on Blood Safety and Availability. This report was developed during the summer of 1999 and was presented publicly to the PHS Advisory Committee on Blood Safety and Availability at its August meeting. The report contained recommendations in five areas.

These recommendations were considered by Dr. Satcher's Blood Safety Committee. Next overhead, please. The Blood Safety Committee is a committee that is comprised of PHS agency heads. The Blood Safety Committee recommended that the recommendations in the report be made part of the existing Blood Action Plan. Incorporation of the recommendations into the Blood Action Plan was approved by the department in November of 1999. Next overhead.

The five areas of the monitoring and supply area of the Blood Action Plan are: first, to monitor the blood supply; second, to encourage more donations by eligible donors; third, improve donor relations as part of recruitment and retention; four, remove restrictions to safe donation; and, five, address economic issues facing the blood industry. We'll go through these, the high points of these five elements.

In terms of monitoring the blood supply, the National Heart, Lung and Blood Institute of the National Institutes of Health on December 10th contracted with the National Blood Data Resource Center to conduct monthly

surveys. This effort will proceed under contract for some time. By October of the year 2001, the Public Health Service will determine if one of the public health agencies should have long-term responsibility for this effort.

Jane, if I could have, there is a clear overhead that Dr. McCurdy, BPAC member from NHLBI, provided to me to give you a sample of the type of data that's being collected. The data collection began with data from October, November and December, which was collected retrospectively after the contracts were let, and the January data which was more real time data, and these data were submitted to the NHLBI in February.

I don't think you can see a whole lot in terms of trends, but this was total red blood cells released during this four-month period, released and made available for transfusion, with the total number of units and then broken down by O positive and O negative, which are the types that are generally more in short supply. Although there was a dip in November-December, there is a fairly constant rate of O positive and O negative.

Now, whether these are adequate supplies, we will need to see. This is only one element. We also have data that is being collected on outdating, bimonthly collection of data representing inventories, and the program will move to collecting data on utilization for comparison purposes.

Okay, we can go back.

The second part of the supply and monitoring area of the Blood Action plan is to encourage more donations by eligible donors. The department offered the support to industry to participate in public service announcements, and it's my understanding that Dr. Satcher has filmed several PSAs in the area of blood supply. I don't know that any of these have hit the airways yet.

In addition, the National Heart, Lung and Blood Institute sponsored a workshop on February 28th entitled "National Strategy to Increase Blood Donations." It was attended by corporate representation, blood center directors, blood donor recruiters, and was an important first step in forming a national message concerning blood donations.

The FDA has committed to publish a donor incentive guidance by June 30, 2000. This will be in the form of a compliance policy guide, and will represent what has been allowed according to our regulations as they are written now. It's not a gold standard on the desirability of donor incentives. That area requires more work, more studies.

The NHLBI is sponsoring studies in this area. At present we don't have a lot of data, but a lot of strong opinions on the use of donor incentives. And also the NHLBI will explore the feasibility of initiating studies on

development of educational programs to encourage blood donation as a civic responsibility by June 30th of this year. Next.

The next part is to improve donor relations as part of recruitment and retention. The FDA has committed to a draft guidance on recruitment practices by the end of this year. In order to do this, we are--well, it's more than possible, I think we're planning now to have a workshop on donor recruitment by the end of the summer, and we're seeking co-sponsorship of this workshop.

Additionally, we plan on providing guidance on what we have approved in licensing for computer interviews by September 30th, and we will initiate simplification and abbreviation of the donor questionnaire by January 1, 2001. You may have heard at this meeting there's a lot of enthusiasm for this one element by the industry and by consumers.

The next is to remove restrictions to safe donation. FDA is to issue guidance for the use of therapeutic hemochromatosis donations by May 31, 2000. I am beginning to worry a bit about this date, not because we don't have a policy; we do. It was in a memo from Jane Henney, our Commissioner of the Food and Drug Administration, to David Satcher last August.

We also have been approving, on a case-by-case

basis, requests to allow use of therapeutic hemochromatosis donations without the labeling, the disease state labeling that made it undesirable, and to allow the collections at more frequent intervals than every eight weeks. We have approved several of these; we have several in-house to review.

The issue on the guidance is trying to generalize what is a fairly easy operation, case-by-case, to a guidance document that can be used industry-wide. In addition, we are looking into having workshops to review some of the donor deferral criteria to see which ones are useful anymore. However, in our discussions, most prefer to have NAT implemented before we tackle this, and so the workshops will be in the year 2001.

The last element is to address the economic issues facing the blood industry. I think Dr. Nightingale told you this morning that in August the PHS Advisory Committee on Blood Safety and Availability heard discussions on safety measures and cost implications. Their April 2000 advisory committee meeting will continue to discuss reimbursement issues related to safety measures, and by June 1st the Department will clarify policies on reimbursement.

And that's the plan and our status thus far. Do you have questions?

DR. HOLLINGER: Any questions of Doctor Captain

Gustafson? Yes, Dr. Schmidt?

DR. SCHMIDT: I don't understand how it's in the mission of the Food and Drug Administration to tell people how to recruit donors or help them recruit donors. I mean, I'm very glad they are. Everybody should be helping. But if blood is really a drug and we think of parallels to other drugs, it doesn't make sense for me to divert FDA funds into promoting donor recruitment.

Of course, to take away some of the barriers for accepting donors, but the concept of donor publicity or whatever is going to be in this--you said you were going to publish a donor, FDA would publish a donor incentive guidance. This, to me, I just don't understand it.

CAPTAIN GUSTAFSON: Well, part of having a safe blood supply is also having an available blood supply. We view that safety and availability are very much intertwined. And yes, it does go beyond where FDA has gone in product jurisdiction issues, but we think it is important. We think blood is a national resource, and we think having an available supply from our donors is very, very important for the public health.

DR. HOLLINGER: Yes, Ms. Knowles?

MS. KNOWLES: Could you give me just a little clarification on point number three under improved donor relations, where it says FDA guidance on computer

interviews, please? Thank you.

CAPTAIN GUSTAFSON: Yes. NHLBI has funded studies on having donor interviews with an interactive computer. They also had funded a study back in the 1980s looking at the best way to interview donors, and part of the information that came out of that study was that a computer assisted donor interview would be useful.

We have approved at least one application using the computer-assisted interview, and I think there are others that will be coming in for us to review, but we would like to make more public what we have approved so that others may pick up on the initiative.

DR. HOLLINGER: Okay. Thank you, Dr. Gustafson.

CAPTAIN GUSTAFSON: Thank you.

DR. HOLLINGER: We are going to now go into a discussion on donor deferral issues, but Dr. Smallwood has something she would like to put up first in regards to this issue.

DR. SMALLWOOD: This is the web site that you may obtain copies of the information that was provided to the committee, and my understanding is that the information that we had provided to us prior to this meeting is already present on the web site.

The other announcement I wanted to make is that for this discussion concerning xenotransplantation issues,

we will have joining the committee as a temporary voting member, Dr. Jonathan Allan, and we will also have as a guest of the committee, Dr. Louisa Chapman. Thank you.

DR. HOLLINGER: Are they here? We are going to go ahead, then, and start the discussion. This is on donor deferral issues related to xenotransplantation. It comes on the heels of a subcommittee meeting that was held recently to discuss these issues, and the introduction and background is going to be given by Dr. Andy Dayton. Andy?

DR. DAYTON: Could I have the first slide? The title to this talk is the implementation of precautionary measures to reduce the possible risk of zoonoses by blood and blood products from xenotransplantation product recipients and their contacts. I have updated this committee in the not-too-distant past on xeno issues. I will just focus on a few basic definitions to jog people's memories and to help the members of the public who aren't as familiar with xenotransplantation issues.

Zoonoses are infectious diseases of animals that can be transmitted to humans through exposure to or consumption of animals. Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live cells, tissue or organs from a non-human animal source, or human body fluids, cells, tissues or organs that have had ex vivo

contact with live non-human animal cells, tissues or organs.

Xenotransplantation products include live cells, tissues or organs used in xenotransplantation. By way of exceptions, biological products, drugs or medical devices sourced from non-living cells, tissues or organs from non-human animals, including but not limited to porcine insulin and porcine heart valve, are not considered xenotransplantation products. So, for instance, vaccines are generally not considered xenotransplantation products, even though they overlap in many characteristics with xenotransplantation products.

Because transplantation necessitates disruption of the recipient's usual protective physical and immunologic barriers, xenotransplantation may facilitate transmission of known or as yet unrecognized zoonotic agents to humans. So it's not just a problem of getting animal viruses, it's also a problem of getting adapted viruses, and xenotransplantation in many cases theoretically can favor adaptation.

Some xenotransplantation product sources, particularly pigs, are being genetically modified in ways that may foster adaptation of zoonoses to human receptors. I discussed some of the details of these technologies the other year, and the critical take-home is just to remind you that there are many factors in xenotransplantation which

predispose to adaptation. Some of them involve in this case genetic manipulation of the donor animal, and others involve things like immunosuppression of the human recipient.

Some xenotransplantation procedures maintain a barrier between host and foreign tissue, and it depends on the particular technology used. This barrier can be involved in transplants or implants into a recipient. It can also be involved in ex vivo exposure. But even when such barriers are non-permeable for virus, the barriers can fail, and therefore situations such as this do represent a risk that requires serious consideration.

Now the risks of zoonotic transmission to xenotransplant recipients and their contacts remain undefined in many cases. I should say the outer limits of risk remain undefined. Some risks are well known. And of course the history of introduction of HIV into the human populations from simian sources, not even--and HTIV--not even involving xenotransplantation situations, makes us doubly wary of the unknown.

We also have to balance our worries about the risks of xenotransplantation with the immediate risk to public health of blood or plasma becoming unavailable. Certainly this committee needs no reminding of that. Withdrawal of plasma derivatives to address even small numbers of unsuitable donations could cause serious product

shortages.

Now, how many xenotransplantation recipients are there? Okay, these are very iffy numbers, and they won't add up, and the reason they don't add up perfectly is because they are so iffy. Probably there are about 1,000 or less than 1,000 in the U.S. It's not 10,000; it's probably not 3,000; probably under 1,000.

Of these roughly 1,000, probably 550 have had autologous transplants of cells grown for long periods of cells grown for prolonged periods on a monolayer of a well characterized murine tissue culture line. The product in particular considered in our minds here is the Epicel. Probably about 500--there are only probably about 50 or 100, very rough numbers again, of the classic xenotransplantation recipients. And I point this out to you so you'll have a handle on how big a threat in numerical terms xenotransplantation is to the blood supply.

Just to highlight some of the recent chronology of events related to this talk, on December 23rd of '99 we published the draft guidance document, which is the precautionary measures to reduce the possible risk, etcetera, etcetera. This is a draft guidance document.

On January 13th of this year the subcommittee, the Biological Response Modifiers Advisory Committee Subcommittee on Xenotransplantation, or for short, Xeno

Advisory Committee, met. There were several members of this committee participating in that committee. And they discussed the highlights--for that committee we discussed the highlights of the draft guidance document and voted on several recommendations.

In general, in rough terms, the Xeno Advisory Committee felt it was in its purview to address the scientific issues, and they had a general preference to have the implementation issues devolve to this committee, the Blood Products Advisory Committee.

Now I'm going to go through the votes that that committee made, because I think they are a very excellent way of summarizing the nature of the discussions, the results of the discussions, and also how unanimous or split the decisions, the recommendations were. There are about 10 or 11 different questions here they voted on.

First, should xeno recipients be indefinitely deferred? And that was a very easy one. That was unanimously "yes".

Now, the draft guidance document said--had discussed what to do with close contact of xeno recipients. The Xeno Advisory Committee felt that the "close contacts" was too broad a definition to deal with in terms of contacts relevant to deferral issues, so they decided to limit contacts of significance for deferral and withdrawal policy

to "intimate" contacts as opposed to "close" contacts. Now, again there was pretty strong sentiment for this. "Yes" was nine, "no" was one, "abstain" was three.

But it's very important to realize that "intimate" was never defined. In fact, it was said, "Well, we all know what 'intimate' means." So we are not sure that we know what "intimate" means even yet, but we're going to try later on perhaps a further definition of it than we got that day.

Then, using the undefined "intimate" contacts, should we defer intimate contacts if xenotransplantation product recipients. It was somewhat split, but the vote was in favor of that, nine yes, seven no, to defer intimate contacts.

Now, the issue of--in the guidance documents, draft guidance documents, we had recommended to defer health care workers who had had percutaneous or mucosal exposure. After discussion of whether health care workers who have had exposure to xeno recipients should be deferred, the committee did vote unanimously "no". However, we probably--we feel that there should be some reexamination of this issue, and I'll get back to that later in my talk.

Then, should we allow case-by-case exceptions for deferral, such as when exposure has been to well characterized cell lines? Well, again, case-by-case gives us a lot of leeway, and the committee was unanimously in

favor of that.

Should we withdraw whole blood and unpooled blood components for donation by a xeno recipient, for example, unpooled plasma, source leukocytes? This was--the committee was unanimously in favor of that.

Now, should we withdraw plasma derivatives, such as pooled plasma, for donation by a xeno recipient? And again this is the xeno recipient, not the contact. And again it was felt unanimously "yes".

Now, when you get to pooled plasma, the issues got a little more complicated. Should we withdraw plasma derivatives, pooled plasma, for donation by an intimate--I'm sorry. When we get to intimate contacts, it gets a little more difficult. Should we withdraw plasma derivatives or pooled plasma for donation by an intimate contact of a xeno recipient? And here it was somewhat split. Only four voted in favor of it. A majority, though, nine voted against it, with three abstentions.

The committee also decided, for the issues of pooled plasma and intimate contacts, not to distinguish between a xeno situation which had been involved in non-human primate or any other animal. The original draft guidance document had suggested handling the two differently, but they had identical votes to handle them this way.

Should there be case-by-case exceptions to withdrawal of pooled products for exposure ex vivo, for example, to well characterized cell lines or across a physical barrier, again case-by-case? And the vote was "yes" unanimously.

Now, an issue which we're going to be discussing today was brought up, should we add--and I'll show you what I mean--about the series of xenotransplantation questions to the donor deferral questionnaire. In the guidance document we had recommended an admittedly fairly complex set of questions to be added to the donor questionnaire, and there was a lot of sentiment against that, as there often is to adding questions to the donor questionnaire, and particularly complicated ones such as we presented, and the committee voted unanimously against that set of questions.

Now, I'm just going to preview the questions that you're going to be asked, that we're asking you to vote on--of course, you can add to that or modify it--basically to give you a heads-up so that you can follow some of the proposed changes we're proposing--some of the changes we're proposing for the draft guidance document.

And what you will actually be given later on is, we have proposed language concerning, and I'll give you that language, xenotransplantation deferral issues to be added to educational material required to be read by donors before

donation, and the question will be: Does the committee agree that donors should be required to read this before donation?

And then the second question, we have proposed modifying the blood donor questionnaire to intercept xenotransplantation recipients and their intimate contacts, and we will be asking you: Does the committee agree with the proposed modification in the questionnaire?

And with that preview, let me now go into the key changes that we have proposed to make to the draft guidance document which are based on our interpretations of the sentiment of the Xeno Advisory Committee. Several of these slides will have "old" on the left and "new" on the right. "Old" is perhaps not the best nomenclature. That refers to the draft guidance document that is published, draft guidance. "New" is referring to changes that we propose to make to it, or what's going to be new.

And instead of the old definition of "close contacts," we will simply remove the definition of "close contacts" and insert a definition of "intimate contacts." And this definition of "intimate contacts" includes persons who have engaged repeatedly in activities that could result in intimate exchange of bodily fluids with a xenotransplantation product recipient, for example, sexual partners, household members who share razor blades or

toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal or other direct exposures.

In the draft guidance document, the older document, we had called for deferral of close contacts. The new one will call for deferral of intimate contacts. The key take-home there is that the definition of contacts to be deferred has been narrowed considerably, going from "close" to "intimate."

Now, in the old guidance document we had suggested deferral for health care workers with percutaneous or mucosal exposure. Now, with the new definition of intimate contacts, health care workers are included in the definition of intimate contacts, so they would be deferred. However, and this was a consideration discussed by the Xeno Advisory Committee, what's important to remember is that under this definition, yes, they are included, which they weren't before, but only if the exposure has been intimate and repeated. So that takes you to a fairly restricted set of health care workers.

Below on these slides I've listed some of the relevant votes from the--and I believe you have copies of that in your handout--from the Xeno Advisory Committee. Those are the same votes that I just read out to you individually.

In the new guidance document, again following the suggestions of the committee, we're calling for withdrawal of plasma derivatives or pooled material for donation by any xenotransplantation product recipient. There will be certain exceptions. And no withdrawal of plasma derivatives for donation by intimate contacts of xeno recipients. Again, there is--the primary consideration here was the threat to the plasma supply of having to withdraw possibly a small number of donations which could have serious repercussions.

And, again, this is not terribly different from the old document, but I remind you that we have allowed ourselves to have case--in the new guidance document--we allow ourselves to have case-by-case exceptions to deferral and/or withdrawal for donation by xenotransplantation product recipients when the exposure has involved only well characterized cell lines, or when the exposure occurred only across a physical barrier. The emphasis here is on case-by-case, and also that we--such situations may be considered.

Now, this doesn't show well on the slide because it is fairly involved. I think it is worth reading out because it is an implementation issue, which is one of the two questions here.

What is here on this slide, and also you have a copy in your handout, is the proposed modification of the

reading material that donors will be asked to read or required to read before they donate. Our staff has done a wonderful effort of bringing the--of taking the level of the language to a level that can be understood, I think it's what, a fifth or seventh grade level you have to make it understandable to, and they've done a very good job of bulletizing the key information here. And I'm going to read through this with you because it's one of the voting questions.

We want to include the following information in the educational material presented to donors before donation:

"Do not donate blood or blood products if you have ever been exposed to animal organs, tissues or cells during a medical procedure or treatment. An individual may be exposed to animal organs, tissues or cells by one of the following medical procedures or treatments: receiving a transplant of a living organ, tissues or cells from an animal; having blood or other body fluids removed from your body, passing it through a machine or procedure which exposes your blood or body fluids to living organs, tissues or cells from an animal, and then returning it to your body."

"Do not donate blood or blood products if you have ever had intimate contact with an individual who has been

exposed to animal organs, tissues or cells during a medical procedure or treatment. Examples of intimate contact activities include sexual intercourse; sharing of needles, toothbrushes, or razor blades; laboratory or health care workers who may experience repeated direct injection or mucosal exposure to body fluids."

We're going to ask you to vote on whether you want this added or not, and if you do, we also welcome comments to modifications of the language, etcetera.

Now, the next issue is again a key implementation issue, and this involves a voting question, and this involves modification of the questionnaire. Now, in the old guidance document--and you have that before you, but there is, as I mentioned, a fairly complicated series of questions, we are proposing to modify--we are proposing to get rid of those and to do a much simpler modification to the questionnaire. And what we want to focus on, is we want to modify the current AABB standard donor questionnaire question on transplantation and transfusion.

And up here I have listed how the question currently reads. The question currently reads" "In the past 12 months, have you received blood or had an organ or tissue transplant or graft?" On the next slide I'll show you how we want to modify that.

First, what we want to do is to change that

question so that it will now read: "In the past 12 months, have you received blood or had an organ or tissue transplant or graft from a human?" We feel that's a very straightforward and simple modification, and not overly complex.

Then after that question we would insert a nested set of questions, and this one underlined here is the key one to consider because that's--if it doesn't pertain to you, you don't get into the more complicated nested questions. And the question here that is supposed to capture the people we want is, "Have you or anyone you know ever been exposed to animal organs, tissues, cells or transplants as part of a medical treatment?" So if that doesn't apply, then you're out of the xeno questions; you don't get into any of the complications.

Now, of course, what does it mean if you know someone? Well, if you know someone who is a xeno recipient, then you get into these subset questions, these nested questions which we have also tried to keep fairly simple. And to read that: "If the answer to this question A. here is yes, were you the one who received the medical treatment?"

And if the answer to that were--well, then there is a subcategory to that: "If the answer to II.A.1. above is no, did you engage with the treated individual in

behaviors which could involve the repeated exchange of body fluids, such as sexual intercourse, or sharing of razors or toothbrushes, or were you repeatedly exposed to cells, tissues, organs, or body fluids from such individuals through your mouth or eyes or open wounds or sores?"

Again, that gets pretty complicated at that point, but there are two things to take into consideration here when you worry about the complication of that question. First of all, it's a nested question. Most people won't get to it. We specifically designed it so that these two very simple questions will intercept most of the people, will take most of the people away from the more complicated questions.

Secondly, although this is a complicated question, donors will have been required to read the material I quoted you before explaining what these issues meant and going into these in detail. We feel that between the two instruments, the addition to the educational material and this nested subquestion, we should be able to effectively capture the people we want to capture without making the questionnaire overly complicated for the vast majority of people who answer it.

And then the guidance is that prospective donors answering yes to any of the questions above should be deferred.

I want to just come to a close, again to reexamine or to get back a little bit to the health care worker issue, and there are important factors distinguishing exposure of health care workers to xenotransplantation product recipients from people such as abattoir workers and veterinarians who get exposed to animals. The reason I bring this up is because this was discussed at the Xeno Advisory Committee, but we felt at this point needed emphasis or reemphasis.

And please remember that the xenotransplantation product recipient represents generally a long term, intimate apposition of xenogeneic tissue. Not always necessarily long term, but in the classic case, yes, long term. Even something like Epicel is fairly long term. This apposition is generally under conditions of host immunosuppression or even a lack of an immune system, which may allow abnormal amounts of xenozoonotic replication, thereby favoring adaptation.

And, finally, in some xenotransplantation scenarios, as I have mentioned, genetic modifications of the transplanted material may pose the risk of additional avenues of xenozoonotic adaptation. So, again, the health care worker's and laboratory worker's situation is very different than the abattoir, slaughterhouse worker's or veterinarian's or farmer's.

And now, Linda, I am going to stop here, and then we have--the next two slides are the questions, but I guess there should be a discussion first? How do we do that? And then if you want the questions, they're on the slides. So I'll turn it over to you.

DR. HOLLINGER: Yes. Dr. Epstein?

DR. EPSTEIN: Andy, could I get you to clarify one apparent inconsistency. In the proposed donor educational material, in the second highlighted sentence, you say, "Do not donate blood or blood products if you have ever had intimate contact with an individual who has been exposed to animal organs, tissues or cells during a medical procedure or treatment," whereas the actual deferral recommendation is only if you have had repeated contact. So I'm just asking whether that is a deliberate inconsistency or something that should be corrected before the discussion.

DR. DAYTON: I think when we originally wrote the sentence, we felt that the explanatory material would go into repeated, but if it doesn't, we should change that so it does. That's a fair point.

DR. EPSTEIN: I mean, I think it would be reasonable for the question to the donor to ask about ever, and then there could be follow-up query whether it was repeated. But to up front defer or suggest that donors self-defer for isolated single time exposure would be

inconsistent with the proposed deferral.

DR. DAYTON: Well, it may be--first of all, if you look carefully here, for the health care workers and laboratory there is--"repeated" is mentioned. For sharing needles, for instance, maybe we don't want to emphasize the repeated nature of that, or even for sexual intercourse. Again, if it's going to lead to self-deferral, I don't think we're going to lose many people. So I think to be correct we should have the repeated in but, you know, this is not something that's necessarily going to lead to withdrawal, which is the big issue, big worry. We could modify that

DR. EPSTEIN: Well, I think the committee could discuss whether we want an over-inclusive self-deferral, but I think for purposes of the committee discussion we ought to propose them as consistent; so, in other words, revise the--

DR. DAYTON: We can just--we could change. I know where that came from. It was getting away from the 12-month concept that is seen in human transplantation, and we could change that. You know, "Have you had repeated intimate contact," that's very easy to do.

DR. HOLLINGER: Yes?

DR. SIMON: I want to ask a question. I didn't go to this workshop and I'm not up on this field, and I've asked a couple of people about this since I got the material. But from what I'm told by them, something like a

porcine heart valve was not meant to be covered, and yet the way the question is phrased, if you had a porcine heart valve--now, people who have porcine heart valves ordinarily wouldn't be donors, but their sexual contacts might be. How are we dealing with that issue, as to what's okay in terms of animal tissue and what's not?

DR. DAYTON: Well, the way this is written, it specifies "living." We might have to add language excepting things like that. That's a good point. People are going to be confused on that. Again, it's very hard to write this--and we absolutely invite comments like this--it's very hard to write this at a level that's very easy for non-sophisticated laymen to understand. Certainly in all of our guidances we say "living" and we mention that issue specifically, and we welcome comments on how to make this language simplified. Because I don't think a standard person who had had a porcine heart valve, they may not know whether it was living or not.

DR. SIMON: Yes, and it says any individual who may be exposed, if you have ever been exposed to animal organs, tissues or cells, is the way you start it. Now, you do have in the bullet--well, someplace I guess you have "living".

DR. DAYTON: Yes, yes. No, but it's a fair point. That's a fair point.

DR. SIMON: Okay.

DR. HOLLINGER: We're going to move on. We're going to have questions you can ask Dr. Dayton in just a second, but I want to go to the open public hearing first, and then we'll come back to the questions and Dr. Dayton will be glad to answer any questions you have.

Yes? First I want to call on Dr. Louis Katz, who is going to speak for both the AABB and ABC, I believe.

DR. KATZ: We had in fact as organizations not prepared specific statements for this meeting. You have the AABB's written comments on the docket in your packet, I believe, and I do want to emphasize some of the high points in that. In addition, I have had discussions with representatives of the American Red Cross, and what I am going to say is consistent with their position, although I am not an official representative of the Red Cross.

Our organizations recognize the important potential risk of transmitting zoonotic pathogens to patients by this route, and agree that xenotransplant recipients as defined are unacceptable donors of allogeneic blood and tissue. Parenthetically, because of donor restrictions regarding medication used in general health, virtually no xenotransplant recipients as defined would be qualified blood donors at this time.

The theoretical risk of zoonotic transmission was

well articulated in the August '96 document entitled "The draft Public Health Service (PHS) guideline for infectious disease issues in xenotransplantation," which states specifically, and I quote: "Consent forms should stated clearly that xenograft recipients should never, subsequent to receiving the transplant, donate whole blood, blood components, source plasma, source leukocytes, tissue, breast milk, ova, sperm, or any other body parts" if they have any left--it doesn't say that--"for humans."

The language appropriately recognizes, and this is we think a key point, the primary responsibility of the transplant community for the apprisal of their patients about these zoonotic risks. We believe strongly that this aspect of the Health and Human Service guidance should be implemented, even pending formal implementation of the draft guidance from 1996. FDA can insist on inclusion of such information in consent procedures as a condition for acceptance of clinical protocols for xenotransplantation. And I would hope that Dr. Dayton or somebody from FDA can tell us whether that is ongoing at this point or not.

Blood collection facilities can reinforce the prohibition on donation by including xenotransplant exclusions in our written materials to blood donors as required study before each donation. This would avoid the issue of time-consuming and, in all due respect to Dr.

Dayton, we believe still confusing and certainly unvalidated FDA questions to the donor interview.

The written materials that we already provide to donors prior to donation include the following information: an admonition not to donate in order to receive test information; description of the signs and symptoms of AIDS and the behaviors that are associated with the risk of HIV infection; a statement to the effect that you'll be tested for, and then a long list of I believe seven agents that we're looking for now; a statement that they will be deferred if positive in infectious disease testing; a statement apprising them that the relevant public health authorities will be notified if required; and a request that they call after donation if they recognize problems that they didn't recognize at the time of donation.

Now, that's the written material they get already. Okay? That's not the donor screening interview, which is already lengthy and complex. The AABB Uniform Donor History sanctioned by FDA contains 32 separate elements that include inquiries into highly sensitive personal areas, including sexual activity and drug use and references to such rare diseases as babesiosis, transmissible spongiform encephalopathies, etcetera. The FDA proposes to add what we would consider an additional complex set of nested questions to this process.

The REDS investigators, Williams, et al. in JAMA in '97 reported that approximately 2 percent of anonymously surveyed accepted blood donors admit to deferrable risk on anonymous interview, and it is our suspicion that a substantial proportion of this is due to the length and complexity of the donor interview. Our concern is that increasing the complexity of the donor screening process for theoretical risks may detract from its efficacy for documented risks like traditional viral transfusion associated infections and malaria. The result could be a paradoxical decrement in transfusion safety.

We maintain that the proposed donor questions in the draft we have seen today remain arcane, and suspect that their addition to the current donor screening process will produce confusion. At a minimum, we would ask that additional questions proposed by FDA for the reduction of a theoretical risk be validated for sensitivity, specificity and predicted value--predicted value may be hard at this point--before being added to the donor interrogation process.

The requirement for deferral of contacts at this point is unsupported by evidence of transmission of potential or unrecognized pathogens to contacts after xenotransplantation. Again, the database is small. We are still concerned, however, that this is a slippery slope from

deferral of such donors to disqualification of large populations with very significant occupational animal exposure, including abattoir workers, farmers, veterinarians, medical researchers working with large animal models. My concern is acute because I run a blood center in Iowa.

We suggest that a risk assessment be undertaken amongst those with close contact to the relevant species for evidence of potentially transfusable disease associations that would support zoonotic transmission of disease-causing organisms. Given the small number of xenotransplants currently being performed in this country and the potentially very large populations with contact in non-human primates and swine, these epidemiologic studies can be carried out long before xenotransplantation becomes prevalent and constitutes a significant zoonotic threat via the contacts of xenotransplant recipients.

Thank you for your attention.

DR. HOLLINGER: Dr. Katz, do you know for a fact, do you have data that suggests that the reason they didn't answer those questions was because of the length of the question, or are you just making an assumption on that?

DR. KATZ: That's basically personal communications with the REDS people that did that study and their speculation. I think that's an important point.

DR. HOLLINGER: But that was unlinked, if I remember right.

DR. KATZ: Yes.

DR. HOLLINGER: That, they couldn't account for it.

DR. KATZ: Yes, it remains speculation. And I guess the other anecdotal source of information on this is the questions that we get from our donors during and after screening, that indicate pretty clearly that some of the more complex questions are not really very well understood.

DR. HOLLINGER: I think, Dr. Shapiro, you had a comment?

DR. SHAPIRO: Yes. Along this line--

DR. HOLLINGER: Can you state--

DR. SHAPIRO: Yes. Ariel Shapiro. I work at Life Service Blood Services in Chicago. I would, because of the opportunity for confusion among the donors, and I work very closely with them, I think it would be very important to put up front on the proposed screening procedures, that you indicate "do not donate blood or blood products if during a medical procedure or treatment" if that's the intent, and then go on to the exposure to animals. Because we have a fair number of donors that I have been called on, that have animal bites, or they have injected themselves, they have accidentally injected themselves, like giving the cats

insulin or the dogs insulin. So I think if we want to try to make this more specific, we need to really drive home that this is during a medical procedure.

DR. HOLLINGER: Thank you.

Could you just please--

DR. CHAMBERS: Yes, Linda Chambers. I'm a senior medical officer for Red Cross.

I would like to first verify that Red Cross endorses the statement you heard earlier from Dr. Katz, and I would like to just read into today's discussion the highlights of the official Red Cross statement on the issue that was brought to the Xenotransplantation Subcommittee meeting in January: the highlights being that the American Red Cross agrees that a deferral policy for xenotransplantation is appropriate; however, believes that only donors need be deferred, that close or intimate or otherwise defined contacts should not be considered within the scope of the deferral; and that specifically donor questions to address the issue are unnecessary.

I would like to expand on that, not as an official representative of the Red Cross but with my own personal comments, and that is that I think it's important to appreciate in the big picture that there are a number of ways of implementing a new expectation for donor eligibility and a new donor eligibility criterion. They run the gamut

from a question on the questionnaire, the information provided to the donor, and the instructions given to the person evaluating the health history of the donor.

I believe it's important to reserve the specific questions to the donor and the information that's in the "what you must know" document that goes with the donation for those components of donor eligibility that require specific attention on the part of the donor and are the most important. In other words, I think there's a limited amount of time and attention, and it's important to take your best shot at eliciting from the donor the kinds of health history and behavior parameters that will most substantively affect the safety of the transfusion.

In earlier discussions in talking about the post-donation information as regards plasma recalls, this was touched on briefly, but I think is relevant to this discussion as well: When you look at circumstances where donors call back with new donation information, and that's all reported to FDA, those are all accidents or errors that are available to be analyzed and evaluated, you will find that there is information that is relevant but not all that important.

For example, the donor that might call back and say in fact they had hepatitis when they had EBV at age 15, that's interesting but probably not substantively important

for the safety of the blood products. And then there are donors that call back after their 15th donation and only then report that they were an IV drug user, or the sexual partner of an IV drug user, or a man who had sex with another man since 1977, or something where you have a behavior that you know not only captures significant known pathogen risk but also covers what we believe to be major routes of exposure for perhaps emerging or unidentified or untestable yet blood transmissible pathogens.

Not all those reports are donors who have a broad streak of denial, and I would speculate, and I think it's as speculative and as valid a speculation as the concern about xenotransplant recipients having transmissible agents, that the failure of those questions to be answered properly with the earlier donations comes from donors who are overwhelmed by the information and overwhelmed by the process of the blood donation. Which means that anything added into the donor information, in the form of the health history questions specifically or the information they have to read, seriously runs the risk of distracting the donor's attention from what we know to be important questions.

So I would personally endorse strongly the concept that anything new to be added to either of those documents be verified before it's put into use as not a question that's going to divert attention and adversely affect the

accuracy or completeness of questions that we know are more important in terms of the ultimate blood safety. Thank you.

DR. HOLLINGER: Thank you. Any--yes? Please state your name and your organization.

MR. HEALEY: Sure. My name is Chris Healey and I'm with ABRA. We agree with many of the comments you've already heard. We also agree that xenotransplantation recipients should not be blood or plasma donors. However, we think the current donor screening procedures already exclude these donors. Donors are currently asked whether they're under a doctor's care, whether they have had any major medical procedures in the last year, whether they have received organ or tissue transplants, blood transfusions. So we think these donors are already being excluded.

A piece of information that I think hasn't been addressed or presented to the committee, that might help inform the decision-making process, is the types of care and selection and cell line treatment that the donor animals receive. At the Biologics Response Modifier Subcommittee meeting I think there was a representative from one of the xenotransplantation communities, and he characterized the donor animals as being, you know, very carefully selected, and cell lines as being purified and so forth. So I don't have any personal knowledge about that, obviously, but I think that is some information that the committee could use

in its deliberation.

DR. HOLLINGER: Thank you. Anyone else in this session on the public hearing?

[No response.]

DR. HOLLINGER: If not, we're going to close the public hearing. We'll now open it up for committee discussion. Perhaps, before we do, we should have the questions that you want us to look at, Andy.

DR. DAYTON: Okay. This is the first question. How do you want to do it? Do you want to just discuss, or do you want to have the questions or--the next slide has the next question, so do you want me to read this question? Okay.

We have proposed language concerning xenotransplantation deferral issues to be added to educational material required to be read by blood plasma donors before donation. That's that bulletized document you have. The question is: Does the committee agree that donors should be required to read this material before donation? And if you are interested in this kind of material being added but would like to make comments on what we have actually suggested, we would request committee members wishing to modify the proposed language to submit revised language to the FDA within the next two weeks.

DR. HOLLINGER: Okay. I think we'll look at this

issue here, what I think Andy's talking about, what is on page 5, basically, of your handouts. Well, it's the second page 5 there.

DR. DAYTON: The top of it says "Proposed Modification of Screening Procedures," Roman numeral I.

DR. HOLLINGER: Thank you, Andy. It's the second set at page 5, on planned changes to guidance. Okay, and I think that's the issue that's brought up here. It's asking about the educational information, not about the information to the donor at the time of screening. This is the stuff that you get prior to donating. So I'm going to open this up now for discussion. Yes, Dr. Macik?

DR. MACIK: One problem is, how does the donor differentiate between what's an organ, tissue, fluid? Rarely used, but an example would be porcine Factor VIII, and in particular a person who acquires Factor VIII deficiency might get porcine Factor VIII, completely clear that disorder, and 10 years later be wanting to donate blood and say, "Well, I got something from the pig one time." How are they able to distinguish these things?

So I think there's some need for clarification, you know, on just what these things are. I find it still confusing to try to put this into perspective, confusing even for me on some levels, and I think for a donor it would be even more confusing.

DR. HOLLINGER: You're saying that perhaps there ought to be some exclusionary things? This does not--well, I mean, for example, like you're talking about, like insulin possibly?

DR. MACIK: They might know, "I got insulin from a pig," or "My doctor said this is bovine or pig," or you know there's a lot of products now that are out there. Depending on the level of sophistication of the patient, they may even actually know a little bit too much and add more confusion. "I got a recombinant product that was made from a hamster kidney cell. I was exposed to an animal product." So I think there's some issues here that need to be refined a little bit.

DR. HOLLINGER: A vaccine from E. coli or something. Yes, Dr. Schmidt?

DR. SCHMIDT: Of course I wasn't at the meeting where all of this was thrashed out, and I have some specifics, but sort of a philosophical statement on this, the whole question of where bugs come from. There was smallpox and tuberculosis and influenza and AIDS, and there's that whole sea of waterfowl off South China, and that's all in the background.

And going back a long time, in the 19th century it was parasites and bacteria for which we can sterilize and we have vaccines and chemicals, and in this century antibiotics

for bacteria; and the 20th century was the century of viruses, for which we can sterilize and have vaccines but we have not been able to cure a single one. And this, at least the Nobel Prize Committee says, is the century of prions, for which we can't sterilize, we have no vaccines, and we have absolutely no cures.

And I think we have to keep that in mind and not talk about the old stuff. I think this came up earlier. But we don't know, this is the first meeting of this committee in the 21st century, and I think we have to look ahead rather than look back.

And then just some comments on what the day-to-day--I think what I was hearing Jay talk about was the problem of "ever" had intimate contact and down below with the health care workers it would be "repeated." Well, those two things are incompatible, those statements, "ever" versus "repeated," and I think I heard Jay leaning towards having both of them as sort of "repeated" contact, where I would want to take the position, if you have ever had intimate contact, and for a health care worker it wouldn't have to be "repeated." I mean, one shot is what's going to do it. So in this text, as we go along, I'll submit in writing the proposal that it's not a question of "repeated."

The other thing in here is this problem of sexual intercourse. We're reading now that many young people don't

consider some things as sexual intercourse. Maybe that all could be changed to "sexual contact" and not use the word "intercourse," but a sexual contact. That's broader. Maybe it's too broad, but I will send that proposal in anyway.

DR. HOLLINGER: Yes, Dr. Linden?

DR. LINDEN: I have noted the same thing that Toby did. On the first statement, it's overly broad to say if you have ever been exposed to organs and tissues because it would include some of these other things, as Gail mentioned.

But I also share Linda Chambers' concern that this is just too long and too complicated, and it's going to divert from people really understanding the material. We know a lot of the donors don't really read the brochure now, anyway. So I think if you're going to have anything, it should be limited to one or two very succinct sentences, and if they have any questions they can ask about it. But this material, I'm concerned, is just too long and detailed and it's just going to confuse the issue, and the way it's phrased is also, it's overly broad, so two concerns.

DR. HOLLINGER: Thank you.

Dr. Mitchell?

DR. MITCHELL: Yes, I agree that it should be limited to two, maybe two, maybe as much as three sentences, but not more than that. And also I think that a lot of the issues should be part of the training for the staff, and the

staff should be able to answer questions about insulin and vaccines and tissue and that kind of things, rather than having it in either the questionnaire or the educational materials.

On the first sentence, I think that the specifics, I would not talk about either "ever" or "repeated," I would just take it out and just say, "have you ever had," and I think "been exposed to" is also very confusing. So I would just say, "Have you ever received a transplant or a graft of animal organs, tissues," blah, blah, blah, and to me that's much more simple. But I'll put something in writing for the specifics, but my point is that I think there should be one question, one question that's asked of everybody, and maybe the nested questions but--

DR. HOLLINGER: Now, Mark, we're just going to deal here with the educational aspect now. These are not the questions to the donors.

DR. MITCHELL: Right. Okay.

DR. HOLLINGER: So this section here is just on the material that they get before they even go and get the questions that they have for that.

Yes, please? Excuse me just a minute, Mark. Jay

DR. EPSTEIN: Yes. I just have a concern that, a little bit, it might be better to take the issue of the donor question before the issue of the educational material,

for the following reason: One of the proposals on the table is not to use a donor question but to utilize donor education and self-deferral in lieu of a specific donor question. And my concern is that if we deal with the comments on the educational material first, we're looking at the fact that, should the committee vote against a donor question, you might view the educational material in a different light. You might want more of it; you might want it more expansive. And some people may not feel influenced one way or the other, but others might.

DR. HOLLINGER: How does the committee feel about this? Do you want to deal with the question first, the issue about the question first? I see a lot of nods. Or not? Okay. All right, so we'll deal with the question first, then, that Mark had started addressing--now you can come in there, Mark--that he started addressing his question about. So that's on the next page.

DR. DAYTON: Do you want me to read the second question?

DR. HOLLINGER: You could read that, yes.

DR. DAYTON: Okay. We have proposed modifying the blood donor questionnaire to intercept xenotransplantation product recipients and their intimate contacts. Does the committee agree with the proposed modification to the questionnaire?

DR. HOLLINGER: And that's on the next page, basically, with several parts to it. So go ahead, Mark. Why don't you go ahead with your--

DR. MITCHELL: Okay, and so I would say that the first thing, I would leave the original question about blood and organ or tissue transplant as it is. I think it confuses if you say "from a human." Then people will say, "What do you mean, from a human? As opposed to what?" And it will throw people off. And, you know, people normally assume that it's from a human, so I don't think that there's a reason to--I think it adds more confusion than it adds clarification.

Then the specific question that would have to do with xenotransplantation I believe should be similar to the statements that are made previously, and I believe that it should ask, "Have you ever received a transplant or a graft of animal organs, tissues," blah, blah, blah, and then may say something about intimate contact either as a second sentence in that same question or--because I think if you say, "Have you or anyone you know," It is still very, very broad. And so I would say, you know, that again as part B of that or maybe even a separate question, you would ask about intimate contacts, and then I think you can get into some of the nested questions.

But I think that you should only have one

question, maybe two, that ask about the initial exposure through receiving a transplant or graft of tissues or cells and intimate contact with someone who has had that exposure.

DR. HOLLINGER: Dr. Linden?

DR. LINDEN: I have a comment and a question. Then I'll have another comment after the answer.

For the people who weren't at the meeting, one of the issues discussed was the fact that a lot of the people who may have these procedures, particularly children, may not know of the risk and they may not know that they need to inform their sex partners. So that you can ask, "Have you ever had sex with somebody who got an animal graft?" and they're not going to know that because the person hasn't told them.

So that I think the committee really felt pretty strongly that the most effective way to address this problem is to tell the recipients at the time, and their parents if they're children, that there is a risk of getting pathogens, whatever you want to call them, from these tissues or organs, and it is important that you, your child, not donate and tell sex partners that they shouldn't be donating blood, and that that really is probably the most effective way to go.

Dr. Dayton, given that the committee voted 16-0 in favor of not having any questions, and opposition from all

the blood banking organizations, could you explain, elaborate a little bit why the agency really feels it's important to have questions?

DR. DAYTON: That's a fair question, of course, and we did give this a lot of thought before approaching it. We felt that what they were largely focusing on was the very bulky--they weren't focusing, the discussion did not focus entirely on the bulky set of questions, but we felt that the questions that we had proposed at that time were very bulky and cumbersome and confusing, in retrospect, and we felt that that was a major obstacle to putting them in, and we felt that the negative reaction to them was based largely on an inadequate design.

We felt that what we have come back with is considerably more simple, although by no means perfect, and we felt that there was a sufficient improvement in the simplicity of the questions that it was worth reconsidering in that light.

DR. HOLLINGER: Yes. Dr. Chapman has been asked also to join us as part of the discussion here from the CDC, so Dr. Chapman?

DR. CHAPMAN: I just wanted to mention that when you're discussing rephrasing the informational material or the questions, you may want to refer back to that definition of xenotransplantation, because while it's true that it's

clearer to say "have you received animal tissue" than "have you been exposed to," one of the components of the definition is that one of the ways in which xenotransplantation products are currently being used is as a sort of biologic dialysis for people in acute hepatic failure, and those people do not receive animal hepatic tissue, in the way that renal failure patients do not receive kidney dialysis machines; they are exposed to animal tissue the way that renal failure patients are exposed to kidney dialysis machines.

That may not influence, still, your recommendations on simplicity of wording, but you need to be consciously aware of that and refer to that definition when you make those recommendations to FDA.

DR. MITCHELL: Could I respond?

DR. HOLLINGER: Thank you, Dr. Chapman.

Yes, please, Dr. Mitchell.

DR. MITCHELL: They are really not exposed. Their blood is exposed, or their body fluids are exposed, and I don't think that people would perceive themselves as being exposed under those conditions.

DR. HOLLINGER: Dr. Schmidt, and then I'll come back to you.

DR. SCHMIDT: I saw something, I forgot exactly, but it relates to this, about physical barriers, and I don't

know what the physical barrier to a prion is.

DR. HOLLINGER: Dr. Boyle?

DR. BOYLE: Thank you. Since I ask questions for a living, I want to take this chance to make some observations. Number one, if you can't ask the question simply, don't ask the question, because all you're going to get is a lot of error and a lot of confusion. And if you're self-administering this thing to a million or more people per year, the potential loss of people who are confused and say "yes" or "not sure" is a serious issue, given what we've been through recently.

Secondly, it is appropriate to have a committee of M.D.'s and Ph.D.'s agree about whether we should ask a question. It is not appropriate to have them frame the question, at least in my experience, because they don't necessarily write very good questions.

Number three, if you are going to ask a question and you're going to administer it to a million people a year, please go through a process of cognitive testing to make sure that the average person who gets it can read and understand the question the way that you plan to do it, because it will save a lot of grief for a lot of people who will be reading those questions.

DR. HOLLINGER: Dr. Epstein

DR. EPSTEIN: Yes, I wanted to follow up on Dr.

Linden's question. I think that part of the agency's bias in putting back the proposal for a specific donor question comes from our experience with AIDS-related behavioral risk questioning. When we first introduced exclusion of donors based on AIDS-related risk, it was done only through education to the donor and then donors were only asked if they had read and understood the material, and they later signed a statement that if any of the information pertained to them, that they wouldn't donate.

And what we learned over time was that that was a lot less effective at eliciting deferrable risk than following up with a question to the donor about their actual risk. And, yes, that was belt-and-suspenders, but we did have actual experience that it made a difference. And as I recall, Paul, you were one of the people that had studied that at a later time over the issue of whether direct questions about behavioral risk, including sexual behavior, would be a big put-off to donors and whether it would be tolerated.

So, you know, we spent a lot of time agonizing over whether to move to direct questions, and what we learned was, (a) we could do it without putting off donors, as long as the rationale was clear, and (b) that it was important in making the self-deferral into effective deferral. That's not to say there was no utility of self-

deferral, only that it got better.

So that's an up-front bias which I want the committee to acknowledge. I also think that we could perhaps simplify the debate if we suggest that the real question for this committee is whether FDA ought to develop an appropriate question, rather than getting us bogged down in trying to design it here today.

We put in front of you our most recent effort to simplify a question. I think we can take to heart the message that, you know, more scientific methods should be applied to doing it, but really the issue on the table is, should the appropriate deferral strategy include a direct question, one or two questions, well designed, and that that would be a better issue for the committee to cut on.

DR. BIANCO: Mr. Chairman?

DR. HOLLINGER: Yes?

DR. BIANCO: Celso Bianco, America's Blood Centers. I would like to make a couple of observations about this issue. I was at the meeting of the Xenotransplantation Committee, and I think those are critical issues because they affect--we should look at them as part of the forest, not each individual tree, and xenotransplantation is a tiny little plant in the middle of everything.

First, Dr. Boyle, it's 13 million volunteer blood

donors, and a similar number of units collected from source plasma, and so the number is much bigger.

The second thing, there is a very big difference between risk questions, risk behavior questions that we ask to pick up somebody that may have been exposed to a virus through use of drugs or sex, and addressing a population of individuals that today are maybe less than 1,000, 2,000 in the country. They are all part of clinical trials. They are all known to the sponsors of the clinical trials. Everybody has a name, has an address, has a physician. We are choosing to ask 20 million people a question to find these thousand, instead of just going directly to these thousand people and telling them that they cannot donate blood and that their sex partners cannot donate blood. I cannot see the logic of that.

And, finally, as an observation, even if it is very important, like CDC has pointed out, the issue of exposed to transplanted and all that, those are issues, but I can guarantee that somebody in liver failure, using dialysis with baboon liver, is not going to show up at the blood center to donate blood. Thank you.

DR. DAYTON: Blaine, can I make a comment?

DR. HOLLINGER: Go ahead. Yes, please, Andy.

DR. DAYTON: There are several things I want to address here. First of all, the complexity of the language

in both the question and the proposed educational material. I think Jay really did focus on what we should really be addressing, is do we want to ask a question or not. I think you should realize that we certainly understood how complex this material is to question people.

The approach we took and suggested was, we know we're not going to catch them all on the educational material, we know we're not going to catch them all on the questions. Let's make it very simple, and hope that the redundancy does the best job that it can. So that, in terms of whether or not you want to ask a question, I want you to take that into consideration, that there are ways to handle it even if it's fairly complex, and they may not be perfect but they may be reasonably effective.

Now, the other point I wanted to address is, there have been--numerous people have brought up the point that xeno recipients go through an informed consent, and there's every reason to believe that you can, except for juveniles who may not be aware that they have had a xenotransplantation product, transplant, there is every reason to believe that they can be effectively deferred from donation, but informed consent is not effective at reaching their contacts, and that's something we need to remember.

The point has also been made that, okay, it has not really been shown that their contacts are at risk and

anything is going to happen, but it's very important to realize that one of the major factors behind this issue is, we don't know what is out there. We don't want to end up with another epidemic like HIV. If there is something there that's going to get out, that's where it's going to get out, because if it's going to be a threat to the population, it probably would be easily transmissible by intimate, close contacts, or intimate contacts.

So that was our thinking in going in these directions, and I hope you will remember those key points. That's all I wanted to put in at this point.

DR. HOLLINGER: Yes, Dr. Simon?

DR. SIMON: Yes. I would like to focus, then, on the question of whether there should be a question, and there is obviously an industry point of view here, and I guess as the industry representative you're not surprised that I'm supporting it, but I would argue against a question at this time. While I think we shouldn't focus on the language, I don't believe the FDA would have come here without putting quite a bit of effort into framing a good question, and you can see how difficult it has been, so I think it's going to be very difficult to frame a good question.

I think this also runs counter to another major effort of the agency which Captain Gustafson told us about,

which is to look at the donor questionnaire and try to shorten it and reduce it, to focus on the major issues. And I would hope that that could go forward without--with limited tinkering with the questionnaire in the interim because this is, you know, I think a process that has been used over the years, is that somebody has expressed concern about a risk and it's been noted by the agency and made its way into a question, and the questionnaire itself has never really been validated to determine that it actually leads to safety.

So I would hope that that effort could go forward and this effort be put on the back burner, particularly, I mean I think one wouldn't be reticent if one thought there was a risk there, but particularly since the committee was unanimous that we didn't need a question. And on this issue of the intimate contacts, while I certainly understand the logic, the committee was very divided as to whether it was even important to defer intimate contacts at this time.

So I think there are a whole variety of reasons to argue against a question, or there are a whole variety of reasons why we should not adopt a question at this time to be added to the questionnaire.

DR. HOLLINGER: Okay. Dr. McCurdy?

DR. McCURDY: I would like to second a couple of comments made by others. Number one, I think if you need

the information, you have to ask the question. I became aware a number of years ago of a colleague who donated blood in a number of different blood centers around the country, ostentatiously took the pamphlet that he was supposed to read and stuck it in his pocket, and not once was he called by the blood center personnel that, hey, you're supposed to read that before you put it down. So I think educational material, I agree with Jay that it has limits.

I also think that it would be highly desirable to get question writing people to help write the questions, and it would almost certainly be desirable to do some field testing before you put it in. Now, if it's important to defer both xenotransplant recipients and particularly their intimate contacts, then I think you have to move forward and not wait until you review the entire questionnaire.

DR. HOLLINGER: Yes, Dr. Chamberland?

DR. CHAMBERLAND: A couple of thoughts. I also want to re-echo some of the comments that have been made, but in a little bit of a different direction.

I'm concerned that, as Dr. Simon said, that no matter how hard folks at FDA and others work with them, it's going to be extremely difficult to distill down into a simple question a very complicated situation. And we've heard a number of people on the panel and in the open committee, open public hearing, bring up for instance the

porcine insulin question, the porcine valve question. Not only will it be extremely difficult and complicated to ask the question, but I think it's going to be very challenging to educate the people in the mobiles and the donor collection sites that have to then engage in a back-and-forth with the donor to really get to the heart of it.

I personally, and my colleagues in the Malaria Branch, for example, are getting questions from Mary Smith: "I'm at mobile in Des Moines, Iowa"--that's not really the place, Lou--"but I've got a donor in front of me, and she's going back and forth about countries in Africa, and are these Group O countries?" And it's very black and white: "These are the countries that pertain. Your person comes from a different country, hence I don't think we have a match here." So just on something that we perceive to be fairly straightforward, in a field situation ends up I think sometimes being more complicated than we anticipate.

So because I think it's a very complicated question, and because I really do believe that our primary focus at least at this point should be on the xeno recipients themselves, which is, as has been stated, an extremely small population at present, although growing, likely to be deferred because of other questions that are asked in the history-taking session, and because the transplant programs should be, through informed consent and

other processes, informing these recipients, that that's probably a better way to go.

I would suggest two things. One is, perhaps FDA or others--I'm assuming that these transplant centers are fairly small in number. Maybe I'm wrong, and I would appreciate anybody giving me some correct information. But I would suggest that FDA perhaps, if they haven't already, consider going to these transplant centers or a sampling of them to see what currently is being done. With what rigor are recipients being given information about the need not to donate? Or if you want to extend that, their intimate contacts, etcetera, and examine that.

And then, secondly, sort of along the lines of what we do with new variant CJD, because I think there is a legitimate concern that's being expressed that we're really only on the beginning of a learning curve in terms of accumulation of epidemiologic and laboratory data, we're at a very early stage, that maybe as a sort of interim measure that there be sort of a systematic reassessment of the data every six months, every year, whatever people think that's a reasonable interval, like we're doing for new variant with an ad hoc working group, so that there is some sense that this is being actively looked at. But I would say that maybe we're not quite ready yet for a question or maybe an information in a donor brochure.

DR. HOLLINGER: Thank you.

Dr. Koerper?

DR. KOERPER: I agree. I think this is a very complex issue. I myself am having trouble sorting out whether Recombinant Factor VIII made from baby hamster kidney cells is a--you know, does that mean the recipient of Recombinant Factor VIII has been exposed to something? I mean, it's complicated for us, as well as for the patients.

However, I do agree with comments that individuals don't read those brochures that they're handed. I think there needs to be a statement in the brochure for those rare individuals who read it, but I don't think we can count on people reading it.

I also agree with Dr. Boyle's point that the questions need to be written and field-tested. For instance, this question II.A here is really two questions. It's not one question. And people are going to get so confused over "has anyone you know ever," and they're sitting there, "Well, was it Aunt Suzy, or was it my first grade teacher," that they're going to forget the point that they are--you know, the first important point is, "Have you ever had this?" So I personally feel that there does need to be one or two well crafted questions, but they have to be much simpler than this nested set of questions that we're seeing here.

I also agree with Dr. Mitchell's point that adding "from a human" to that first question is just going to also set off a whole train of "What are they talking about?" that people will then be diverted from the point of the question.

So I think we need questions. I think they need to be extremely carefully worded.

DR. HOLLINGER: Dr. Macik?

DR. MACIK: Well, for one, if you look at the way the original question, the question that currently exists, you know, we don't have "human" there. But I think one thing you just have to be very careful with and very simplistic is to say, have you been infused with, you know, have you gotten anything?

Why are you separating out human from animal? If they've gotten a blood transfusion or had a surgery or had a transplant or had--you know, do you have to specify was it animal or human? Because you're going to be deferred regardless of the source, of where it came from, and it would take away maybe some of the confusion from that standpoint.

I just don't know if I want this to be a question or not. I think at this point I'm so confused about--I would find it very difficult to say whether I wanted a question or didn't want a question, having listened to a lot of things that are going on.

You know, I like the idea that we're being very prospective, we're thinking of some new risk that right now is very small but might some day be very big, and how do we get this--how do we attach this early on in the process, before we find out when it's 500,000 people have had this and all of a sudden there's an infection, you know, to look at these issues early on. But maybe we're going a little bit too early, getting back to the idea that most of the people who have xenotransplants, probably a very small group and probably already too sick to donate blood, and what risk do we really have from their intimate contacts?

I would also think it very unlikely that people who were being dialyzed on--say a liver failure patient, that the discussion of whether or not they would donate blood ever even comes up in that informed consent or any discussion of their management at that time. The critical situation you're addressing at that point, you're not going to think about later talking about donating or your wife donating.

DR. BIANCO: Dr. Hollinger, I would like to make--I would like to support the suggestion made by Dr. Chamberland. Celso Bianco again.

And I would like to go one step ahead and suggest that the most effective way that FDA could deal with xenotransplantation issues and the potential risks of

transmission of disease would be to establish requirements for all the sponsors of clinical trials that are related to xenotransplantation, that they provide an educational program to all recipients, their families, their contacts, and that show them the risks--because we say "intimate contact" but we don't know if this couldn't be transmitted by aerosol, it is just an assumption that it would be transmitted like HIV--that they should be very careful because that possibility exists.

It would be much more effective, and we could, since we know who these people are, we know where they are, if such a campaign, pamphlets, appropriate informed consents, appropriate discussions, an 800 number for xenotransplantation recipients and their families. There are so many things that would be so much more effective than just putting a question to donors. I really would like to support that proposal.

DR. HOLLINGER: Mr. Rice, did you have a question?

MR. RICE: Well, yes. It may sound strange coming from me, but I kind of support Dr. Bianco and Dr. Chamberland. I support Dr. Mitchell, Dr. Linden, Dr. Boyle. I think all of them had important points.

I think that, like somebody who may be exposed to CJD, this population, xenotransplant individuals, are pretty much well known. We know where they are, and it may be more

effective to target, as others have said, those particular avenues that we can identify the patient and basically educate there.

I think it would be quite difficult that someone who has had some sort of contact with someone who is a xenotransplant person, I mean, it isn't the first thing you say to somebody, "By the way, I'm a xenotransplant patient." I mean, frankly, I'd ask some other questions before I'd ask that question. And so here you've had sexual contact, you've gone on for three or four years, and now you're reading a question.

I mean, I think that maybe at some point a question could be designed, because I think that that is the--ultimately the fail-safe is that those are the people, that maybe the xenotransplant person hasn't really discussed this with everybody they meet in their lives--that that could go on at some point in time. But I think the merits of that question right now are--well, I don't think there's any consensus.

DR. HOLLINGER: Yes, Dr. Boyle?

DR. BOYLE: I think I have a simple solution. The critical question here is whether we need the question on the questionnaire to be able to identify these people. We don't know whether we need it or not, and we're having to decide on this.

The simple solution is, have the FDA administer 50 of the blood donor questions to 50 people who have been through the transplant process. If in fact they all fall out on one of the other characteristics, you know that. If in point of fact half of them don't indicate anything else, then you know you've got a problem. And if it's one or two one way or the other, I don't know, but at least we would have some real data, and it should be fairly simple to do.

DR. HOLLINGER: Thank you, John.

Colonel Fitzpatrick?

DR. FITZPATRICK: Dr. Chamberland said everything I was going to say. I don't think we need a question right now, because of the complexity involved and all the questions that those questions lead to. And the other is that when interviewing donors, of which I have done several thousand, a lot of them are going to say "I don't know," and then we are faced with how do we address that donor, and what FDA guidance are we going to get about the donors that say "I don't know"?

And I was at the advisory committee meeting, and my recollections from that is that there was a great deal of discussion about the ex vivo expansion portion of the xenotransplantation definition. And I recall, and I don't have my notes with me, that the FDA was going to take those comments into consideration and consider refining the ex

vivo portion of that definition, and I don't see that here. And there were even discussions there about in vivo fertilization and exposure to animal cells during in vitro expansion in fertilization, and that's a whole area that is so broad that it's very difficult to put into a question or define.

And one more comment, and I'll be done, that I think it's all well and good to say we need to tell the FDA to go develop a question, but as we have heard over the past few years, there is not a process for question development for blood donor questionnaires. So they don't have a process to go to, and we've seen them go back to our historic process of beating questions around the bush, bringing them to the committee, and then going back and trying to work it over, and we don't know if that works or not.

So we need a process to have a valid questionnaire, that we see whether it's effective or not, with pilot studies and random groups and with the appropriate set of questions in them. And that's an even broader thing, but if you're going to go do a question, then you need a proper process to make the question.

DR. HOLLINGER: All right. I'm going to call for the question, then. I'm going to call for the question here, Mark, if I can. Oh, Jay, do you want-

DR. EPSTEIN: I just wanted to answer Colonel Fitzpatrick, that the question of ex vivo expansion was addressed by the Xeno Advisory Committee and a strongly voted recommendation was made that the agency could exempt both from donor deferral and product withdrawal, conditions where there was exposure to well characterized cell lines derived from animals. So the situation you're talking about falls into the case-by-case exemption policy which is part of the current guidance proposal.

DR. FITZPATRICK: But that's really hard to define in a question to 12 million donors

DR. EPSTEIN: I understand that, but I think there's a little bit of confusion going on here: Where does the sorting out come? I think the concept is that if the donor has a positive history for some question asked, you then have the medical director sorting out whether that's a relevant history for deferral or not a relevant history for deferral, and FDA would be providing guidance and/or the FDA could be queried on a case-by-case basis.

We don't really expect the question to the donor to do all that sorting out. I mean, that would be my answer also for issues like heart valves and, you know, porcine Factor VIII and recombinant made in BHK. You might elicit those histories, but then the doctors sort it out, not the donors.

DR. HOLLINGER: Mark?

DR. MITCHELL: Yes, I think that the issue here is, you know, that xenotransplantation itself has a potential for developing new diseases. Now, if we see the diseases, they're probably going to happen in the recipients first before they happen in any household contacts to those recipients. It's a relatively risky procedure right now because we don't know and we have such small numbers.

And, you know, it seems that the approach would be better to actually track these people until we have good--people who have received xenotransplantations--until we have enough confidence in our abilities and in the safety of xenotransplantation, and then perhaps, you know, because it is so rare, perhaps--I guess I've changed my mind--I think that we should not have a question on that on the questionnaire, since again if we're tracking the individuals who are most likely to get disease, we will have some time to react if there's a disease that does develop among that group. But I think it's important, so I think that, you know, maybe there should be something in the literature but not a question.

DR. McCURDY: I think that we're not probably concerned with the recipients, although I could be wrong, because they're going to be relatively sick or have been relatively sick and probably not show up with donors, but I

think we do have to be concerned about the intimate contacts.

And I think also that if there's anything that can be learned by a number of the things that have happened in the last 15 years or so, it's that the public wants us to fall down on the side of safety. And if we are acting with insufficient information, that's fine, but the public in various different forms wants you to come down on the side of safety and not delay until you actually have things happening and hitting you in the face.

DR. HOLLINGER: Okay. David?

DR. STRONCEK: One short comment: When we brought this up, what, six months ago, I thought it was crazy to ask this question, but the more I thought of it, I agree with Paul.

And a couple of reasons: One, if you don't ask the donors directly, you're never going to know. They won't read the pamphlets. At the time of the surgery and the transplants, too much is going on to worry about donating. So I think the question is the only way to get at it. And, yes, we have a problem with the donor questions, but that's a whole huge issue. That doesn't mean we shouldn't ask the right questions.

DR. HOLLINGER: Okay. I'm going to call--

DR. MITCHELL: I want to clear up one point,

though. When we talked about this six months ago, we said that over half of the people were skin graft recipients, and those people aren't particularly sick, and so this is in fact something that the recipients may in fact want to go and donate blood.

DR. HOLLINGER: I think the committee, if I remember right, the subcommittee voted actually that that particular group could donate. That's not an issue.

I'm going to call for the question that's up there, at least for right now, and the question is: Does the committee agree with the proposed modification to the questionnaire?

And this is the proposed modification that you have in your handouts here, the part I, part II, II.A., II.A.1. So the question is, do you agree with those proposed modifications to the questionnaire, not whether there should be a question or anything of that nature, but do you agree with the proposed modification as it is stated?

All those in favor of--all those that agree with the proposed modification to the questionnaire, raise your hand.

[A show of hands.]

DR. HOLLINGER: All those opposed?

[A show of hands.]

DR. HOLLINGER: Those abstaining?

[No response.]

DR. HOLLINGER: And I would like to ask our industry representative and our consumer representative how they would vote. Ms. Knowles?

MS. KNOWLES: I'm going to abstain.

DR. HOLLINGER: Okay, and--

DR. SIMON: Opposed.

DR. HOLLINGER: Opposed.

Linda, could you read the results?

DR. SMALLWOOD: The voting results for the question: Does the committee agree with the proposed modifications to the questionnaire? There were two votes which agreed with the proposed modification. There were 10 votes against the proposed modification. The consumer representative abstained from commenting, and the industry rep agreed with those that opposed.

DR. HOLLINGER: Paul?

DR. McCURDY: I'd like to make one quick comment about my apparent inconsistency. I don't think I like the questions the way they are now, but I think a question should be asked, and I think it ought to be wordsmithed by people who know what they're doing. I think that the institute, the NHLBI, would certainly be willing to talk about doing some field testing in some of the REDS centers. I can't guarantee that we would do it, but certainly we'd be

willing to talk about it.

DR. HOLLINGER: Let me ask the committee, then, let me just throw out another question, then, for the committee. I'd just like to see how the committee feels at this time. And that would be something to the effect, does the committee agree with excluding any specific donor question on xenotransplantation at this time? I'm not saying for the future, but at this time. Would the committee agree with excluding any specific donor question on xenotransplantation at this time? I'd like to see--

DR. BOYLE: Don't you mean adding? You don't mean excluding, do you?

DR. HOLLINGER: Adding, yes. Well, it could be excluding. Okay, that's right, it couldn't be excluding. Does the committee agree with adding any specific donor questions on xenotransplantation at this time? I'd like to just see how the committee feels about that, so all those who agree with--let's see--yes, all those who agree with adding a specific question or specific questions on xenotransplantation at this time, I'd like to see you raise your hand.

[A show of hands.]

DR. HOLLINGER: And those opposed?

[A show of hands.]

DR. HOLLINGER: And those abstaining?

[A show of hands.]

DR. HOLLINGER: Okay, and Dr. Simon?

DR. SIMON: Opposed.

DR. HOLLINGER: And--

MS. KNOWLES: Abstain, again.

DR. HOLLINGER: Okay. This is not official. I just wanted to get the feeling here. Go ahead.

DR. SMALLWOOD: The question being asked was: Does the committee agree with adding any specific donor questions on xenotransplantation at this time? The results of voting are: Five agreed with adding questions; four were in opposition; three abstentions. The industry rep agreed with those that opposed, and the consumer representative abstained.

DR. HOLLINGER: Well, I think that gives the FDA at least some--Andy, I think you may be up here as long, maybe, as Ed Tabor will be.

Okay, I think this concludes this session here. We're going to take a break until--

DR. SIMON: What about the issue of adding information to--

DR. HOLLINGER: Oh, sorry. Toby is right. Thank you. I would like to then see, unless there is some discussion on this, about adding educational information to the packet that a donor has, that a donor receives at the

time of donation. That's really what the issue will be dealing with.

Mary?

DR. CHAMBERLAND: I guess I just wanted to make the observation, I was glad that Lou Katz went through in outline form what is currently in the brochure, and I guess I was struck with what I felt was kind of a disparity. The information that's in the brochure, that several people have said is barely read or largely ignored, seemed to be pretty important stuff. And to add to the brochure information about xenotransplants just seemed to me a little out of sync in terms of prioritization, and I think that was along the lines that Linda Chambers from the Red Cross spoke. So I guess I just wanted to put that out at this point, my sort of reaction to all that.

DR. HOLLINGER: Are you saying you thought it was more overwhelming than what the other information that was being asked, or not enough, or what?

DR. CHAMBERLAND: I guess I felt that the brochure should be reserved for the most critical, important information, trying to get at the highest risks that you're wanting people to really think hard about, and admittedly it seems to be mostly focused on HIV, and by default a lot of that would overlap with hepatitis B and C, the current known viral pathogens that people are, continue to be--you know,

that we're worried about.

And to add to that xenotransplant as a possible concern, and you need to know this and you might need to defer yourself, I was just struck with to me what I thought was kind of a disparity, that going from situations or behaviors that we're very concerned about wanting to exclude donors because of known or emerging pathogens, and then to drop down to xeno where we're still struggling with trying to identify what the risk is to the recipients themselves, and then into these concentric circles of intimate contacts or health care workers, etcetera, I just--it may not be the first thing I would want to put in the brochure.

DR. HOLLINGER: Yes, Dr. Simon?

DR. SIMON: Yes, just to amplify, as you know and I've sent you, that we and many others in the plasma industry use a video to inform donors, and it's much the same issue as we're dealing with in the questionnaire. We're really trying to emphasize the significant risk factors of male sex with male, ever use drugs intravenously, and so on. And the more of this sort of thing that you have to get in there, that's complicated to explain, I think the more potentially dilute the important message.

So certainly, again I guess I'm agreeing with Mary, that the state that we're in and the state that the committee was in, I would favor leaving things as they are.

And then as we revisit the issue, if the importance of it begins to come up to a level where it's more important, then we have to go ahead and make these revisions.

DR. HOLLINGER: On the other hand, I guess, Toby, you know part of the time it takes to do things in getting blood from patients, processing it, obtaining, collecting it, is the actual collection process and asking the questions. You sit there for a long time in the donor room waiting, sometimes, to go and have your blood collected, and therefore there is time to sit and actually read the document or look at your video or things like this. And that doesn't take out time from anybody else, because you're there waiting to--

DR. SIMON: Right. I would agree it's not as critical an issue as it is with the questionnaire. I would certainly agree this would be a less intrusive thing to do than the questionnaire, so if you're going to do one or the other, I would agree with supporting this. On the other hand, it is the same issue, though, that you really want people to focus, and the more you put in there, the potentially less focus you get.

DR. HOLLINGER: Any other comments about the educational material?

[No response.]

DR. HOLLINGER: I'm going to bring this, then, to

a vote also. I guess one should, without getting into the proposed language that was placed in there, I guess the question really should be, does the committee agree that donors should be required to have information on xenotransplantation as educational material before their donation. Is that a fair phrase of what the issue is here?

So those of you who are in favor of having educational material on xenotransplantation before donation to be given to the donor, so signify by raising your hand.

[A show of hands.]

DR. HOLLINGER: Those opposed?

[A show of hands.]

DR. HOLLINGER: And those abstaining?

[No response.]

DR. HOLLINGER: Okay, and Ms. Knowles?

MS. KNOWLES: Abstain.

DR. SIMON: Opposed.

DR. HOLLINGER: Linda?

DR. SMALLWOOD: I'm sorry, I'm going to have to ask you to vote again because I'm coming up one short on those that are eligible to vote.

DR. HOLLINGER: Those who are in favor of having educational material on xenotransplantation, raise your hand.

[A show of hands.]

DR. HOLLINGER: Okay. Those opposed?

[A show of hands.]

DR. HOLLINGER: And abstaining? No one?

[No response.]

DR. HOLLINGER: And you are staying the same, one opposed, one abstain. John, you can't vote.

Okay, could you read those, please?

DR. SMALLWOOD: I'm trying to repeat the question as best as I was able to: Does the committee agree that donors should be required to have educational material on xenotransplantation before donation? And the results of voting: There were five that agreed. There were seven that opposed. The industry rep agreed with those that opposed and the consumer rep abstained.

DR. HOLLINGER: Thank you. Well, I think FDA has their work cut out for them, as does the blood banking community. So we're going to take a break until 1:45. I would like you all back here at 1:45, and then we're going to get into the session on the site visit. Thank you.

[Recess.]

DR. SMALLWOOD: We're ready to reconvene. May I ask all advisory committee members to please return to your seats?

Dr. Hollinger, if you're ready, we are ready.

DR. HOLLINGER: Thank you, Dr. Smallwood.

The committee is sitting today on an important issue, and that is to review the information from an intramural site visit. It's one of our responsibilities to approve or disapprove or modify information that is given to us about these site visits for the various laboratories or divisions of CBER, and this is one such intramural site visit.

We were hoping that Dr. Kagan, who is on our committee, was supposed to be here to go over the assessment that the committee made, or Dr. Allan, who is the chairman of this committee. Neither one of them are here, so I'm going to have to read for you just a short portion. I have sort of redacted this, if you will, what's going on here.

But we have some introductions and overview about what this site visit was about and what the issues are, so Dr. Goldman is going to give us an introduction and overview, to be followed by John Finlayson, Mark Weinstein, and then Basil Golding, and somewhere in here we're probably going to have the presentations from Dr. Scott and Dr. Alayash. Yes?

DR. SIMON: Just a question for a new member. The packet we received had what looked like the materials that were given to the site visitors, but I didn't see that we got the site visitors' report. Is that correct?

DR. SMALLWOOD: Yes, I can answer that. Only

those committee members that were permitted to participate in the closed session received that information, and unfortunately your position on the committee would not permit that. That's why you did not receive that information, but you may participate in the open discussion that we're going to have now.

DR. SIMON: So other people on the committee got the report of the site visit?

DR. SMALLWOOD: Yes.

DR. SIMON: And I specifically didn't. Okay.

DR. HOLLINGER: It's exclusive. No, it's not, really, but I think that's the issue. But, please, we would like your input on the information.

DR. GOLDMAN: Okay?

DR. HOLLINGER: Yes, please.

DR. GOLDMAN: Thank you, Dr. Hollinger. Good afternoon. I am Neil Goldman. I am the Associate Director for Research at CBER, and I would like to actually begin by thanking you for the valuable role that you all play in the quality control of our research programs at the Center.

And I thought for the next approximately 5 to 10 minutes I would give you just sort of the abridged version of the importance of research at the Center, based on responsibilities that the Center has, as well as the critical need for oversight of our research programs. And

of course following me you will hear presentations from the Office of Blood, from the Division of Hematology, and also from the members of the Laboratory of Plasma Derivatives, who I think will provide you a more focused view of the needs for research to support the regulatory issues.

So if I could have the first obligatory slide, and I say this is obligatory since we always customarily start all of our talks with this. The mission of CBER, of course, is to protect and enhance the public health through regulation of biological and related products, including blood, which is why you have a committee here for the last two days; vaccines; biological therapeutics; and also, by the way, devices, and of course we handle some of the blood transfusion or collection devices, and now some new devices. These are new devices that are composed of new biotechnology products in conjunction with new biomaterials.

Next slide. The regulation of these products is founded on science and law to ensure their purity, potency, safety, efficacy and availability, and to fulfill this mission we conduct research as an essential element of our science based decision-making on regulatory issues. Thus, we see that research in fact is the linchpin to our other areas of regulatory responsibility, as you see up here, and they include review of product submissions, development of regulatory policy, product surveillance, and that entails

such things as our lot release testing, our inspections, and adverse event monitoring. And of course, lastly, manufacturer compliance, and of course all the enforcement aspects that go along with that.

Next slide. Now, just historically, we were mandated back in 1955 by a PHS order that we, CBER--we were not CBER at the time--shall conduct research on problems related to the development, manufacture, testing and use of vaccines, serums, antitoxins and analogous products, including blood and its derivatives. We shall conduct other studies to assure safety, purity and potency of biologic products, to improve existing products, and to develop new products. In fact, these mandates have been broadened quite a bit over the last 45 years to include a whole host of new products, some of which you talked about today in terms of xenotransplantation, but then as well some others that you mentioned like the Recombinant Human Factor VIII.

Next slide. Now, this is the current organizational structure of CBER, and the currently the Director of CBER is Dr. Kathryn Zoon, and underneath the Office of the Director there are seven offices. And the site visit report that you will be listening to later, and I apologize, some of you may not be able to make it to the closed session, but that site visit report in fact will involve investigators in the Office of Blood. And you will

see in the Office of Blood that there are three divisions. Two of these divisions in fact are laboratory-based divisions, and the laboratories, the two investigators are in laboratories in the Division of Hematology, and they are in the Laboratory of Plasma Derivatives.

Next slide, please. Now, currently at CBER we have approximately 440 lab-based scientists, and approximately 72 of them are what we refer to as permanent career appointment principal investigators, and there are about 57 who are what we refer to as conversion track investigators. This is similar to what you will recognize in academia as your tenure track investigators. Now, most of this staff who are in this latter category are either Service Fellows or Commission Corps Officers.

Next slide. Just a few words about our Service Fellows. CBER has a Service Fellow program where a research scientist comes in at a journeyman-like level, and usually these researchers have approximately seven years of postdoctoral experience under their belt, and as they scientifically develop, they themselves will be given additional research support, in particular their own postdoctoral fellows and technical support.

Service Fellows also have regulatory responsibility that progressively increases each year. It's usually about 20 to 30 percent in the first two years, and

on average about 30 to 50 percent later on. The two investigators that will be discussed here, and who actually the site visit is about in fact, spend probably at least 50 percent of their time doing regulatory work.

Next slide. In CBER all researchers are fully integrated into the review process. Their regulatory duties include the review of INDs and BLAs, development and presentation of regulatory policies, meeting with manufacturers as well as meetings with the advisory committees, as you have already had--I know Dot Scott presented already--and they also participate in biennial and prelicense inspections, as well. In total, this is what we refer to as the researcher/reviewer model.

Now, as I have put down in that box in red at the bottom, it was pointed out by our External Committee for the Review of CBER Research, and I'll get into that committee in just a couple of minutes, but this was a large committee that came in to review all of CBER's research, they commented that they felt that the researcher/reviewer model is essential to providing CBER with top level expertise in a regulatory culture.

Next slide. Now, the types of research at CBER which are considered mission-related include, number one, research on a specific product, including for example such aspects as mechanism of action, potential toxicity, or

surrogate measures of efficacy; and, second, research on a specific policy issue, and this may be related to a particular product class, a disease area, or a therapeutic modality; and, third, and of course probably of major importance to a regulatory agency like ours, research associated with the development of methods and standards to maintain product safety and quality, and I think you are going to hear briefly, at least, some of what the site visit team had heard presented to them by Dr. Alayash and Dr. Scott, and I think you will see how each of these aspects play into the type of research that they do.

Next slide. Now, actually, as Dr. Hollinger just mentioned, and I'm sure you are intimately aware of the varied roles of the product advisory committees, you certainly provide technical advice on products and product classes, advice on appropriate design of clinical trials, as well as advice on surrogate markers and choices of endpoints, and of course advice on how to interpret many of these clinical protocols, as well as you talked about this morning, in terms of xenotransplantation, advice on risk assessment. But, lastly, of course, as Dr. Hollinger had mentioned, your last responsibility is to assist us in the peer review of our intramural research programs, and of course the research scientists involved in them.

Now, this accomplished by use of a site visit

team, and this team is usually a subgroup of this particular Blood Advisory Committee, and therefore the Blood Products Advisory Committee is in fact the parent committee of now this subgroup, this site visit team. The site visit teams is usually composed of at least one member of the advisory committee, and in this case Dr. Kagan was that member. Dr. Alving was chosen as the Chair of the committee, but in addition there were other ad hoc members. These are experts in the field of the individual being reviewed, so that the committee is usually--usually brings in at least two to three additional, per person, per individual being reviewed, an additional two to three people who are experts in that field.

Next slide. The charge that was given to the site visit team was to assess, and that was to assess both the strengths as well as the weaknesses, the quality and appropriateness to the regulatory mission of the research being conducted. That includes relevance, scientific rationale, validity of approaches, creativity, design and solution, as well as level of sophistication.

Can I have the next one? We also ask the site visit team to evaluate the accomplishments of the individual scientist, which includes demonstration of his or her abilities in experimental design and performance, independence of effort, originality, stature and recognition

amongst his or her peers, and productivity.

Next slide. In addition, we ask the site visit team to provide us advice on the current direction of the research program, whether new direction should be considered, any changes in the way the research program is administered or the level and utilization of resources in that program. And, lastly, we solicit advice on promotion of the staff member being reviewed, or whether or not conversion of a candidate to a permanent position, for example, as a principal investigator is appropriate at this time.

Next slide. Now, finally, after the site visit team has had an opportunity to actually review each researcher and their program, there is an oral summary at the end of the day that is provided by the team and is provided to the management at CBER. This actually gives CBER sort of a preliminary picture of the team's observations and conclusions.

Now, the Chair of this site visit team, of course with the help of the ad hoc members, goes on to prepare a written report. Now, that is the report that actually was given to the members of the committee here, and again, this report certainly reflects, as was in the previous slides, an evaluation of the research program, the individuals in the program, the resources being utilized in that program, as

well as any recommendations for, for example, personnel actions.

Now, this report then is presented in closed session, and that's what will happen after this open session, and is usually presented by the site visit Chair. In this case, this site visit Chair could not be present, so Dr. Hollinger has been kindly willing to take on that responsibility. And it is presented to the entire product advisory committee for your review and your approval.

Now, after approval, this final report will be sent back to the Center director, who then will send it back down the chain of command, and it will eventually go down to the investigator who was actually reviewed. Any responses to comments that are made in the final report are then prepared, and these responses are in fact forwarded back to the appropriate advisory committee to show that in fact we do respond when questions do come up.

Next slide. Now, you may or may not be aware, but I think most are probably aware that we actually at CBER maintain visual and oversight and quality control of our research programs by actually utilizing three independent mechanisms: First by our periodic in-depth site visits of our laboratories which occur every four years. Each laboratory is site visited on a four-year cycle.

The second mechanism is by internal prioritization

of the research programs which is performed annually by our senior management based on a number of criteria. And the criteria include not just scientific quality and mission relevance but also the public health impact on product availability; the unique position of CBER to address critical safety issues pertaining to a particular product; or relevant regulatory research that would not be done elsewhere, in relation to a particular product area.

The third mechanism in fact for our oversight has been by a high level review of the Center's entire research program, which was in fact carried out in February of 1998 by an external blue-ribbon panel that was composed, in fact, of highly regarded scientific experts from academia, from industry, and from other government agencies. This was a very successful review and a very positive one, and will probably occur now every 8 to 10 years. This will be true of all of the Centers in FDA. Each will be reviewed as an entire Center approximately every 8 to 10 years.

Last slide. Now, just to give you a flavor, this blue ribbon panel, and we referred to this as our Subcommittee for Review of CBER Research, as it called itself, this by the way was a subgroup that was in fact a subcommittee of our FDA Science Board. So they acted like our site visit team does to you, where you are the parent committee. The parent committee for our Subcommittee for

Review of CBER Research was in fact a subgroup of the agency's Science Board.

This subgroup provided us quite valuable suggestions and insightful recommendations about our research programs, and I thought I would provide you one example right here: For our industry to receive prompt and appropriate reviews, and for our regulatory agency to respond to urgent needs, it is of utmost importance that the scientists in CBER have research capabilities at the cutting edge that allows them to understand the rapidly expanding methodologies, to evaluate vaccines and biologics, but also so that they can interact with their colleagues in industry on a knowledgeable scientific and technologic basis so that the appropriate recommendations can be made.

I think actually from the discussions I heard here today around this table, I would most agree, especially for those from industry, that it is very important for us to be able to see how you feel about these various issues that come up before the FDA.

Well, again I would like to thank you for the important role that I think you may or may not realize you play in this whole process, and if there are any questions before I turn this over to Dr. Finlayson, I would certainly be willing to answer any.

[No response.]

DR. GOLDMAN: No? Okay.

DR. FINLAYSON: Thank you very much, Neil, and good afternoon. I am going to be very brief, in fact uncharacteristically brief.

The site visit was carried out on December 8, 1999. Sorry, Toby. You voting members have a copy of the report, and so I am just going to begin by reiterating what Dr. Hollinger said, namely, what is it that you are expected to do? And some of you have been through this before but many of you have not, so I think a little redundancy is in order.

You, as the parent company--company, that's very good, think industrial--as the parent committee of the site visit team, are being asked to endorse the report. And you have, as Dr. Hollinger pointed out, three options. You can accept it, you can reject it, or you can modify it and accept the modified form.

Now, you heard from Dr. Goldman the general procedure for these reviews that take place on a rotating basis, so that a given laboratory unit is reviewed every four years, and you heard that the usual thing is to review a laboratory at a time. "Laboratory" in this case does not mean a room, and we'll get to that in just a moment; it means an operating unit, an administrative unit.

This particular site visit was an exception to

that, and I will tell you why. As you heard from Dr. Goldman, if someone comes in on a conversion track, he or she has a life span of seven years, and Dr. Dorothy Scott joined the organization in 1993, and if you do the subtraction, you will see we are coming up on the seven-year point here. So it was very important, as we reached the end of 1999, that in order for her to be proposed for conversion to permanent status, we had to have a current site report.

At the same time, Dr. Alayash, whom both of these people you will meet very shortly--actually, you met Dr. Scott this morning because she made a presentation about CJD--Dr. Alayash joined the organization in 1989 and was converted to permanent status in 1996, but in order for him to be proposed for promotion, we needed also for him a recent site visit report. So, accordingly, these two people were reviewed on an ad hoc basis, not as part of an entire laboratory review.

Fortunately, however, to make things convenient, they both are in the same laboratory, which is the Laboratory of Plasma Derivatives. And if I could have the first overhead, if it looks familiar to you, it's because it should look familiar to you. The committee has handouts. For those of you in the audience, this can be obtained on CBER's external web site.

As I look at this, I am always impressed by the

fact that it looks like the things, when you take these courses in audiovisual aids, the things they show you what not to do. And I say this is, admittedly is a ridiculously busy slide, but if I may be so bold as to say, CBER is a ridiculously busy Center.

If you can read the first line of little boxes going across there, you will see the third one from the left is the Office of Blood Research and Review, the next one is the Office of Vaccines Research and Review, and the next is the Office of Therapeutics Research and Review. These are the three offices with large laboratory components. There are also other laboratory activities throughout the Center, but these are the ones in which the lion's share of the research is conducted.

Now, if I can have the next one, I will expand the Office of Blood Research and Review, and you will see there is the immediate Office of the Director, there are two staffs off to the right, and down at the bottom you will see we have the three divisions. The one on the far right is the Division of Blood Applications. This is largely a review and administrative division. The two on the left, Division of Emerging and Transfusion Transmitted Diseases--I'm learning to say that because they have just introduced the word "emerging" into it, and I have to condition myself to put the "e" into it--and the Division of Hematology, in

the middle of which Dr. Mark Weinstein, from whom you will hear in just a moment, of which Dr. Weinstein is the Director.

Now, if we look at the next overhead, we are expanding that Division of Hematology, and you will see that there are four groups under that, of which three are laboratories. And this is what I meant when I said a laboratory not as a room but as an administrative or operating unit. The third box from the left is the Laboratory of Plasma Derivatives, of which Dr. Basil Golding is the laboratory chief. It is in this box that both of the people from whom and about whom you will hear today reside. They are both in the Laboratory of Plasma Derivatives.

And I think that I have probably said enough, unless there are any particular questions that I can answer.

DR. HOLLINGER: Thank you, John.

Dr. Weinstein?

DR. WEINSTEIN: Well, you have heard from Dr. Goldman and Dr. Finlayson about the importance of research in CBER, the position of the Division of Hematology in the organizational structure of CBER, the part that this committee plays in reviewing the progress of our scientists, and the role that science plays in the regulation of blood products.

Now, following my presentation, you will hear from

Next, I would like to turn to the regulatory accomplishments of Dr. Alayash. Dr. Alayash is in a different regulatory arena compared to Dr. Scott and most other reviewers in the Division of Hematology. His area of expertise is in blood substitutes. There are no licensed blood substitute products; all are in the developmental IND stage. Thus, the standards for assessing the quality of these products are not yet established.

Currently, Dr. Alayash is the lead product reviewer on nine blood substitutes in clinical trials. A major focus of Dr. Alayash's regulatory work has been to evaluate the safety of these products and to determine what the critical elements are that should be considered to assure safety. Recently Dr. Alayash led a team of CBER reviewers that investigated the likely cause of one blood substitute's failure in a Phase III clinical trial.

Among Dr. Alayash's accomplishments has been to organize workshops on blood substitutes that have helped to inform the FDA and the public about current state-of-the-art of these products. He assisted in organizing workshops in 1990 and 1994 that dealt with the safety and efficacy of hemoglobin and fluorochemical-based products. He then helped draft points to consider documents on blood substitutes that were published in the Federal Register.

Yesterday you heard from Dr. Lee about the outcome

of another workshop held last year that dealt with the safety and efficacy of these products. Dr. Alayash chaired and organized the steering committee for this meeting.

In sum, Dr. Alayash is the product expert at the FDA on blood substitutes. He is the person whose knowledge and judgment we rely upon to assess the quality and safety of these products. He is internationally recognized as an expert in this field, and his research work is directly relevant to his review competence.

FDA has recognized Dr. Alayash's outstanding contributions by awarding him the agency's highest scientific award this year for excellence in laboratory science. His FDA citation reads: "For studies that contributed fundamentally to current understanding of hemoglobin toxicity and potentially to the design of safer second generation blood substitutes."

Thank you.

DR. HOLLINGER: The final presentation, then, is by Dr. Golding from the laboratory in which the two people we are going to be reviewing reside.

DR. GOLDING: My job is to give you some idea of how the Laboratory of Plasma Derivatives is organized. We have four sections. Each section has a section head. Abdu Alayash is head of one of the sections related to hemoglobin-based substitutes. We have a physical

biochemistry section, a biosafety section, and an immunology section. Dr. Scott has been a senior staff fellow in the immunology section of the laboratory for several years now. This is her seventh year. I would like to point out that all these section heads have already been promoted to the GS-14, except for Dr. Alayash, who is the most recent section head to be appointed.

I don't want to go into too much detail, but just to concentrate on the groups that we are--in terms of the people that are being reviewed today, Dr. Alayash is a section head. He has several people working in his group, so he has developed a program. As you have heard, he has developed a program to do research on hemoglobin substitutes which is very critical for assessing the safety and efficacy of these products. And, in addition to that, he is a mentor for people who will then learn how to be involved in the review process, and this will provide continuity and ability for them to deal with these products as some of them start to become licensed and as the work load increases exponentially over the years to come.

Okay. In the Laboratory of Immunology, as I have pointed out, Dr. Scott is a senior staff fellow in this section. She came to the laboratory and set up her own independent research program to look at various aspects of immune responses, TH1, TH2 responses, looking at immune

globulins and their subclasses, and also looking at dendritic cells and their responses to bacterial products. She has worked most closely with Ko Ti Huang, who has a master's degree, but she has also supervised several people in the laboratory, and is an integral part of the laboratory in terms of providing ideas and in propelling all of the research projects in the laboratory.

This is the Viral Safety Group headed by Dr. Yu, and I'll just kind of mention briefly some of the important products that we regulate. I have highlighted the products that are regulated by Dr. Alayash. You have already heard several times that he is the point person in relation to both the review and the research on hemoglobin-based blood substitutes. And Dr. Scott is involved with review and research on immune globulins, both general and specific.

So these are the--finally, I am just showing you a slide on the various research projects that are currently being carried out in the Laboratory of Plasma Derivatives. Again, I have highlighted the important ones in connection with what your work is today. This is the project in Dr. Alayash's lab, "Investigation of the Safety and Efficacy of Hemoglobin-Based Blood Substitutes," and these are the projects that Dr. Scott is involved in, "Development of an Anti-HIV Therapeutic Vaccine, Class and Subclass Responses," "Studies of Cytokine Regulation in Human and Murine Immune

Responses," and "Studies on the Safety and Efficacy of Immune Globulins," and I would include the "Study of Dendritic Cells and the Effect of Bacteria on the Migration and Secretion of Cytokines by the Dendritic Cells."

Thank you.

DR. HOLLINGER: Thank you, Dr. Golding.

At this time we're going to ask Dr. Alayash and Dr. Scott if they would mind just coming up here and maybe spending five or so minutes telling us just a little bit about the exciting work that they're doing, so that the committee can sort of hear about that. Are they here? Let's have Dr. Alayash first.

DR. ALAYASH: Can I have the first slide, please? Actually I will have about 10 minutes just to give you a very brief outline of what we do in terms of research. The focus of the lab is basically to try to understand the mechanisms of toxicity of hemoglobin-based blood substitutes, with some emphasis on finding ways and means, if possible, to control some of the unwarranted and unfavorable side reactions of hemoglobin.

This figure basically shows you the different approaches used by industry to modify hemoglobin and the other components, the synthetic compounds. In fact, we have two classes of these compounds, fluorochemical-based compounds and hemoglobin-based compounds. I'm not going to

talk about these. They are basically synthetic compounds.

The hemoglobin-based compounds are largely derived from outdated human blood or animal blood. Hemoglobin is isolated, purified extensively, and--I'm sorry--the hemoglobin derived from the red cells, outdated red cells, either chemically modified, either cross-linked to stabilize the tetrameric form of hemoglobin. In some instances the hemoglobin is degraded with some non-protein components.

In some examples here, the protein is actually polymerized to increase the size of the protein and to increase the retention of the protein in circulation. In some instances the protein is actually encapsulated with the liposomes to mimic the red cell. And all of these approaches are presented in what we have, what we deal with in terms of product.

If you want to summarize what we really--as we start now, in terms of what is there in the open literature in terms of clinical experience with these proteins, these are the sort of things you will encounter when these proteins are infused: vasoconstriction and hypertension seen in humans; GI distress, which is basically localized spasm of the GI; and of course in one or two instances we had excess mortality in patients with ischemic stroke, more recently in trauma patients. Both of these published studies belong to Baxter, primary product the DCLHB, and