patient is transmitting virus to somebody. But that is not easy.

We have been through, I think, discussions on how you can follow up on contacts and whether you can do that voluntarily. It probably, almost certainly, has to be voluntary on the part of contacts and so on. Even in the case of HIV, examination for virus in saliva and semen and other bodily secretions is not very revealing as to what is going on for transmission.

The levels are low here and they are low there, but transmitted one way and not the other. So it is not going to be easy without being able to do sort of significant contact tracing and that is going to be very, very hard to do.

DR. HENEINE: This is to second basically what John has said. I think it is very difficult to answer the question that you asked to define the criteria of infection, of PERV infection, in a human because, given the current knowledge, we cannot define those markers.

Or, what we can do is use those tools, diagnostic tools, available to us and then, longitudinally, follow up these patients that show any sign of positivity, either seropositivity, serologic or molecular.

Beyond that, it is speculation. It is extrapolation from the FELV system. John would argue that,

no, we see things different in the HIV or HTLV systems. So we really can't define those markers today.

DR. AUCHINCLOSS: I think everybody would agree, we don't know the meaning of the implications of positive. But the implications for the FDA are probably hold and get their experts back.

MS. MEYERS: I am impressed by Novartis' protocol because they had contingency plans on what to do with the person if they are found positive and the fact that they can transmit it. I am sure that all of this information is going to have to go into an informed consent so that people in the future who go through any type of procedure are going to know that if they are positive and if there is any doubt, they may be isolated. Their spouse and their family may be tested, et cetera.

But what about the people now who have already gone through it. They didn't give permission to be isolated. The fact is, if you find them shedding virus and they are contagious, obviously, they should be isolated. If it is totally voluntary, and they don't want to be, what are you going to do?

DR. CHAPMAN: I read this question a little bit differently than the way I think it is being discussed. I am not sure what the FDA wanted from it, but, perhaps, it is worth framing the way I read it and seeing if that is the

response you wanted.

There has been discussion, if a person is identified as positive, as infected, what sorts of labor studies could be done or epidemiologic studies or contact tracing. You are bringing up the issue of what sort of isolation precaution should be put onto someone and that would, in part, be dependent on what the laboratory studies shows about presence of virus and different secretions and, also, the law because I will say we have discussed, in our Public Health--within the PHS in our meetings these issues when people bring up, from time to time, the issue of quarantine.

Without going into any details about the discussion, I will say what you can do to involuntary confine someone is limited by law and is defined in law and it varies from country to country. And there are also ethical issues involved.

It is not clear to me that FDA wanted us to struggle with those things now. My interpretation of this was--what I thought you were asking was--well, in my mind, I boiled it down to this. What would be the criteria, what would you identify, that would raise the expectation that this would be an appropriate point for the FDA to call a clinical hold on all trials until certain issues were clarified.

DR. AUCHINCLOSS: Louisa, I agree with you. That was the way I was reading it. I don't think we need get into the issue of precisely which samples you need from which patient.

DR. CHAPMAN: Who would clarify them? How do you clarify them? How far you do you go? That can be asked later.

DR. AUCHINCLOSS: The question is where is the stop point on all trials that leads to an effective clinical hold here; is that correct?

DR. WILSON: Yes; or, alternatively, whether a certain result may impact a single trial where that result is found versus all trials--

DR. AUCHINCLOSS: Of the three positives that have been brought up that one can imagine, is there any one of them that would either enable that or other trials to go forward while additional data was being gathered is, I think, the heart of the matter. Is that not correct? What I thought I was hearing from the group, but I don't think it has been explicitly expressed, is pretty much that if you get a positive anywhere, you are going to need to stop everything and get your experts together to look at it carefully.

DR. ALLAN: I would say not.

DR. AUCHINCLOSS: Is that too strong a statement?

DR. ALLAN: Too strong. We have already heard one case where there are two potential positives that look like microchimerism that disappear or are transient.

DR. AUCHINCLOSS: I understand. Now we are on to a question of what is really, really positive.

DR. ALLAN: Not even the question--and I believe that there is a strong possibility that those were microchimerism. So even if we were sure that those were positive, I would still not say that we need to stop a particular study based on microchimerism. We are really moving past that to something like antibodies.

DR. SALOMON: The key thing here is, I think, what you are trying to say is, without defining it for the moment, I think that if it is positive, if we infect a patient, and we all agree that the patient is infected, details aside for the moment, then I think all studies should stop then. And I feel strongly about that.

I think that part of the deal that we are making with the public to rationalize moving forward cautiously with clinical trials is that we are monitoring. Therefore, when I said to Jay, you can't just tell them, "Don't worry; we are banking all the serum," that isn't going to work.

No; we are studying them. As it gets better, then we will study the banked serum. I don't care. But we are doing it, an insane reason here. If someone is really

infected, you have got to stop all studies. Then we can discuss.

MR. BENEDI: From a recipient perspective and one whose immune systems is compromised, and so is Bill's, and we worry about every single day of even catching the common cold, when you talk about someone getting infected and then everybody watching and stopping and seeing, that patient is going to be gone very quickly.

If, in fact, that patient is infected positively, they won't be around very much longer, only because of the compromised immune situation that they are going to find themselves in with the medicines they are going to take so they reject the organ that has been placed in there.

DR. HIRSCH: I think we are overstepping the bounds here by a long shot. We don't know if an infected person with this virus will even get sick let alone be around in a few weeks. So, it would seem to me, that it wouldn't surprise me at all if someone along the way, in one of the xenotransplants, becomes infected with an endogenous pig retrovirus.

You still have to weigh the pluses and the minuses. If this has, by that time, proven to be a useful bridge technique for cardiac transplantation or for whatever, one infection with one pig endogenous virus, to me, doesn't mean you stop the whole program, but you watch

that individual very closely and you monitor all the other people who have had this kind of procedure.

But to put an immediate stop on everything seems to be overkill, to me.

DR. ALLAN: I would think that, since we are early on in clinical trials, that if you do get a positive, regardless of what trial it is, you really need to stop at that point. Once you are into a place where you are into a therapeutic mode or into that, that is a different story. But we are in an early stage of the clinical trials. I think you really need to put a stop--

DR. KASLOW: I think we have a paradigm--I don't know whether it is totally applicable--and that is with most, certainly, large clinical trials, there is often a data and safety monitoring board that would have some certain trigger points available to them. When those trigger points come into play, that group is convened to discuss whatever that evidence is and make a decision, at that time, on an ad hoc basis as to whether the trial should continue and what other things should take place at that time.

It seems to me like, in general terms, that is what we ought to be doing.

DR. AUCHINCLOSS: I think that is exactly right.

DR. SIEGEL: Or only have purview of the trial

that they are authorized to monitor.

DR. KASLOW: I understand, so that the analogy may not be complete. On the other hand, we could create a variation of it in which, since there is a known number of trials going on and it all comes under a common rubric, you could make the rule that any or all of those trials, if there were any single event that led to that threshold, it would trigger the same convening of whatever group you decide to monitor.

DR. AUCHINCLOSS: You did a clinical hold once before; right? There is nothing that keeps you from doing that at any point; is that not true?

DR. SIEGEL: It should be pointed out that, in Dr. Hirsch's comment, once there is a proven effective therapy and, presumably, if that is an FDA-approved therapy, then the whole legal framework changes. Those therapies can also be seized, market-withdrawn, or whatever. But it is a different situation from the IND investigative situation where the clinical hold is a relatively simply administrative measure whereby we can stop a clinical trial.

DR. AUCHINCLOSS: I understand. But we are a ways away from--

DR. SIEGEL: Exactly.

DR. AUCHINCLOSS: I don't think that is necessary to get there.

DR. SIEGEL: I am just saying where that is necessary in the experimental environment.

DR. AUCHINCLOSS: I guess, to sort of characterize it as everything stops is not the way I would want to do it. I thought the expression here is that that is the moment where you would your experts to look at the information that you obtain rapidly and size it up, that would be the thing you would be doing.

I am guessing that we are really not very far apart on this topic is what I really mean to say.

DR. SALOMON: I just want to be clear. I don't agree. I think the minute you have a positive infected patient, then everything stops. It is okay if, five minutes later, you get everyone together and you have this big discussion, et cetera. That's fine. But I think that is important in terms of maintaining the trust of the public in us.

DR. KASLOW: What you need to define, then, is the sequence of events that leads up to the decision that that positive is there as well.

DR. ONIONS: If I could just very briefly--first of all, I still hold the view that there is this hierarchy of difference of positivity. I would have, before this discussion started, and I think what is useful about this discussion, is that you don't stick to rigid views and I am

listening very carefully.

My view before had been that--first of all, one point. This is a complex issue. It is not quite straightforward when you say something is positive that that patient is infected. For instance, if you find low-level virus in the plasma, that virus might actually be coming from the donated organ and it might not have ever infected the human cells.

That might be true with a large solid organ transplant, for instance. Similarly, antibody might be an antibody response device actually to that organ and, again, that patient's cells may never have been infected. So there are all sorts of caveats here that would have to be investigated. But I still hold to that hierarchy of positivity.

My own view had been that if the top two--that is, if the patient was plasma viremic or the patient had PCR-positive peripheral-blood mononuclear cells, that certainly would be my criteria for a stop. You stop clinical trials. You hold. You review the data and follow these patients until you knew what the resolution of those patients was.

My caveat would be on that, my hold, was that antibody would not necessarily have triggered that, in my view. That might have initiated more intensive surveillance of that patient, certain body fluids, probably in contacts,

all the usual more intensive kind of surveillance without necessarily putting a hold.

But I am listening and I am hearing both Dan and I am hearing Jonathan saying that that might not be good enough. I begin to understand and, perhaps, respect that point of view. So I wouldn't be unhappy with that view either.

DR. GORDON: Al Gordon, the Islet Foundation. I just wanted to comment on the suggestion that a single positive would bring the sword down and all clinical trials would stop. I think it is important to realize that there is going to be a spectrum of activity in these clinical trials.

There will be vascularized whole organs with immunosuppression. There will be cellular transplants with immunobarriers and no immunosuppression. We also have assays that, as we know, are very prone to false positives and, therefore, in recognition of that propensity for false positives, it would really be an unwise decision to drop all clinical trials should one occur.

I think we are also dealing, as we know, with the chain of events. So far, no animal has been infected with PERV. So even the first requirement of infectivity has not been satisfied. Does it cause disease? We don't know. There has never been an infection. If it causes disease,

can it be transmitted to other people? Well, it has never caused disease.

Therefore, we are now concerned about something several steps along a highly improbable chain and some are proposing that we take very draconian actions today. I just want to put it into perspective.

DR. AUCHINCLOSS: I appreciate your perspective. We will come back to some of those issues this afternoon. I don't mean to be using the sword characterization here.

DR. VANDERPOOL: I think our basic commitment to the public is to make sure, by every conceivable means possible, that nothing like this ever occurs. Should a bad situation present itself, it seems to me you handle that not by an overall stoppage of all the trials, but by immediate and thorough review of the that particular situation.

It may have been due to the herd. It may have been due to the type of compromised state the patient was in. It may have been someone on the surgical team that made some sort of mistake. Who knows what it would be.

So it strikes me that we are trying to cross too many bridges before we get to them. But what we are giving is a very clear indication that we don't just act like the measures we are taking will ever keep anything like this from happening. We go ahead and, as we are going, we allow ourselves thinking about worst-case scenarios and have in

our minds, and perhaps in policy, what we intend to do about that.

MS. MEYERS: Could I respond to that quickly? I think that if a patient accepts risk, no matter what that risk is, even death, that is fine. It is up to the person who signs the paper and agrees to the risk. But the public doesn't have to accept that risk. If you have somebody with a transmissible virus getting on the bus, taking taxicabs, going to work and interacting with other people, then it is really up to the FDA to protect the public from what could possibly happen even if it is only one in a million chance.

The situation in Indonesia proves that maybe, if somebody had recognized what was happening with the first case, or the first five cases, so many hundreds of people wouldn't have died.

DR. COFFIN: I was just going to weigh in on the point that I think this last comment points out how complicated the situation is going to be and I think basically supports the "call us back when it happens" approach to this, but be ready to put at least a very short hold, as you suggested, onto things while it gets sorted out but then be prepared to move as fast as possible to relieve that.

DR. AUCHINCLOSS: I think that is right. I would like to comment about too many bridges too quickly. It is

hard to speculate about all the possible events.

DR. CHAPMAN: I wanted to try to bring some clarity to this discussion by stating a null hypothesis, if you will. Instead of talking in terms of positive--first of all, I am not sure if everybody is meaning the same thing when they a positive. So, instead, I would like to state a hypothesis that, instead of taking about a positive, we talk about evidence strongly suggestive of an active infection of a human.

And how you decide what that is--I don't care to talk about lab criteria. That may be convening a panel of experts or a series of consultations, but at the point that you have evidence strongly suggestive an active infection of a human, then what action should the FDA take and, instead of talking in terms of everything coming to a halt or stop or something like that, let's talk in concrete terms.

It seems to me when my colleagues at the FDA are faced day-to-day with having to make a decision about intentionally allowing additional people to be placed at risk--not an experiment of nature; intentionally allowing additional people to be placed at risk or not.

So the question, it seems to me, to them is not when do you call a global halt on the entire progress in this field, when do you stop all clinical trials. The question is what are the criteria under which the

responsible move would be to desist from intentionally placing additional people at risk until enough investigation had occurred to sort out the issues and the level of the risk, risk assessment and containment control and prevention, which is what we do every day.

DR. MIKELSON: Thanks, Louisa. I agree. That was one of the comments I wanted to make. I think the other one was the comment was made by a member of the public which points out that we still don't have a good animal model. That was another issue that I would like to hear the committee discuss some more about because, as you pointed out, the lack of positive data in all of the animal models really puts this whole question of how do you decide what to do if you do get a positive, or some indication of infection, into doubt because this has moved down multiple steps.

We started out the morning asking for more indications of tests of earlier events in a potential infection cycle, asking for antibody tests. And those are all sort of agreed. But we still don't have any idea of--we don't have a good animal model out there.

I also agree with Dan. If there is any indication of an active infection, we should stop until it is analyzed. But how do we proceed without a good animal model? That is what I want to know.

DR. HIRSCH: Even without an animal model, I agree with you that--

DR. MIKELSON: I don't want the people to be the animal model.

DR. HIRSCH: But there are a few things that might be worthwhile. One is we now have fourteen FDA-approved antiretroviral drugs for other retroviruses. In a good replicative in vitro system that various people in this room might have, you could test a number of drugs and at least have the vaguest idea of what drugs this virus might be sensitive to so that, if some untoward event came along, you would at least have a head start there.

DR. AUCHINCLOSS: I am inclined to kind of lean on my colleagues to see if we might end the discussion, but Jonathan looks eager so I will let him go.

DR. ALLAN: Just the one point about what Dan said which is the active infection that Louisa added to. The reason I think Dan is--I am not going to read your mind but the reason why Dan feels so strongly, and I agree with him, and it goes across all the clinical trials, is because if you get an active infection, it means that PERV infects humans. That is the reason to stop, because you go, "Oh; my god. It infects humans." That is as simple as it can be.

DR. ONIONS: Hugh, I don't want to prolong the discussion, and I don't want to disagree because, actually,

my instinct with this thing is a degree of conservatism, but I think it is the definition active infection that I have a problem with because I think this is such a complex issue that actually defining whether these patients are actively infective is not straightforward.

I will reiterate it is quite possible you could have virus in the plasma from a solid-organ transplant, from a large number of cells, I am talking about here, that is not active infection, that is actually virus coming out of the donated organ.

You could have an antibody response to virus producing that organ that has nothing to do with active infection but, by conventional criteria, you would call that an active infection.

DR. HIRSCH: What is an active infection? What do you mean by an active infection?

DR. ONIONS: That is my concern with making--

DR. AUCHINCLOSS: In many ways, it reduces to that, doesn't it? The FDA is really more likely to face a situation where they are looking at that and not knowing exactly what it means. That doesn't, necessarily, put everything on hold. It means it is time to talk to your experts just to evaluate the data.

And then there is Louisa's stipulation that if you really, truly knew what that data meant, that would be the

indication for a hold. I think that there are levels like that.

DR. CHAPMAN: Or maybe until you know what that data means.

DR. SACHS: I gather the definition of active infection is going to be very different, quantitatively or even qualitatively, from what we have been talking about all day so far; is that right, Louisa? How do you define active infection?

DR. CHAPMAN: I don't know.

DR. SACHS: A replicating virus?

DR. SIEGEL: The shift I was trying to get people to make was from talking about a positive which may mean a positive test result and, with the state of the art at this time, may mean a false positive test result, to talking about evidence of some sort of state in the recipient.

So I think it may be more productive to discuss whether people think if there is data that an appropriate consultation with appropriate people with appropriate expertise develops a consensus that this is reasonably suggestive that there is an infection in the human.

I don't know what that data is but would that be criteria for a hold, as opposed to if you get a positive antibody test, would that be criteria for a hold?

DR. AUCHINCLOSS: My fault. I kept talking when I

said I was going to stop talking. If I were the FDA, I would think that I had heard what I needed to hear on this subject, but what do you think? What does the FDA think?

DR. SIEGEL: It is very difficult, other than on a case-by-case basis, to determine when you have enough evidence to have a high enough level of suspicion. My take on the issue, having heard everyone, though, is that there comes a level of suspicion where, even if there is uncertainty, it is time to stop treating additional patients until you both develop the certainty, relevant data, and have public discussion.

I see a lot of--since the transcript never shows head nods, I will say that I see a lot of positive nods. If that is what the committee means, I am comfortable moving on.

DR. AUCHINCLOSS: One of the pleasures of coming down here and talking to you is that we don't deal with hypothetical questions. We deal with real questions. Here we are dealing with a hypothetical and it is very hard to be precise and specific. But you have just characterized what I think people have been saying, there is a level of concern at which you stop.

One more comment and then we are going to break for coffee.

DR. WALTERS: I think the data monitoring

committee notion is a worthwhile one to come back to. There are committees that do monitor multiple trials. For example, in the National Institute of Allergy and Infectious Diseases, there are a couple of committees that monitor quite a large number of trials and if there were a subgroup of this group that could be designated on a standby basis if something untoward comes up, that group could be called into action very quickly and could give an outside reading.

DR. AUCHINCLOSS: I think that is perfectly reasonable.

DR. SIEGEL: We have the capacity to telephone any member of this committee for advice as information comes up. Once you talk about groups, then we get into the laws about consulting advisory committees and what you can do in closed session and what you can do in public session. We will have to look into that because to convene people without public notice is something that you would have to ask Gail about but isn't so easy to do.

DR. HIRSCH: But he is right. Certainly, the AIDS clinical trials group and those have standing data safety monitor boards not for single trials but for a number of--

DR. SIEGEL: So some organized group.

DR. AUCHINCLOSS: Time for a coffee break. We will come back here at 3:20 for an hour's worth of presentations.

[Break.]

DR. AUCHINCLOSS: We will begin the second half of the afternoon session. The schedule will be slightly different from what is on the printed agenda. We will be starting with Eda Bloom with an introduction and review of recent policy developments. Then we will have a break and go directly to Taylor Wang and then come back to an examination of risk posed by different types of xenotransplantation with Eda Bloom from the FDA.

So I am going to introduce Eda Bloom at this point.

II FDA Xenotransplantation Policy Development

FDA Perspective

DR. BLOOM: Thank you to the committee and the audience. We have heard a great deal this morning about recent developments in science that are relevant to xenotransplantation. For the rest of the afternoon, we are going to discuss the translation of that science into regulatory policy.

[Slide.]

First I would like to go over the definitions that are current for xenotransplantation. We are defining it, and I say "we" meaning FDA and the Public Health Service, as any procedure that involves the use of live cells, tissues or organs from a nonhuman animal source transplanted or

implanted into a human or used for ex vivo contact with human body fluids, cells, tissues or organs that are subsequently given to a human recipient.

The corollary of that is that xenograft products are live cells, tissues or organs from a nonhuman animal source used for xenotransplantation. A little later, we will get into some of implications of these definitions but, for now, we will just continue with a brief background of the development of xenotransplantation policy.

[Slide.]

In 1993, FDA published a document that was entitled The Application of Current Statutory Authorities to Human Somatic Cell-Therapy Products and Gene-Therapy Products. Among the somatic-therapy products used for human treatment were listed xenogeneic cells. That was none too soon because the first xenograft product IND was submitted to FDA in 1994, the very next year.

It became clear very early on that the use of xenotransplantation raised a number of safety concerns that could be very problematic not only for the patient but also for the public at large; that is, the transmission of xenogeneic infectious disease to the patient and subsequent transmission to their close contacts and to the public.

[Slide.]

Immediately, there began a series of cooperative

efforts among PHS agencies including CDC, NIH, HRSA and FDA. But it was not, in fact, as my slide suggests, limited to PH. The Department of Defense was involved, is involved. The Department of Agriculture. And so, in fact, there are a number of government agencies that have been cooperating in the development of xenotransplantation policy and issues.

In 1996, the Draft Public Health Service Guideline on Infectious Disease Issues and Xenotransplantation was published in the Federal Register. Before, and also subsequent to, that, the FDA, as well as various other Public Health Service agencies and including as well private agencies and private foundations have held a number of public meetings.

These public meetings have enabled us to obtain public input and, in fact, today of course is another in a series of that in which we do hear the public and we do hear the discussions.

The most recent document that has been published, and I will discuss this one in a little more detail, is entitled Guidance for Industry, Public Health Issues posed by the Use of Nonhuman Primates Xenografts in Humans. That appeared in April of this year as a notice of availability and the document, itself, is available on the Internet.

This document is a good example of what happens as a result of a lot of scientific evidence that has

accumulated and a lot of public input.

[Slide.]

The document was issued by FDA to address concerns specifically regarding nonhuman primates as sources of xenografts. The infectious-disease risks posed by nonhuman primate sources was obtained both from historical data and, of course, there was a recent publication that HIV-1 most likely, if not definitively, was sourced from a chimpanzee.

But there were two other issues that really moved the publication of this article. One is that the proximity of nonhuman primates to the feral or wild state is still very, very close and the various Public Health Service Guideline recommendations, as Dr. Chapman alluded to, would be very difficult to apply to nonhuman primates if not impossible at this time.

That also refers to the husbandry issues of nonhuman primates. For these reasons, the FDA decided to go ahead and publish this document. We discussed the document in very great detail with the other Public Health Service agencies who accepted the principles of the document prior to its publication.

[Slide.]

FDA concluded, regarding the use of nonhuman primate xenografts that health concerns within the scientific community and general public were raised. The

current data indicate that recipients, their close contacts and the public would be exposed to significant risk by the use of nonhuman primate xenografts.

It was further concluded that additional research and evaluation would be needed to obtain information to assess and reduce the risk posed by the use of such xenografts.

[Slide.]

We made three recommendations based on these conclusions. The first was that an appropriate federal xenotransplantation advisory committee such as the Secretary's Advisory Committee on Xenotransplantation, which is currently under development within the Department of Health and Human Services, should address novel protocols and issues raised by the use of nonhuman primate xenografts in humans, that such a committee should conduct discussions including public discussion as appropriate and that the committee should make recommendations on the questions of whether and under what conditions the use of nonhuman primate xenografts would be appropriate in this country.

[Slide.]

The second recommendation is that clinical protocols proposing the use of nonhuman primate xenografts should not be submitted to FDA--that is our recommendation--until sufficient scientific information exists addressing

the risks posed by such xenotransplants. Consistent with particular regulations under the IND regulations, any protocol submission that does not adequately address these risks, does not justify the safety of nonhuman primate xenografts, is subject to clinical hold due to insufficient information to address the safety risks.

[Slide.]

Finally, at the current time, we believe that there is not sufficient information to assess these risks and we believe that it will be necessary for there to be public discussion harkening back to recommendation No. 1 before such issues can be adequately addressed.

At this point, I would like to stop this topic. We are now going to proceed to the discussion of risks in transplantation. Dr. Taylor Wang will make a presentation on a new kind of encapsulation. Part of what FDA has to do is not, as you can tell from much of our discussion today, only deal with what is here and now but we have to be able to deal with what is happening. And our policy must be able to be flexible and to be appropriate enough to deal with what is coming in down the pike, not just what we have at our door at the moment.

Dr. Wang, who is Centennial Professor at Vanderbilt University, has something to say about space-age technology and encapsulation.

Guest Presentation: Immunoisolation Technology

DR. WANG: Thank you, Eda, for the introduction.

As Eda said, I came from a different background in more ways than one. Actually, I am a physicist by training. My colleagues have asked me the question why a self-respecting physicist wants to get involved in this blood mess. I will let you know the answer later.

[Slide.]

What I wanted to say is this is not a one-man operation. Actually, this is a team operation.

[Slide.]

As you can see, it is a very large team. It consists of an interdisciplinary approach from physicists to fluid mechanics and material scientists and surgical research, molecular physics and polymer science and pathology technology. That is at Vanderbilt University where we team up with the University of New Zealand and which their primary responsibility was looking at islets and the isolation of islets and function of islets and retrovirus is one of the things they are looking at.

[Slide.]

The technology we are talking about is not very new. People have seen it before. It is called immunoisolation. Immunoisolation is a very elegant procedure. It is very beautiful, very simple. In this

instance, you have a capsule encapsulating the islet inside. The capsule is designed in such a way that its pore size is controlled in that manner. The glucose can come in. Insulin can go out, antibodies and lymphocytes. It is a very simple picture, very elegant and very simple picture.

Up to this point, it has not worked as well as it could for some reasons. One of the reasons is to make a second assumption.

[Slide.]

The assumption is that the pore size is very uniform and that it is defect free. But it turns out that the reality is that they are not uniform in pore size and not defect free. So, therefore, in this circumstance, different laboratories get different results.

Therefore, we have to look at how to overcome that problem, accept the fact that there is imperfection in the processing that nature gives us.

[Slide.]

What if the processing imperfection is this; immunoisolation devices assume almost uniform size but, in reality, the size is a Gaussian distribution. Not only a Gaussian distribution, people always assume--say, this is the cutoff so we assume anything above that size does not come in. As they say, well, it is only a very small tail so, therefore, maybe you can get away with it.

[Slide.]

But in reality, if you really look carefully, that is not the picture you should be looking at. You should not look at the pore size density. What you should look at is essentially the surface area that has a larger pore that allows the immune system to come in.

So, in other words, you can have 10 million pores that don't allow your immune system to come in. You have one bloody big hole, and everything comes in so it doesn't do you any good. So the pore size; density is not the question. It is, rather, total surface area is the control.

[Slide.]

Therefore, the physical picture you end up having is actually what we call a barrier model or entrapment model. The membrane serves as a finite thickness that the immune system will actually try to come in. It will come in part of the way. It will get stopped and eventually it can wiggle its way in and you can calculate the time involved to allow that to happen.

[Slide.]

As I say, my background is in physics. The first thing I would do, I would write an equation down. I was told this is not a community that favors the equation, so I will just show you the equation to try to tell you what is the significance the equation is telling you about.

[Slide.]

In the immunoisolation system, really, it is a random-walk model. It is telling you, essentially, how long the system will take to get into the capsule. In other words, you have the immune system outside the wall. How long will it take to get in? The primary thing I want to emphasize is the d^2 of R^2--that is, the thickness squared versus the pore size squared.

[Slide.]

This is important. The reason it is very important is for mass transport, it so happens the R and d are flipped essentially in order. Now, instead of d^2 of R^2 it is R over d. That means there is are two requirements, or a dichotomy. What is good for immunoisolation is lousy for mass transport. What is good for mass transport is lousy for immunoisolation.

Fortunately, when we are looking at those equations, we can see they have different dependence, they have different R and d dependence. By having different dependence, there is one advantage, that you can manipulate that way to optimize both of them which underlines the fact you must be able to independently control all the parameters of the view of the capsule.

If you can't, then you have no hope. But if you are able to do that, you can control the mass transport, you

can optimize the mass transport and, also, you can try to optimize essentially immunoisolation and also mechanical strength and plus a whole host of other things which I will not show you.

[Slide.]

But in able not to do that, one of the first things that you have to do is you have to make sure that the system you have chosen has allowed you to independently adjust the parameters. Now, the current system you will be using is what we call a binary system.

The binary system has one drawback with everything tied to one chemical reaction. With everything tied to one chemical reaction, therefore, when you adjust the one parameter for the benefit of one function, you ruin the other ones. So, what you have to do, you have to become a multicomponent system.

[Slide.]

By having a multicomponent system, and how do you start to do it, you start to do bloody what we call grunt work. What you do is you take all the matrices, all the possibilities, looking at all the reactions. We spent two years looking at grunt work, we call it. It is a 30 by 30 matrix.

[Slide.]

Not only is a 30 by 30 matrix, you are talking

about they are dependent on molecular weight, depends on concentration, depends on pH. So what you end up with every day, when you come to the lab, we have got a table full of trays and we just go through every day for two whole years.

[Slide.]

Eventually, you get to the point you can find the system, a multicomponent system, that looks like it will do what you want it to do.

The drawback of the multicomponent systems is very complicated because not only do we have a primary reaction, there is a secondary, tertiary reaction. But a nice aspect of this multicomponent system is if you can find out which reaction controls what, you can, in principle, fine-tune one reaction to control one parameter at a time.

Therefore, for the first time, you can talk about optimization effect.

[Slide.]

In order to do the optimizing it is not just finding the polymer system. You also have to optimize, essentially, the processing. The process must be also optimized. The process has two aspects; one transient effect and one the steady-state effect.

The transient effect we call it the impact criteria. The impact criteria is very simple. What you started with is a droplet of one polymer with islets inside.

In order to enter the second medium, you have to go through, impact the surface and enter.

When it impacts the surface, what happens is the islets are slightly heavier so that the islets start to accelerate out to the wall. Then there is a whole bunch of criteria that you have to be satisfied and I am not going to bore you will all the equations.

If you want to know it, I will show it to you.

[Slide.]

This is the equation. But I am not going to derive it for you at this time.

[Slide.]

But I will show you the results of that. The results are that you can see it, that if you control what we call the center mechanism, you actually can let the droplet inside start off-center and make it very concentric.

There are two reasons why it is very important to make it very concentric. One is because the concentric wall thickness guarantees essentially the behavior of the property because any type of weakness in the one spot is basically the weakness of the capsule.

The second thing is you want to be able to keep it concentric. You want to be able to keep the islets getting away from the wall because, during the processing, you do not want the islets exposed to the chemical reaction.

The second thing is you do not want the islet to be very close to the wall because, when it is very close to the wall, they actually might influence the growth of the membrane. So those are the things which you have to do.

[Slide.]

Then, in a certain sense, if you do it right, you know what you are doing, this thing will show you essentially the system can be reasonably adjusted in a certain time. This is the process that you have to be able to control. You must be able to control this thing so that, therefore, the islets and the membranes are very uniform and then you can start the formation.

[Slide.]

Another thing which you have to be very careful about is during the formation process, the convective flow is involved. Any time you have convective flow involved, what ends up happening is the two poles will tend to have a different characteristic than the rest of the membrane. That is something you cannot live with because that becomes a weak spot in the system.

What you do is, in order to do all those, this is, in a certain sense, what I will say what I learned from sort of a space flight. What you do--this is a very simple-minded picture. What it says is this; in order to do this properly and control everything you want to control

properly, you let the drop come in falling down through the medium, engulfed by the medium.

The medium and the drop fall in together. You do not have any relative velocity. Without any relative velocity, therefore, you don't have imbalanced forces on the droplet. Not only do you not have imbalanced forces on the droplet, the growth has become isotropic because it is through the diffusion process growth. So it is radially inward.

Let me show you what I have done.

[Slide.]

If you don't do that, this is what the capsule looks like. They have got tails. They have got wiggles. They have got surface, everything. So it is not really as pretty as what you like.

[Slide.]

But if you do what you are supposed to do, you know what you are doing, and you use the processing, this is what the capsule looks like. Each one is the same as the one before. Today you make this one. Tomorrow you make the same one. And that is the process control we are talking about.

In order for this thing to work, you are talking about you have got to transfer 2 million capsules into a human body. And you cannot have a weak spot. Therefore,

what you have to do, your process must be controlled in a manner that every day, when you are making it, it will come out the same.

[Slide.]

At this point, what we call--you start a smoking test. We are not talking cigarette smoking but we are talking about--from a physics and engineering point, a smoking test means, let me take a preliminary capsule. Let's see how this works. It is not a final product, but what we see is we can control the mechanical strength. One of the problems with mechanical strengths, you want the thing to have reasonable longevity inside.

You not only want reasonable longevity, you want is that the capsule stays alive longer than the islet stays. So, therefore, things eventually will fall and what will end up happening is that islet died before the capsule falls apart. Therefore, nothing from the islet will come out. Therefore, the mechanical strength very much has to be controlled. In principle, we can control the two in the parameter space.

[Slide.]

Another thing you have to control is immunoisolation. This is very important with regard to pore size. What you do is you find out one of the concentrations allows us to change essentially the pore porosity, the pore

size, independent from everything else. By allowing to do this, I can basically set how long I want the immunoisolation time for preventing the immune system to enter the capsule.

The third thing, of course, the thing works. It is strong enough to hold it. It protects it, but the question is does it function.

[Slide.]

The question has to be asked, essentially, does the islet still survive its function inside the capsule. That is, in a sense, tied to the mass transport effect. What we show here is the perifusion data and it looks reasonably well and even after six months--this is actually nine-month data. After nine months, if we retrieve it from the animal, the system is still working reasonably well.

[Slide.]

How is the biocompatibility, the question is. Biocompatibility, for instance, you can transplant those things in an empty capsule into the animal. This one is for mice. And it seems to do very well. What we find out, however, this biocompatibility, as you go up in the animal, the biocompatibility requirement becomes more and more stringent.

For C54 mice, the normal mice, we almost can slap it together and it will work. Now, the question is NOD mice

which is essentially the autoimmune system has--it turns out to be much more selective. You can see for the same parameter space which I just showed you for the last one, the two ends are no longer working. The center part still works.

[Slide.]

Another thing which you have to look at with the biocompatibility question is the surface characteristics. You have to be able to control the surface characteristics, how smooth this thing is and all those parameters. With all that, then you can say, "All right; how does it really look after putting it in an animal."

[Slide.]

This was retrieved from the animal about nine months after. The islet was still working. The perifusion data we showed you before has come from this drawing. The islet is reasonably clean. This, obviously, I will say that some one here is not looking so good so it is not in the picture.

[Slide.]

This is what we look at essentially from a rat islet transferred into the NOD mice and we are able to control the permeability.

[Slide.]

Now, more important for you guys, porcine islet

into the mice, NOD mice. Essentially, it is still working fine so even with a very big specie difference--mice and the pig are fairly far apart.

[Slide.]

So I would basically to draw a conclusion, essentially. The immunoisolation works. It works in a certain sense. The immunoisolation will do what we design it to do. The question of whether it will really do what you guys want to do in the long run has to be tested. That is something we are working on.

We are in the process. We have put it in the large dog, in a dog trial, and the data looks very nice. So right now we are doing an optimization effect; that is, we know there are a little things that we want to tidy up so now we are no longer talking about a smoking test. We are talking about a real trial, so we are tidying up the parameter space. We are making it a little bit smoother on the surface.

We make the membrane binding mechanics a little stronger. We will make the materials a little purer. All those little things we can do. We are hoping that, in time, soon, we can get FDA's advice and approval so we can start to proceed.

One other thing which I want to emphasize, Al Gordon reminded me to emphasize, this approach does not

require immunosuppression drugs if it works properly. Obviously, if it works properly, it doesn't require. Up to this, all the data is without immunosuppression drugs.

One thing that is it a very much a tradeoff study essentially because there are so many dichotomy requirements. This is the tradeoff. The most important is because they are very host-specific. On the C57, the tradeoff is much easier. In NOD mice, it is a little tighter. The dog gives me a different requirement and I wouldn't be surprised when we finally go to the human we still have to fine-tune it.

But, as long as we can allow this ability to fine-tune the system, I think that is the criteria we have to be able to, that we can allow us to do. Then I think we have a good chance.

This capsule has a finite lifetime. It is not going to say you transplant once for the next eighty years and you are going to be free. It is almost like--the way we look at it, this system, the capsule, should work about a year to a year and a half. The islet probably works a little bit less than that but we would design the islet to work a little bit less than that.

So the islet essentially will die for various--whatever the reason, because immunoisolation has a finite time, as I said. The islet will die and the capsule

eventually disappear and the capsule would just basically--the body would somehow dispense of it.

What you do is you end up having to replenish on a regular basis. The scenario we are talking about essentially you will transplant once and then, every six months, you will come and have booster shots. However, by having these booster shots, you will be able to live in a sort of, hopefully, a semi-normal life.

So this is the approach that we have been talking about and we have been talking to FDA. There is no guarantee that absolutely that this is--but I think it has a good potential to do a lot things that we want to do.

Thank you.

DR. AUCHINCLOSS: Thank you. Let's just have a moment or two for specific questions relative to this presentation. And then I think what we are going to do is hold the open public hearing or at least see if there are questions or comments or presentations that people want to make from the floor, and then we will group, after the remainder of the FDA presentation, the entire committee discussion together.

DR. ONIONS: I enjoyed your presentation very much. But I wasn't quite sure what you meant at the end when you said that you could design the capsule such that the islet cell died first and then the capsule was, in some

way, disposed of by the body. Clearly, the concern would be if the capsule integrity is destroyed while the islet cells are still alive.

So what do you know about the process at the end, there?

DR. WANG: For instance, we have been doing some of sort of in vitro studies right now. What we find is we put the islets in a medium in the incubator, the capsule, encapsule the islet. What we look at essentially is what is the mechanism that causes the capsule to break.

What we find out is essentially about the fifth month, we have got 5 percent of the capsule starts to disintegrate. 95 percent fine, 5 percent. So we start looking at what was the reason the 5 percent started to disintegrate. It turned out to be that really what you see it--I am a physicist and you see this very often. What happens is the inclusion problem.

When we encapsulate the islets, some loose cells get floating around the place. The loose cells can be included in the membrane. Apparently, when they are included in the membrane, in time, the cell will die and become a void. That void causes the membrane to break. That is one of the reasons.

The second reason that sometimes happens is that the material is not pure enough. Then you can stimulate

essentially a certain inflammation and that is what happens. So those are the things that we know how to deal with and we are looking at. Now we are getting materials. It is coming down to what we call a 5EU per cc.

Before that, in a smoking test, it was 60,000 per cc. So, even the 60,000, we didn't see major problems. We see some residual inflammation probably, some low-grade inflammation. So we believe if we scale down, we can get away with that problem. Inclusion is just something that you have to do it properly.

DR. AUCHINCLOSS: Other questions?

DR. GORDON: Dr. Wang, I am just wondering what is the volume of 2 million capsules and where do you put them?

DR. WANG: Actually, each capsule is less than a millimeter in diameter. So we are looking at about 100 cc's in volume, a little less than 100 cc's. We put it into the peritoneal cavity. That is where the experiment has been done up to this point.

DR. AUCHINCLOSS: Thank you very much.

What I would like to do at this point is to declare an open public hearing.

Open Public Hearing

We have had one advanced request for time from Dr. Michael Schmoeckel. I believe he is not actually here at this point but, if he is, can he identify himself? When he

arrives, I, of course, will make time for him to give his five-minute presentation which may, in fact, turn out to be tomorrow morning depending on how our discussion goes and the time of his arrival.

Are there any other presentations from the public that we do not know about at this point?

MS. STEWART: Sue Stewart with Genzyme Corporation. We wish to make a statement about the nonhuman primate guidance on the standard definition of xenografts and xenotransplantation.

The definition used in the Draft Document for Use of Nonhuman Primate Xenografts in humans published in April of 1999 for the use of those materials. If there is a decision to modify the definition to encompass other products that come in contact with nonhuman animal materials during the production process, special care should be taken to avoid impacting products where the product or the nonhuman contact material can be characterized to a level that eliminates concern for infectious agents' transmission.

Currently, there are many products which are being used to treat human subjects where this is the case. These include live-virus vaccines, the radiated cancer vaccines, cellular products that use feeder layers in their production and gene therapies using living cells expressing viral vectors.

Care also needs to be taken in an approach that would broadly define xenografts and then apply a tiered level of regulatory compliance based on perceived or actual risk. We agree that a risk-based model regulating xenografts has merit within the current class of products as defined in the 1996 PHS guidance and for nonhuman primate material as outlined in the April '99 FDA document.

However, a broader definition which would incorporate products not currently defined as xenografts could potentially make these products unavailable to patients in countries which have banned the use of any xeno material based on their classification as xenografts not on their level of risk.

DR. AUCHINCLOSS: Comments or questions on this presentation? Now, because the open public hearing was originally on the agenda for 5:30, I will try and make note of that and see if anybody else shows up at 5:30 for a presentation or we can reopen tomorrow morning with an open public hearing including Dr. Schmoeckel. We want to include everybody who does with to speak but I just didn't want to have these dangling at the end of the open committee discussion that we will be having. It looked like it would fall awkwardly at that point.

MR. MORE: I am Alan More with Primedica Corporation. I just wanted to kind of echo a comment that

was just made and that was in defining what xeno products are. We do have to be careful about the way that we approach them in a testing sense. I think if what I heard Sue say was that cells or cell lines that are living cells are going to be considered xeno.

That has an entirely different safety approach. So I do want to echo care being taken in terms of how these products are defined.

DR. ONIONS: Could I just make a comment. I think Alan More's comment is very pertinent. If I remember correctly, and I could be wrong, and there are colleagues here from GTI in the audience that can correct me, as I understand it, the GTI protocol involved using packaging cell lines in the treatment of glioblastoma. This was, in the United Kingdom, views as a xenotransplantation as well as a gene-therapy trial which complicated their life, I'm sure.

So I assume here, in the United States, that that was regarded purely as a gene-therapy application not as a xenotransplantation which I assume sort of encompasses the kinds of things you are hinting about.

MR. MORE: Right. I think that is a great example because there are some very well-defined principles in approaching that type of therapy as opposed to approaching the concerns that we have regarding xenotransplant or tissue

transplants where we don't have control over the cells.

DR. AUCHINCLOSS: Anybody from the FDA want to comment on this distinction? It is not necessary.

DR. SIEGEL: I think we are right at the focus of topic II which is whether the distinctions between cell lines or vascular organs or distinctions between species, between ex vivo and in vivo exposure, between barrier exposure and not, how they should impact what safety measures should be taken.

The points are raised and I think we should move on and then discuss them in the full context.

DR. AUCHINCLOSS: Then I will, at this point, end the open public hearing unless there is any other speaker. I would ask Eda Bloom to resume the FDA presentation and then we will return to committee discussion.

FDA Perspective

DR. BLOOM: Thank you, again. In my last presentation of policy, I think that I probably put my spacer in the wrong place because there seem to be a couple of slides that I missed. There is a slide missing.

What I also wanted to mention was that, in the realm of policy, many of you are aware of the 1996 PHS guideline. That guideline also, as you are aware, is currently under revision. I just wanted to not miss mentioning that the revised document is likely to address a

number of issues.

The first slide, which appears to be missing or not dropping, is the idea of informed consent, the idea of FDA taking regulatory authority, the idea of the sponsor having the ultimate responsibility for safety of the trial.

[Slide.]

In addition to those, the new guideline is likely to address safety on animal husbandry and pre-transplant infectious-disease screening to a greater extent than the earlier one, development of diagnostic assays and methodologies, maintenance of healthcare records, both for the source animal and for the patient and biosafety precautions.

[Slide.]

So, as far as the policy is concerned, the published policy papers include the 1996 PHS guideline for which a revision is in progress and the FDA document on nonhuman primate.

[Slide.]

Now we will move on to the examination of risk posed by different types of xenotransplantation for which Genzyme has given us a terrific introduction and I thank you.

[Slide.]

Again, with the definition that is raising

concern. At this point, I would like to go into it with a little bit more thoroughness, especially with the line that the ex vivo contact with human body-fluids, cells or tissues or organs with xenografts, and those human body fluids, cells, tissues or organs that are subsequently given back to a human recipient or given to a human recipient.

It is important to note here that what needs to be given back to the human recipient would be human body fluids, cells, tissues or organs, not, for example, supernatant.

[Slide.]

However, there are a number of concerns for things that are still exposed ex vivo to xenograft-type products and the concerns were what caused us to include the ex vivo exposure in the definition. The potential for transmission of zoonoses or other xenogeneic infectious agents could, in fact, come through ex vivo exposure whether it be extracorporeal perfusion or co-culture.

For example, there are techniques in which fertilization and early embryonic development are done on a monolayer of nonhuman primate feeder cells. The reason for including all nonhuman animals rather than just limiting to mammals or to vertebrates is because cross-species infectivity of viruses cannot always be predicted.

So, therefore, we have made the definition of

xenotransplantation intentionally large. This does pose problems for us and for everyone as far as how, then, do we apply the recommendations that were set forth, for example, in the PHS 1996 guideline to promote safety of such products as much as possible.

[Slide.]

The implication of the definition is that all sponsors of xenograft products should consider these recommendations and that complete implementation of approaches to risk control, however, may not be appropriate for all of the products. What we want to do this afternoon is initiate the public discussion on the relative risks of certain classes of xenograft products which might be more easy to control the transmission of infectious disease.

[Slide.]

Thus, there is a spectrum, or we believe there may be a spectrum--we would like to discuss this--of xenografts as far as what kinds of risks they pose. For example, would brief ex vivo exposure to a well-characterized cell line such as an insect cell line, for example, pose the same risk as the permanent implantation of a whole organ from a wild caught animal.

[Slide.]

We believe there are a number of factors with potential impact on the risk of xenotransplantation. Some

of these are product-related including the species of source animal. For example, would a primate xenograft pose the same risk--and I say fruit flys here because we actually have a protocol in which CTL are produced to treat melanoma patients and those CTL are produced by contact ex vivo with antigen-presenting cells that are derived from the drosophila cell line. That would fall under our current definition of xenotransplantation.

How about ex vivo exposure versus in vivo exposure? For example, again, would exposure to a feeder layer such as antigen-presenting cells or other feeder layer cause the same concern as a kidney graft that is implanted? Again, the issue that was brought up by our public input, cell line versus fresh tissue.

Can a cell line that can be characterized and screened be considered of less risk than fresh cells--that is, fresh cells, for example, of the same dose. Again, that leads us into dose. We have heard a number of presentations today in which the number of cells from a xenogeneic source animal might have been a few million.

Tomorrow, we will hear about suggestions of implantation of whole organs which would be severalfold more than that. Do such transplants pose differential risks?

[Slide.]

Other product-related factors that might impact on

risk would be whether a graft is temporary versus durable. So if you have, for example, an ex vivo exposure to a extracorporeal perfusion liver-assist device as a bridge for transplantation, or whether you have ex vivo exposure to a whole organ, or whether you have a xenograft that is actually in place in the person intended to be permanent.

We have heard a couple of examples of the kinds of barriers; capsulation, those that are currently in use and ones that could be in use. Do barriers provide sufficient protection that that might impact on the potential xenogeneic infection that could be transmitted from a xenograft?

[Slide.]

In addition to the product-related characteristics that we need to consider, there are also patient-related characteristics that had impact or that may have impact on whether or not a xenograft poses serious, or more serious risks. For example, if a patient has strong immunosuppressive therapy, does that, then, predispose that patient and that patient's close contacts to a greater risk than someone who may, say, just receive a xenograft that might be either only temporary, if the patient may be either temporarily immunosuppressed or may be using blocking antibody or something that would be less of an effect on the patient's entire immune system.

Another issue that we want to consider would be whether the patient population would be one that one could be assured would be a compliant population that would come back for screens, that would come back for follow-up exams and that would be available or willing to undergo whatever may be necessary should an infection occur.

[Slide.]

The current PHS recommendations for clinical trials in xenotransplantation has many different thrusts in order to apply known procedures to minimize the possibility of xenogeneic infection being transmitted. These include the composition of the xenotransplantation team which would include everything from the veterinarian to a surgeon to the clinicians to the laboratory; the clinical transplantation site; protocol review by the IRBs, by FDA, by a federal committee; informed-consent procedures specific for xenotransplantation; and procurement sources. Certainly, we have to wonder whether it is important to have a closed herd of drosophila and if you can trace back to the original source of a mouse cell line.

The source animal facilities, again, present the same kinds of issues; pretransplant screening, preclinical studies and assay validation. Now that might be something that--should that have a sliding scale? Maybe not.

[Slide.]

The current PHS recommendations also include, again, the herd and colony screening and surveillance; certain criteria for source-animal qualification; the screening of the graft, itself, for infectious agents; source animal archives and records which may be maintained for many years; surveillance of the recipient which could happen for many years; infection-control practices for the healthcare workers, for the close contacts; and a database maintenance for, again, many, many years.

[Slide.]

So what questions we will have for the committee are--we have a spectrum, or possibly a spectrum. We would like for you to comment on whether we really have a spectrum of risk posed by different kinds and different classes of xenografts and, if we believe that, then how this spectrum might actually be used for the application of the recommendations in the PHS guidelines.

DR. AUCHINCLOSS: With that, I think we will have discussion and then go to the questions. But, actually, I am going to confuse you still further. I am actually going to reopen the open public hearing, because Dr. Schmoeckel is now here, and offer him the opportunity to make is five-minute presentation.

Dr. Schmoeckel?

Open Public Hearing

DR. SCHMOECKEL: Good afternoon.

[Slide.]

Mr. Chairman, ladies and gentlemen, on behalf of the Munich Xenotransplantation Research Group, I would like to give a brief presentation of our initial experience on pig-to-baboon orthotopic heart transplantation.

[Slide.]

We performed two series of experiments due to the requirements of the German regulating authorities. We had to perform a feasibility study which comprised four non-transgenic pig hearts that were transplanted into baboons. This was a feasibility study which means that these animals were not allowed to survive long-term but had to be sacrificed on the table after weaning them off cardiopulmonary bypass.

In a second series of experiments, we transplanted hDAF transgenic pig hearts provided by Imutran Novartis, into immunosuppressed baboons.

[Slide.]

As donors in our first series of experiments, we used normal landrace piglets at a body weight of between 13 and 14 kilograms. The hearts were preserved with iced Celsior cardioplegic solution and the ischemic time was about 3.5 hours.

[Slide.]

As recipients, we had baboons, adult baboon, between 17 and 26 kilograms and orthotopic heart transplantation according to the technique of Lower and Shumway was performed which means that the native hearts were removed before the hearts were placed in situ.

In three experiments, we performed perioperative immunoadsorption for the depletion of preformed natural antibodies. One experiment served as a control and no immunoadsorption was performed.

[Slide.]

Immunoadsorption consisted of the Ig-Therasorb column. The blood of the recipients was divided into plasma and cellular components. The plasma was then directed to the Ig-Therasorb column which contains f-coupled polyclonal sheep antibodies against human IgM, IgG and IgA. The depleted plasma was then reinfused into the animals and we used a total of four cycles per experiment.

[Slide.]

The outcome was that, in all three cases in immunoadsorption, we were able to wean the animal off extracorporeal circulation, after 100 minutes, 11 hours and 21 hours. In each case, it was a deliberation termination of the experiment. ECG showed normal sinus rhythm. No ST-segment elevation. Echocardiography showed a normal pump function, an ejection fraction of 65 percent and a

fractional shortening of 32 percent.

Invasive hemodynamic measuring showed a normal cardiac output of 1.9 meters per minute. Histology confirmed that there was no hyperacute rejection. In our control experiment, the graft failed after 29 minutes. Of course, we were unable to wean this animal off cardiopulmonary bypass and histology, indeed, confirmed all signs of hyperacute rejection.

[Slide.]

This graph shows you the immunuadsorption procedure. These are the hemagglutinating anti-pig antibodies. In our three experiments with immunoadsorption--that is the black line--you can see that we were able to deplete the antibodies below a critical deadline of a titer of 1 in 64 while, in our control experiment, the antibodies were presumably absorbed on the graft and led to hyperacute rejection and graft failure.

[Slide.]

Now, to our second series of experiments. We used hDAF transgenic piglets provided by Imuntran-Novartis. Again, these hearts were preserved with Celsior cardioplegic solution and after an ischemic time of 160 minutes, they were reperfused in the recipient.

[Slide.]

Recipients were, again, baboons, adult baboons of

a weight between 17 and 32 kilograms and we performed the same orthotopic heart transplantation according to Lower and Shumway. These baboons were immunosuppressed with cyclophosphamide induction therapy from day -1 until day 4 and a maintenance therapy consisting of a triple-drug immunosuppression with cyclosporine A, mycophenolate infected with ERL, and steroids.

[Slide.]

Rejection monitoring in the post-operative period consisted of daily assessment of hemagglutinating anti-pig antibodies, a daily ECG and echocardiography and physical examination of the recipients.

[Slide.]

This is the outcome of our first four experiments. In the first experiment, the graft failed, indeed, half an hour after reperfusion. We think that this is due to a technical failure because, during the procedure, it seemed that there was a nonperfusion of the transplanted heart. But, at this stage, we, in fact, can't differentiate this possible ischemia-reperfusion injury from hyperacute rejection.

Our second survivor survived for 20 days and had to be sacrificed due to progressive anemia. In fact, we were unable to transfuse these animals because we had no baboon blood available.

Our third baboon was sacrificed after 11 days. In this case, we had anemia on the first post-operative day and transfused the animal with human blood. However, the animal developed renal failure on day 11 most probably due to hemolysis.

Our fourth experiment, actually, is still ongoing on day 8 today and the animal is still well and alive.

[Slide.]

Just briefly, a couple of functional data of our 20-day survivor. Again, ECG showed always sinus rhythm. Echocardiography showed a normal cardiac function. The ejection fraction was 69 percent the fractional shortening was 37 percent. We had a minimum HB, as I already mentioned, of 4.4 g/dl on day 20. This led to the termination of the experiment.

Due to the cyclophosphamide-induction therapy, we had a very low white-blood count on day 9, 0.2, which recovered to 2.0 again on day 20 and a minimum platelet count in day 13 of 19 which recovered again to 103.

[Slide.]

From this limited experience, I would like to draw the following conclusions. Hyperacute rejection of non-transgenic pig hearts can, indeed, be prevented by immunoadsorption and hDAF transgenic pig hearts are, indeed, able to sustain the life of an immunosuppressed baboon for

up to three weeks at least in our experience.

Thank you very much for your attention.

DR. AUCHINCLOSS: Thank you very much. Any comments or questions?

Thank you very much.

Now we will close the open public hearing again.

Committee Discussion

The reason for this convoluted performance is that now the remainder of the day is just committee discussion which can involve questions of any of the people who have presented but also an effort to address the questions that have been posed to us by the FDA.

I am, frankly, perfectly content to have comments as we did this morning from the floor as well. We basically have two things in the big picture to deal with. One is this issue of the definition of xenotransplantation and I think we will start there. And then we want to debate the value, usefulness, of the concept of relative risk.

Let me start, then, with the definition of xenotransplantation that the FDA has presented. Is there anybody on the committee who wants to suggest some modification of that?

MS. MEYERS: I want to ask, under that definition, would insulin from pigs or cows be considered xenotransplantation or the heart valve made from pig tissue.

DR. AUCHINCLOSS: I think it says "live cells," does it not? The definition; "any procedure that involves the use of live cells, tissues or organs."

MS. MEYERS: So the heart valve is not live cells.

DR. NOGUCHI: The key word is "live.":

DR. AUCHINCLOSS: The heart valve is not live, the insulin is not a cell or a tissue. Is that correct, FDA?

DR. NOGUCHI: That's correct. Heart valves are fixed and deactivated.

DR. AUCHINCLOSS: Live cells, tissues or organs.

DR. ONIONS: I think this just takes me back to that earlier point and it is related to the one that Alan More raised that this would imply that people using cell lines that have been grown in the laboratory and reviewed in the laboratory when put into a patient, for whatever reason, would then have to come up with a definition of xenotransplantation. At least, I assume that is correct.

DR. AUCHINCLOSS: I believe that FDA intends it to mean that; is that correct?

DR. NOGUCHI: Yes.

DR. AUCHINCLOSS: A cell line from a nonhuman source is xenotransplantation.

DR. ONIONS: My only comment about that is that it is duplication of regulation. I think that is a lot easier to do in the FDA where you have a much more defined

structure. I know that that did raise complications in other countries where conflicts between different regulatory bodies arise. That probably isn't such a problem for the FDA where you sort of an overarching structure.

That is my only comment, that you might find something that is both a gene-therapy protocol and it is also a xenotransplantation protocol.

DR. SIEGEL: You are looking at the same people.

DR. AUCHINCLOSS: It's them, either way. My question was that the pig Factor VIII that we heard discussed this morning would not fall under this definition even though there is concern that PERV might be there. Is that a problem and what do we do about that?

DR. BLOOM: You are right. That is a blood product but it is not a live cell or tissue so it would not fall under xenotransplantation. But that doesn't mean that we wouldn't look at such products and take precautions for them.

DR. AUCHINCLOSS: Okay. So there are other ways of looking at those products and we don't have to consider them as part of our xenotransplantation.

DR. BLOOM: That's correct.

DR. AUCHINCLOSS: Does anybody want to modify the definition or are we content to push on to the bigger questions.

DR. SALOMON: Can I ask just one question? Then what is a vector, a retroviral vector, let's say?

DR. BLOOM: That is a good question. If a retroviral vector, let's say, is produced by a mouse cell line, it is ex vivo and then the vector, itself, is what is administered or the vector, itself, then is used to infect human cells ex vivo. The mouse-producer cell line, itself, under those circumstances, hasn't had direct contact with the human cells going back or with human body fluid going back so that would not be xenotransplantation.

However, if you do direct contact between the mouse-producer cell line and the human cells, it would be. If you implant the mouse cells that are producing the vector into the human, it would--

DR. SALOMON: So the vector is not alive.

DR. BLOOM: Well, it is not considered a nonhuman animal. We haven't gone down to viruses.

DR. ONIONS: I am not trying to be awkward, but the very kinds of issues they use where people put packaging cell lines that are irradiated in contact with, say, CD34 stem cells, just for clarity, that would still come under the definition of xenotransplantation?

DR. BLOOM: They are irradiated but they are still alive.

DR. ONIONS: Yes; I appreciate that. That's fine.

DR. AUCHINCLOSS: That is xenotransplantation.

DR. SIEGEL: That's right. Under this definition. We don't have any notion or belief that this definition or any definition captures those products that are most at risk and fails to capture those products--and that all the products it excludes are less at risk. There is a lot of discussion, then, do we have a narrow definition that only includes a transplantation of organs, or only transplantation or implantation of cells? Or do we have a broader one. We started out including ex vivo perfusion.

What is clear to us, and I should say, too, that as far as this definition goes, in part it is part of--the next definition or the newest definition will be part of a PHS guideline. It is not simply an FDA decision what the definition should be but what is clear to us is that, particularly with the broader definition--at least it is clear to us and we are seeking your input, there exists a spectrum of different risks, maybe not a unidimensional spectrum, maybe not only high and low, but just lots of different types of risks.

It is hard to imagine applying all the same policies to all the different types of things we are talking about and we are looking for guidance as to how to cope with that.

DR. AUCHINCLOSS: That is question 2; right?

DR. SIEGEL: It is in all the questions.

DR. AUCHINCLOSS: It is everything we are going to do from now on, I think. So we are content with what we have here. A definition is a definition, but there might be implications to different wording.

All right. Let's move on this concept of relative risk and the particular implication--correct me if I am misphrasing this--is that if we could identify forms of xenotransplantation under this definition that were so unrisky that they would potentially not be subject to the guidelines that you are proposing, that would be an important thing to identify.

That is the real implication. It is not that there would be some--let me rephrase it. The baboons, or the nonhuman primates, you basically said no to for the time being. So you have taken one category of xenotransplantation and said, "We are not interested in that right now."

I didn't hear or sense in the questions that you gave us that you were looking for us to give you other examples of such risky xenotransplantation that we should put them in that category. What I got from the series of questions you gave us was that you were looking for examples of xenotransplantation that would be the other way, so unrisky that they wouldn't necessarily have to face all of

the same stringent--

DR. SIEGEL: Sort of. Unfortunately, I don't see the question as nearly that simple. I think that different factors are likely to predict different types of risks and it is not a question of something being so unrisky that nothing needs to be done but rather that, perhaps, by virtue of being a cell line or by virtue of being an invertebrate or by virtue of having a barrier, maybe we don't need to have, let's say if it is drosophila, a veterinarian on the team. Or maybe you don't need to know what the grandparents of the origin of that drosophila cell line ate, for example, because the concerns about foods were, perhaps, more based on TSE issues and I don't know if drosophila carries TSE.

And the issues of who is deferred from blood donation or should tell all their sexual partners or should donate blood annually to a bank for the remainder of their life. It is already late in the day and this is not going to be the beginning and the ending of these discussions--it might be the beginning. It won't be the end by any means. But we are being faced with a lot of protocols and we are seeing a need to draw some distinctions and not to apply all the same rules, many of which were written with the thought of vascularized organ transplantation.

We are seeking further guidance as to which of these factors do or don't matter. How much comfort should

we take in the fact that it is a cell line or that it is transient or that it is only a few cells or which ones matter more or that it is an invertebrate and how do they matter.

DR. AUCHINCLOSS: I am going to get the discussion going by suggesting the opposite point of view from the one that I think you have just come up with. To me, in this situation of extraordinarily low risk, it is meaningless for us to try to quantify greater and lesser extraordinarily low risks.

There is no evidence that I have seen, and now we will come up with exceptions, but, in general, there is no evidence that I have seen that any particular form of xenotransplantation, whether it be with a barrier or cells or cell line or any of the things, frankly, that are mentioned in your list, that would lead me to say we can relax our guidelines.

There are clearly some exceptions to that. In a cell line, probably, the grandparents of the origin of the cell line may not be as important but they become relatively trivial. I think the concept is wrong.

DR. VANDERPOOL: While you are confronting the concept, I want you to confront something more and that is the title of the document of this session of Xenotransplantation: Public Policy Development. I notice,

in our deliberations today and in the subject at hand that we are still dealing with risk.

That is great. I think we ought to deal with risk. But when it comes to moving xenotransplants to clinical trials, risk is one-half of one-third of the equation and that has to do with risk-benefit assessment. I think we need to keep in mind the ethics of xenotransplantation clinical trials involve a balancing, or at least a consideration, of what the risk-benefit profile should be.

Tomorrow, we will see some protocols that, ipso facto, talk about benefit. Risk can't be the only factor involved. Benefit has to be the other side of that portion.

Secondly, to follow the Belmont report, respect for person is another factor in clinical trials, respect primarily through the process of informed consent which is daunting for xenotransplant clinical trials particularly any that would involve organ. And the final issue is the issue of justice, who gets recruited under what situations and who gets the chance or who takes the chance.

I just want to preface my comment by saying, preface this discussion by making a fervent declaration that xenotransplantation public-policy development should include additional things besides risk.

Perhaps this could be a division of tasks.

Perhaps the FDA is primarily concerned about risk and the NIH and the Office for the Protection of Research Risk will be concerned about the other features of the ethics of clinical trials. But I want to register this because even though we may not talk about it now, when the time comes tomorrow to talk about the possibly proposed protocols, benefits, respect for persons, informed consent and justice will be part of the equation of that discussion.

DR. AUCHINCLOSS: I agree entirely. Thank you very much. Tomorrow, we will be talking about some potential applications and benefit will become very much a factor in the discussion.

DR. VANDERPOOL: Just to make sure what my question is, we are talking about policy development. I don't know what all the FDA sees in terms of its policy development but, as we go through these documents, the first couple of introductory pages do have some of these issues, but if we look at the actual policy statements, they do dwell fundamentally on risk factors.

I just point that out, not to say that is a mistake but let's just be sure that we recognize what the focus so far on policy development within the FDA has been regarding xenotransplantation.

DR. ONIONS: I wanted to slightly disagree with our chairman, with some reluctance, but I think--

DR. AUCHINCLOSS: Do you want to get onto the relative risk issue?

DR. ONIONS: Yes; I was actually talking about your--

DR. AUCHINCLOSS: Let me just hold for half a second. Someone was about to respond to Dr. Vanderpool.

DR. ONIONS: Sure. Sorry. Of course.

DR. NOGUCHI: Not to try to take this too far afield, but I think the reason that it is framed in this way is by no means does FDA defer or accede its role in deciding the ethical component of risk and benefits and further societal issues. We are an integral part of that.

However, it is always the risks that come at us and that hammer us first in the face and so that is why we are trying to bring that as one component of the overall discussion of developing public policy.

You are right on target where the ethical considerations, by necessity, must be integrated in that.

DR. VANDERPOOL: And, Phil, you and the other FDA persons here are the last people I would ever say you are neglecting something. The point is that, as you think about policy development, will you see it as your purview to move beyond risk with a particular concern for other issues involving clinical trials.

It is a question I ask of you. It is your

decision, but you are so right. I mean, I am not criticizing you for focusing on risk. Someone has got to and you are doing it and we are doing it. But will you move beyond risk, focus on risk or other matters is the question.

DR. SIEGEL: That really has to be done on a case-by-case basis. After all, we are not talking about benefits. We are talking about potential benefits as none of these therapies are proven to have any benefit. So it is hard to talk about the general principles.

As we debated a clinical hold, we heard a lot and took into account the fact that there were people dying of liver failure who felt that this device gave them their only chance. We take that into account. We would certainly deal with a heart-transplant protocol differently from the xenotransplant protocol, say, to change hair color or something like that.

But it is a little bit hard to spell out or to get advice on what the general rules are. It is much easier to talk about the specific rules such as we will do tomorrow in talking about specific applications. We look at the scientific feasibility that has come into play. At the first advisory committee meeting on xenotransplantation, there was a great deal of discussion on the baboon bone marrow as to the balance, does that have any chance of helping, was one of the big issues.

So, not only in the future, but I think as we go along, we certainly do agree and take those issues into account.

DR. AUCHINCLOSS: Now, Dr. Onions?

DR. ONIONS: I think Harold's point about benefit and risk is a very important question we would come back to. But what I just wanted to do with this risk issue is I think I disagree in the sense that if you have a cell line produced from a clonal cell and produced as a multicell bank, such as many other biotechnology products are where you can extensively test that cell line, then that, to me, is likely to be intrinsicly safer than an organ from an animal.

However well-controlled the cohort of animals going up to xenotransplantation is, you cannot have the same degree of definition of that product. I would also suggest that the kinds of procedures that now come under the definition, like irradiation of those cells, add a further level of security.

The next level of security, slightly weaker, might be some form of encapsulation technology. If you can validate that technology to show that it reduces virus egress, then, clearly, that would be safer. But you have to validate it.

So you can go up the level and then you go the

primary cells which you still might be able to do some testing on before they go into the patient. So, again, that increases the level of security. So I think there is a degree of gradation security. I couldn't quantitate but I think there is a gradation.

DR. AUCHINCLOSS: I have overstated my case to stimulate a little bit of discussion, but I will keep on overstating it a little bit longer. Let's take the barrier device. The barrier device, we are told, I think the numbers were that it reduced the risk of viral transmission by, what was it, five-log or something like that? It was big. That is terrific.

But, again, if you have got a risk that is so small anyway and now you make it even smaller, does that really affect policy? Do you approach your policy issues differently? I don't see that you do. I don't think you are any less careful about an islet transplant from pigs that are encapsulated from an islet transplant from pigs that are aren't.

DR. ONIONS: I don't think it makes any difference to the kinds of criteria of surveillance, any of the criteria of informed consent, any of those issues. I don't think it makes any difference. All I am saying is I think those processes are probably intrinsically safer.

DR. AUCHINCLOSS: I agree. But my translation of

the FDA questions was into an effective change in regulation. There is no doubt in my mind that, scientifically, there are gradations of risk. But do they affect what the FDA should do? I can't find any. When I say any, the cell lines is an example of where, yes--

DR. ONIONS: Clearly, the case of the cell lines because, in most cases, it is impossible to go back to the source animal so, very clearly, that must be an exception. At least it would seem so. It seems to me that the public has guidelines. I mean, this is a remarkable document, a very good document, in that they try to encompass everything.

But it seems to me that the FDA is being excellent in terms of producing points to consider that are very specific about certain issues. It seems to me, clearly, as we progress, then a points-to-consider document on porcine xenotransplantation might be well worth while because there is, clearly, where most of the activity is going to go on. So you could see specific documents that relate to specific activities.

The odd balls, and they may not turn out to be odd balls, like using drosophila cells, can be dealt with on a case-by-case basis. I don't see a great difficulty.

DR. ALLAN: The only issues that I would think would impact relative risk in terms of what the FDA would do

is if you were using, let's say, a whole organ from a monkey versus something that was as simple as injecting a few cells because what we talked about a year ago--we talked about allowing certain clinical trials to go forward in thinking that whole-organ transplants will weigh off in the future and we didn't have to worry about them.

So the idea, then, is if people are ready to do whole-organ transplants into people, is that a significant enough risk they need to do something different or decide to allow that to happen on a different basis that you would allow what we have already--

DR. AUCHINCLOSS: At this point, the FDA has taken the nonhuman primate donors off the table.

DR. ALLAN: No; I am just using that example. But a pig organ.

DR. AUCHINCLOSS: Let me ask you, do you see any difference in the guidelines of the regulations that the FDA should provide for pig cell transplants into the brain for Parkinson's compared to pig heart donors or kidney donors? I don't.

DR. ALLAN: That is the issue. I think that is one of the questions--maybe I am wrong, but that is one of the questions, a major part of this.

DR. AUCHINCLOSS: That is the nature of the question.

DR. ALLAN: Yes.

DR. AUCHINCLOSS: Are there some kinds of xenotransplantation that should have different levels or regulation? I just can't find the examples, and then we find the exceptions to my statement, like a cell line doesn't have to have its grandparents identified.

DR. WANG: This is just a comment. Let's take a hypothetical case. Some day in the near future, we can prove to the scientific community's satisfaction encapsulation will work. Say we have a great deal of confidence this will work for a long duration, say, will work for a year.

Encapsulation in many ways will prevent a retrovirus to leak out into the body. If that can be proven, would the committee considering saying, all right; you might not have to go through all the pedigree of looking at the virus and looking at the islets, the history of the islets, for three generations for five generations.

I think what we are looking at is a certain amount of guidelines which say, can you relax a certain amount of requirements, not that you do not have control of the whole transplantation or the whole procedure, but the requirement relaxation, you can probably look at it as a function of degree of risk.

DR. AUCHINCLOSS: The committee members can

disagree with this statement, but I cannot imagine an encapsulation technology that would convince me that no virus could possibly escape because no encapsulation device would ever break allowing cells free. I just cannot conceive of such a technology. Does anybody want to disagree with that?

DR. PAUL: I would concur with the chair on this. I think, going back more generically, the guideline really, whether it tissue or whether it is a cell, and even cell line--perhaps they pose a different degree of risk but they also pose a different risk. For example, cell lines could be persistently infected with agents that we don't have identified yet.

Going back in time, we can come up with example after example. There is one incidence in canine vaccines. A vaccine was produced and distributed and used on thousands and thousands of dogs and then USDA isolated a blue-tongue virus. Blue-tongue virus was not one of the agents that was required to be tested.

So I think, going back to circovirus, circovirus contaminates PK15 cell lines, PERV. So I believe that going back to relaxing guidelines for encapsulation, the defects in manufacturing, you can validate all you want but there is always, in nature, an immune response and immunosuppression. There are a number of uncontrollable factors.

So I really believe that we need to--we may have different tests, or different, for example, cell lines. The one advantage would be that you can have the cells with a particular lineage, very tested, well controlled in freezers or at least you can go back--you don't have that luxury with the organ transplant.

On the other hand, the genetic lines of pigs could be well characterized. But I really would recommend that we have similar guidelines regardless of whether it is tissue, cells, cell lines or encapsulation.

DR. ONIONS: Could I just endorse that statement. I absolutely 100 percent agree. I have heard this sort of comment before that maybe we can get away with "dirtier pigs" if we use such-and-such a technique. In my view, that is absolutely not the case for exactly the same reasons that have just been enunciated.

But I think there is another very good reason and that is, by using barrier conditions, we will be keeping out the things we probably don't know about and that may be in the cell lines. I think circovirus is a very good example where we know that a wide number of porcine cells lines are infected by circovirus. People really didn't realize it until quite recently.

And there may be other agents like this that we don't know about. But, possibly, by having very high

standards of pig husbandry, hysterectomy-derived and so on, that we will keep out at least a proportion of those agents.

DR. WALTERS: The first five criteria that the FDA laid out have to do with the cells, themselves, and the last two have to do with the patients. The first of these is fairly straightforward and fits quite easily into a risk-benefit framework, namely the degree of immunosuppression of the patient.

However, I would like to caution that the last one, which is behavioral factors, opens up a variety of very complicated issues that, I think, differ in kind from the first six. And they really take us back to the early 60's and renal dialysis in Seattle in a committee that chose people on the basis of how upstanding they were in the community which led one commentator to say that the Pacific Northwest was no place for Henry David Thoreau with a pair of bad kidneys.

I do think that these issues are important. They really get into an area that Harold Vanderpool has recommended that you open up in more detail and that is the question of justice or criteria for the selection of patients to participate in trials.

For example, should a candidate for xenotransplantation, in principle, be simultaneously a candidate for an allograft, or not necessarily. Nothing in

the policy guidelines that have been laid out thus far addresses that question. Would you like all or some of the early xenotransplantation trials to be placebo-controlled; for example, the introduction of neural tissue for the treatment of Parkinson's disease.

So there are issues--if it is going to be a well-rounded policy development, it really needs to go beyond the risk-benefit question.

DR. SIEGEL: Of course. I think we address those issues in other ways and in other settings. But I want to give a little background to this issue of behavioral factors because it is a complex one and one that has left us somewhat troubled.

There are obvious inherent dangers, as you point out, in how such a screening--what it could mean in terms of justice and access. But when we discussed before this committee--or not this committee, the parent committee which was totally different members and probably the case of a baboon-marrow transplantation in 1995, it was pointed out by several, including non-committee members, the issue that it was important that it was important that such studies be conducted on somebody and in a population of people, potentially, who one could thing would be pretty reliable in terms of following up with recommendations regarding getting follow up medical care, regarding perhaps, if necessary,

barrier precautions, regarding, if necessary, lifetime surveillance and blood sampling as recommended.

And then we were faced with discussion, for example, of the fact that patients with severe alcoholic liver disease and acute alcoholic hepatitis who may not be doing well may not be candidates for human livers and wouldn't it be great to do xenotransplantation in this population.

The question arose are these individuals that one can draw the same presumption about and should that be a factor in determining whether or not such a protocol is appropriate.

I am not sure I know the answers, but if you have any help with them, that would be useful.

DR. AUCHINCLOSS: I think it is the most complicated question of them all. It was on my list of exceptions to my general principle, but it is an exception that, again, goes the other way. I do think that you can define a population of people under behavioral factors that would make them a more risky example of xenotransplantation from the point of view of the public's welfare for exactly the reasons that you indicate.

But that puts you in a terrible dilemma as far as the ethics of informed consent and the ethics of selecting people for trials. I don't know what the right answer is

but I suspect the answer is that there are some people who should be excluded from xenotransplantation at this stage.

DR. VANDERPOOL: I completely agree with you on what you are saying about the degree to which these behavioral issues fall under the question of risk. But as soon as you do that, as Dr. Walters has said, as soon as you start talking about risk and start moving into human behavioral risk, you move into the whole human arena of who is willing to take which risk, beyond physical or physiological risk, health risk. What about psychological risk?

Or what about psychosocial risk of people who don't have the right support system? They are not alcoholic. I also would add my voice to an appeal to make this question of risk a broader--the last factor needs to be made its own subset of issues in which justice and other factors are brought into that discussion in order to decide what to do.

I have one other quick point to make, and that is, on the surface, I don't see a problem with rating risk according to whole-organ versus cellular, and so on. I don't know why you would want to ask this this early. It seems to me, with more scientific data, there is going to be, naturally, a time in which the person who comes in with an encapsulated cellular protocol shouldn't have to jump

through all the same hoops as the person who comes in with a protocol for pig's heart transplants will.

But is it too early to be asking that question? I can see why the urge would be there, but is it too early to ask the question?

DR. SIEGEL: I think probably it is for encapsulation. I am inclined to believe, as some have commented, that we are a long way from having validated them. I just heard this morning about microchimerism resulting with a product where there was a barrier--not encapsulation, but a barrier. I heard about maybe a five-log reduction but, nonetheless, viral transport in a product where there was a barrier.

So I think that one would want to have a lot of data about any barrier approach or encapsulation approach before taking much comfort in its protection.

A lot of things are happening already though that it may not be too early to look at. I would look to the issue that Dr. Onions picked up first, the use of cell lines, the use of cell lines ex vivo for antigen presentation, for co-culture, whatever. There are a lot of particles that do that.

The application of the full extent of the guidelines would pose a substantial resource drain on companies and potentially on the federal government as well,

for example, if we begin to, or plan on, archiving sero and tissue specimens on a regular basis on all patients who might have received their own lymphocytes that had antigens presented to them by well-characterized drosophila or murine cell line ex vivo, or who might have received a certain tissue of that nature and the implications regarding the source animals so also large.

So it is not really too early because we could start conservatively but we could wind up actually creating problems if we do.

DR. AUCHINCLOSS: Jay, I want to come back to the specific examples that you, obviously, have encountered so that we can talk about them directly with you. But I had failed to recognize a comment from the floor.

DR. PITKIN: Thank you. Zorina Pitkin, Circe Biomedical. We wish to make first a comment regarding the revision of the guidelines. In particular, we feel that, in the guidelines, should be recognized the use of cryopreservation, cryopreserved cells. That allows for conclusive, comprehensive quality-control testing prior to clinical use.

Certainly, the importance of use of clean animals, good husbandry practices and thorough testing is important and that should be applicable to all of the sponsors. However, if the final product could be tested, then maybe

the quarantine time or animal derivation or some of the testing that is currently applied to the animals of the source of the tissues could be applied to final product only.

Secondly, if I may just respond to the use of the system with the barrier, I was shown that there was at least a five-log reduction where the highly loaded--well, PK15--that was shown to produce PERV in high volumes, that is when the five-log reduction was shown. However, the hepatocytes were shown not to produce infectious PERV. So I think that should be taken into consideration.

The second comment I would like to make is about the microchimerism with the use of the barrier. It wasn't shown microchimerism as--first of all, you have to define what microchimerism is and, in the case of the use of the system with a barrier, there was no microchimerism but I think further studies have to be shown whether or not it was just a DNA detection that was not detected further down.

Thank you.

DR. COFFIN: I was going to get back to the cell line and the cell-line issue. We should be a little bit careful about thinking that this is actually very different from some of the things that we have been discussing here today.

For example, many mouse-cell lines harbor

infectious, endogenous xenotropic virus which, on co-cultivation with human cells, are very likely to give quite a good infection of those cells doing exactly the same things, kinds of things, that we have been discussing for introduction of pig organs into people.

So one wants to be careful about sort of, in a blanket way, saying that these have some reduced risk on this--

DR. SIEGEL: I guess that is our thinking, in part, as to why we would include those cell lines. But the thinking, also, is that, as opposed to a fresh organ, which you can do a certain amount of testing with, or a live animal that you can do a certain amount of testing with, with a cell line, you can do, and a sponsor potentially can do, rather extensive testing prior to administration.

That may obviate some of the concerns that we otherwise would have, for example, as to the source animals for that line, or as to even the extent of risk and risk-control measures necessary within the clinical protocol.

DR. COFFIN: It would certainly reduce the need to do it more than once but it probably has to be done at least once on a cell line and then adequate protection. Most of the cell lines that are used are often ones that have been around for a long time and are used because they work well. I think there is probably quite a bit of resistance, in

general, to going back to well-validated sources and actually, under GMP conditions, deriving brand-new cell lines for use.

My guess is that most manufacturers are loath to do that when they have a cell line that is producing a product or a system that works well already.

DR. SIEGEL: It might, paradoxically, decrease safety, I would think, to try to supplant well-characterized cell lines with new ones.

DR. ONIONS: I would just agree with John about the last point. The point about using cell lines is that you can characterize them. It would concern me if people were using certain murine cell lines because, clearly, in gene therapy, we spend a lot of time screening retroviral vectors for RCR. Then, if you start putting in a cell line, you have subverted that whole process, it seems to me. So that would concern me.

But I just wanted to pick up Zorina's point because I think it is a point that perhaps we didn't respond to, and I think it is important one and the point I was trying to make earlier. Where you can characterize cells, that does seem to me to have an advantage in terms of risk evaluation.

Clearly, a cell line offers the greatest opportunity because it is clonal, it is derived from a mater

cell bank and you can exclude things like using murine cell lines that express retrovirus. In the case of a primary cell system, you still may have that opportunity and there is a limited opportunity, I think, for instance in the kind of work that Circe does where they can do some screening before those cells go into a patient.

That seems to me to be at a higher level than just putting a whole organ. Therefore, you might reasonably, and it is something that maybe this committee should consider, defer some of the testing from the source animal to the cell line, itself. That does not seem, to me, to be unreasonable intrinsically.

My final point is, however, that usually in regulation, we start tough and get weaker as you begin to work out what the problems are and where there are not problems. I am not entirely convinced we have done that with xenotransplantation entirely. We have spent a lot of time considering PERV and, like my colleague Prem over there, I have as many or more concerns about certain other viruses and certain of the protocols that people are considering.

Some people look for certain viruses. Others don't. There is a degree of consensus about certain viruses but there is not a uniformity here. I think that, perhaps, more emphasis should now be placed on what should definitely

be excluded in the source material that goes into a patient, whether that be excluded at the herd level or whether it be excluded at the cell-line level.

I don't think we have yet had that detailed consensus on those viruses.

DR. WANG: This is maybe because, as I say, my background is a little bit different from everybody on the committee. You guys have been talking to do cell lines. Basic source herding means an increase in the comfort zone and, therefore, in a certain sense, reduces the risk.

As you know, the risk factor is a series matter. You reduce the risk here. If you have a series of risks factor, then you can essentially multiply then and tell you the total risk. Can you guys sort of have some idea what is the risk that is acceptable risk. In the final package, what is the acceptable risk? One in ten million? Something quantifiable so, therefore, people like us, me, we can start thinking about it.

DR. NOGUCHI: Let me try to address that particular issue because that comes up time and again with xeno, with gene therapy, and so forth. If you want to take a crude example, it is our impression, and you would do this for human allo, you want it as sterile as possible when you start. If it is infected, you do everything you can to not use that organ unless it is a life-saving sort of thing.

I think we are taking that same approach here. But, in terms of getting an actual numerical value, we will not do that because that is the wrong road to go. What we are really saying here is, as a society, do we feel comfortable enough with the available data, because the data can always be improved as to what the actual risk really is.

Some of what we are talking about here is, for this particular issue, we broaden our definition of xeno. We, the FDA, think that, perhaps, we have captured a few things that don't need the full panoply of full federal not only regulation but oversight. As Jay has pointed out, if you are doing a tumor vaccine using drosophila cells, but you are going to have to archive not only that patient but every other patient, enroll them in a database, bring it to a national committee which has yet to be formed, that can seriously impede something that, perhaps, is not necessary for that class of product because we already have a lot of experience with that.

What we are saying here is, by far the bulk of what is captured under our new definition is still totally experimental. We have no idea of risk. When we don't know the level of risk, even if we put all these factors together, we are still talking an unknown unknown unknown. And that could go any way you really want.

But I think, here, we are just really trying to

struggle with the fact that is FDA in the right place with this definition for the current level of xenotransplantation recognizing that we are capturing some things that were already regulated but under a less full public oversight with full NIH and CDC participation.

FDA regulates all these things anyway. So when we say can we take some things off the table here, it is not like they won't go through all the risk-benefit evaluations. Prem is absolutely right. We know all about the problems with cell lines and unknown agents in them. The SB40 is a classic example.

So we are not talking about, necessarily, less regulation. We are talking about somewhat less public oversight.

DR. MICHAELS: I was going to ask a question regarding that as well. I was going to query if we knew enough about, say, the drosophila cell line that, perhaps, the nonvertebrate cell lines and tissues and organs and such might not have to go under this type of regulation. I don't know the answer to that. It was really a question to throw out.

DR. AUCHINCLOSS: Is there anybody on the committee who would like to offer an opinion? Are there categories of nonhuman animals from which cell lines would not need the scrutiny that we are suggesting in the pig cell

lines?

DR. MICHAELS: Or the mouse cell lines.

DR. AUCHINCLOSS: Whoa. Don't touch the mouse. We know that is a bad one.

DR. MICHAELS: Right. That is what I am saying. That is actually what I meant. I think any of them that are mammalian derived should stay in the definition but I am just querying whether--

DR. AUCHINCLOSS: Nonmammalian cell lines; are they safe?

DR. PAUL: Even a lot of nonmammalian cell lines use mammalian media supplements. Like fetal calf serum; a number of examples of bovine virus diarrhea, contaminants in serum. So I think that that is another factor.

DR. MICHAELS: But you are not saying that they wouldn't be going under regulation, still. It is just that you would not be storing the samples in the same fashion.

DR. SIEGEL: We have lots of products that are made at various points in the presence of animal serum but we don't regulate them as xenotransplants. But we sure do make sure that they don't get contaminated.

DR. SALOMON: Can the virologists comment on insect cells?

DR. ONIONS: An insect cell has some retroviral-like elements in it which are quite interesting. But if we

take that up--I think there is a degree of clarity which comes from Marian's posing the question. It seems to me that mammalian cell lines, I think I would concur, would stay in because if you go to more obscure mammals than are currently used, then often those are not being evaluated thoroughly.

So, for that reason, I would keep them in. Sub-mammalian, then, I think, perhaps, the same degree of rigor in terms of sampling and storage probably would not have to be present.

DR. SALOMON: How about an avian cell line. We already know about the resorting of influenza. I always venture into the virology with caution.

DR. COFFIN: You also venture into an area for other subcommittee meetings having to do with the question of reverse-transcriptase-containing particles by these cell lines in vaccine products.

DR. PAUL: The question that I would have would be the number of insects that serve as vectors for viruses. Really, the burden should be on the manufacturer to show that they are not a risk. That is the approach that I would use.

DR. COFFIN: Help Canada had a workshop I think about a year and a half ago--I think it was November of '97--as part of their national policy development. There were

some ideas that came up in an infectious disease workshop within that workshop that I did not anticipate and have not heard discussed in other forums but I think are relevant here.

There are several people here who were in that working group but I don't recall that any of the virologists here were in that working group. So I would like to put them on the table for the virologists to discuss. I am sort of switching topics here but there are two suggestions in here for the committee to discuss whether a temporary exposure, like a bridging xenograft, may pose less risk of infection than what is intended to be an endstage organ transplant, and the other is whether the bulk of the xenograft, like a large organ may pose more risk than a xenograft that consists of a few cells.

I think the intuitive assumption I have usually heard was the assumption that more is riskier and longer is riskier and the proposal that came out of the retrovirologists in that group and that I would like to hear the retrovirologists and other virologists here discuss was that, in fact, those may not be significant determinants of risk, that, in fact, a small number of cells in the host for a short duration but that are proliferating may be riskier, given what we know about retroviruses, HIV for example, needing activated cell lines to proliferate than a large

bulk organ that stays in for years with inactive cells.

DR. COFFIN: I would, in general, more or less agree with that position. But I would also go with the principle of our chairman that, again, relative risks here are not necessarily, particularly in the context of where it is sort of the same experiment, really what is on the table, I think, in a sense.

I would certainly not automatically line up the risk. In any case, if I were to asked to line up the risk of infection, I would not automatically do it with the bulk of the organ or, even, necessarily, the duration of the transplant because the risks that we are talking about also include other factors such as the risk of transmission subsequently.

So you have to also take into account the subsequent lifetime of the individual and things of that sort if you are going to take the overall risk altogether to help creating a transmissible agent.

DR. HIRSCH: I think you can't make absolute conclusions but you can certainly say, from experience with other situations--for example, HIV and transfusions and needle-stick injuries--that more is worse than less.

But, on the other hand, a very short exposure can transmit virus. And we know, in the situation of scalp electrodes and CJ prions that it can just be a very

momentary exposure and you can get transmission of these things. So you can't make any absolute conclusions but, certainly, the principle of more is more likely and longer exposure is more likely, I think, are reasonable generalizations.

MS. MEYERS: In discussing this question about risk, it is impossible for anybody to come up with any kind of a formula because you have all of those little problems called human diversity and human weaknesses and a whole other bunch of factors that can complicate the question.

So I agree with Leroy that the ethical questions including risk need to be handled very carefully but I am going to say this for the five-hundredth time, FDA does not have even one bioethicist on staff. It is not right that decisions about maybe excluding alcoholics, or whatever, should be made by the people at FDA who are basically scientists and really are not familiar enough with these types of ethical problems.

Another problem is that the IRBs, as we are learning in recent days, are not reliable. I think that anybody's institution would be very pleased to say, "We are the first to do xenotransplantation in Cincinnati," and rubber stamp whatever protocol is put in front of them.

So I think that there are a lot of things here to worry about that are not scientific but are very, very

important in the long run.

When it comes to how people interpret risk, healthy people interpret it much differently than sick people. To healthy people, any risk is unacceptable. They assume that every drug they take is going to be safe and they are shocked if they get a side effect. So they are not willing to take any risk at all. I hate to see the day when we find CDC, instead of running around in a jungle looking for pig viruses could be running around in a department store or a MacDonald's because everybody who ate in there got sick and got a pig virus and whose fault was that.

On the other hand, a person who is dying of heart disease or liver failure is going to take any risk. So risk is very relative. Until anybody here can promise me that there is no risk, the general healthy public is going to say that they don't want a person who has gotten transplant that has contained any animal virus before we know whether that virus is going to be safe in human beings, they won't want to be exposed to that person.

That, I think is the bottom line, because if anything goes wrong, FDA is going to be blamed for having caused a major disease.

DR. WALTERS: I would like to come back to the behavioral factors one more time. One of my concerns about the overtones of that point as it is currently phrased is

that it could seem to exclude certain groups of patients who I don't think ought to be excluded.

There was mention of chronic substance abuse. I would want to be sure that this doesn't apply to people who are recovered alcoholics and that they will not forever be stigmatized because of bad decisions that they made early in life.

Also, I think mild psychiatric disorders like depression or anxiety disorder ought not to be disqualifying even though they might complicate a person's participation a bit. I think one has to be careful even not to exclude poor people who, perhaps, don't own a car and who might find it more difficult to get to a clinic on a regular basis for surveillance.

Maybe programs have to be a bit more proactive in helping patients get to the clinic if they find themselves in that kind of relative poverty. So whatever is said about behavioral characteristics, I think has to be said with a great deal of sensitivity.

DR. SACHS: I think one of the major problems in this discussion is the fact that it is impossible to separate a discussion of risk with a discussion of benefit. It is only the ratio of risk and benefit that makes any sense. If a procedure had no benefit, you wouldn't be willing to accept any risk.

On the other hand, if the procedure really had benefit to an enormous number of people, then I think people are willing to take a risk, even if it is exposing them to something that is not of direct benefit to them, because people do care about their fellow man. But it has to be demonstrated that there is enough benefit.

I think the problem there is, at this point, we haven't gotten to that stage in the field of xenotransplantation. Hopefully, we will get there but I think it is premature to start worrying so much about defining what the risk should be until we have a better handle on the benefit.

DR. AUCHINCLOSS: I agree with you. But the question will come up tomorrow morning in some of our discussions there. Right now, I think the FDA has put a question to us. Are there certain features of some tissues that have so little risk that they can relax their guidelines? So far, we haven't come up with a whole lot to help them.

There are some comments, but I want to come back to see if we can find some things that help you.

MR. BENEDI: I just wanted to touch in on the behavioral issue. In my tenure of President of the largest transplant recipient organization in the country and in the world, really, I saw a lot of people die on the waiting

list. There are over 70,000 people waiting for transplants today. That is why we are all here, to try to save lives.

But, having said that, I think, and I do take issue with the comment that patients will take more risk or any risk. I think we have a responsibility, those that we benefit from this type of procedure, to the community and to society as a whole not to unleash something that we will regret later at the cost of just having our lives expanded for just a little period of time.

As far as behavioral criteria, I think it is essential. We have it now. There are profiles in every hospital of patients. If they don't have the support mechanisms to take the medicine on a regular basis, to come to labs, those people are not transplanted. Why would we do less for--we really don't know what the outcomes are going to be. I think there should be very strict criteria, behavior criteria.

As far as justice, the justice part of it comes to the society as a whole and not to the individual patient.

DR. ALLAN: I just wanted to come back to what Louisa said about what the risks are depending on dose, organ type, that kind of a question. I think it is important because we didn't really address it last time. I think it is very difficult to address.

John Coffin was saying even if you had certain