really focus this next meeting on issues pertaining to our reports so this committee will not just continue to hear and discuss things, but really get something out there for the public. So that may be the strongest possibility with our session on news and reports and updates that we had yesterday, bringing in maybe one or two of these other issues in addition to focusing on the content of the reports. As you say, if you have 12 or 15 people, that's going to take a full meeting. The informed consent people probably ought to think of what candidates we ought to bring in to discuss, for example, issues involving surveillance and monitoring. Others? Robyn and Bill?

MS. SHAPIRO: I just have a question for Megan. Is one of your experts that you want to call in someone who knows about the embryonic stem cell issue?

DR. SYKES: We spent a lot of time discussing whether or not we wanted to do that. And Jon, why don't you summarize that.

DR. ALLAN: Yeah, we had sort of a lengthy discussion. We went back and forth over that, and we decided that it was something that we did need to address. Whether or not we folded it into the sort of feeder layer scenario rather than setting it apart as a specific, because the FDA has been dealing with this issue under the xenotransplant product, and so we weren't clear about what we thought would be a good way to handle that, but

I know that Bill had said that he would go talk to Jamie Thompson and get his input, and then we'd discuss it within our working group, but obviously you guys should have an input into what we really should do about that.

DR. GROESCH: Also in that context the group thought it would be helpful to have copies of the recent NIH report on stem cells, and Don Fink had mentioned that included there is a chapter on safety issues that addresses this a bit. So I will procure copies of that and provide them to all the members of the committee.

MS. SHAPIRO: I think it would be very helpful, just to register my own preference, to have Jamie Thompson or someone like him come.

DR. VANDERPOOL: Bill?

DR. SCHECKLER: Yeah. I had actually intended to try to get over to Jamie's lab before I got to this meeting, and something called anthrax came up, and it sort of took away some of my time. I think it would be very difficult to get him. There might be somebody like him at the NIH that can address some of those issues, but I still will visit his lab and see exactly what kind of an issue does he think it is because he's the guy that sort of invented the way to grow the cells to begin with.

The other comment that I had was that Bob Mendez and I sort of agreed to work with a couple of members, Harold, from your working group, and your working group would designate the primary author for the introduction to both working groups' papers, and we sort of sketched that out what that meant, and I think it would be useful to try to have a draft of that, what's the potential implication of doing this. And it's in some of the review articles and so forth, but it would be nice to begin to have a draft of something to look at at the next meeting as well. And I don't know if Jon or Megan talked to you about that, but that was sort of in our to do list.

DR. VANDERPOOL: That would be excellent. I presented our committee with a possible introduction that obviously deserves editing and revision. But yes, I think we need to be moving as much as possible toward a draft stage, and obviously drafts can be thoroughly reworked given the content of the next meeting.

Well, I think we're reaching a good point of view here given our time frame, and I'm sure some of our schedules are fairly tight, but it's so important for all of us to stay till 2:00 o'clock that we should close off now and take a very brief break and come back very quickly. Mary, do you have anything to add to that?

DR. GROESCH: Yes, I do. It's now 10:36. How about if we reconvene at 10:45. That's a nine-minute break. I will ask for all the members at the table to leave their signed pink form, the confidentiality form, on top. I will go and collect those. And then members of the audience I need to ask you to vacate the room, take your materials, all your bags and papers with you, and when we come back in, the members that are going to attend the closed session will come through one door, and I'll ask you to give me your signed confidentiality form, and I'll check you off. So 10:45.

(Whereupon, open session ended at 10:36 A.M.)