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FOOD AND DRUG ADMINISTRATION

XENOTRANSPLANTATION SUBCOMMITTEE

OF THE BIOLOGICAL RESPONSE MODIFIERS

ADVISORY COMMITTEE

AFTERNOON SESSION

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

(1:26 p.m.)

DR. AUCHINCLOSS: If I could bring my subcommittee to the table, if we could get a quorum here and we can open our public hearing. I'd like to open the afternoon session be resuming the open public hearing and asking Alix Fano to address us. She is from the Campaign for Responsible Transplantation.

MS. FANO: I didn't really have a prepared statement, but I felt the necessity to make a comment based on what I've heard here so far today.

Just for everybody's information, the Campaign for Responsible Transplantation is an international coalition of physicians, scientists, and about 80 public interest groups very concerned about the public health risks inherent in xenotransplantation and feel that ultimately if the FDA really wants to protect the public health that it should

ban xenotransplantation. So, that is where we are coming from.

The first observation that we will make, and we will make these observations and comments that we will submit to this guidance, is that the guidance itself is imbued with what we see as biased value judgments about the purported desirability of xenotransplantation to being with; and this despite the fact that the public has yet to be consulted about technology's risks in a democratic forum; and the fact that the secretary's advisory committee on xenotransplantation which is advise Donna Shalala on policy has yet to be formed.

Moreover, in 1996 the Organization for Economic Cooperation and Development raised several important issues about xenotransplantation. Among them are the fact that the economic impacts of the technology had yet to be addressed. That is still true today. OECD also stated that the technology

would have adverse impacts on the medical system by preventing efforts to keep medical costs down, by contributing to the development of multi-tier medicine, conflicting with efforts to develop better approaches to preventive medicine, and possibly discouraging donation of human organs, and may not be consistent with striving with humane and fair medicine. That's number one.

CRT has also expressed its belief that pigs pose just as great a danger as nonhuman primates as donor species in xenotransplantation, and that the FDA's exclusion of this species in guidance is arbitrary, in our opinion.

We are stunned that the FDA continues to make comments about the danger of this technology, and yet continues to allow clinical trials to go forward. Paradoxically, by their nature these guidelines are an admonition that the

practice of xenotransplantation poses a threat to the nation's blood supply and to our public-health system. It reveals, we believe, this guidance, the vulnerability of a system that is devoid of enforcement or legal safeguards that instead depends on the goodwill and honesty of individuals, patients and nonpatients alike, to protect public health.

A method for protecting the blood system from zoonotic agents which relies on voluntary monitoring and a series of three questions which now have obviously been deleted as troubling. There was no explanation about how hospitals and hospital staff would administer the precautionary measures outlined in the guidance. Equally troubling is the absence of a national registry to keep track of all the patients dead or alive who have heretofore received xenotransplants, as well as a list of their close contacts which seems to be important

now.

Given the concern for close contacts expressed in this guideline, such a national registry and database, if it existed, would presumably list xenograft patients as close contacts and their current addresses.

It's strange that casual contacts don't seem to be a issue for some reason. One can only assume that the possibility of aerosolized disease transmission à la swine flu for example has been arbitrarily dismissed. This demonstrates quite a bit of hubris considering the fact that swine flu killed 20 to 40 million people worldwide in 1918 and that the Malaysian nepa viral encephalitis virus killed over 100 people just this past year alone and left dozens of survivors brain damaged. Also Dr. Paul's raising the issue of numerous pig viruses that are constantly being discovered such as the circoviruses, parvoviruses, gamma

herpesvirus, and the hepatitis E virus.

The ramifications of contaminated blood supplies have been serious and deadly. Between 1994 and 1996 some 40,000 people received blood that had been improperly tested for HIV, hepatitis B, and hepatitis C, as well as human T lymphotropic virus. The Manhattan Blood Center tried to reach patients through newspaper and radio announcements, though it's unknown how successful this outreach effort was.

More recently, U.S. and Canadian health authorities announced an indefinite ban on blood donations from citizens who spent 6 months or more in Britain since 1980. This affected about 285,000 Americans, and 25,000 Canadians. This was for fear of transmission of mad cow disease through the blood supply.

Because it takes years or possibly decades before symptoms of CJD appear in humans, authorities are concerned that many

people may be carrying the disease without knowing it. If the disease can be spread by blood carriers who are blood donors, may be unknowingly infecting large blood pools. There is no test currently to detect traces of the disease as far as I know, unless someone knows otherwise.

A recent report by the European Union said that one infected cow could contaminate 400,000 people with CJD. It is possible that as yet unknown porcine viruses may already be lurking in the blood supply for all we know, and they're undetected by commercial testing methods.

HIV nucleic acid detection tests were not commercially available when CDC revised its AIDS case definition in 1993. Today blood banks can use nucleic acid testing to screen for hepatitis of HIV, but those tests can't detect a brand-new virus, only one that's related to an existing virus.

A novel zoonotic agent therefore

could slip through the cracks. However, it is discovered in the blood supply one year, five years, or ten years from now it would have a major impact on the blood supply and our health care system. It would be virtually impossible, as it was during the AIDS crisis, to locate all infected individuals or those who may have had contact with infected individuals. More importantly, it may be impossible to determine the original source of infection.

Given that xenotransplant proponents would like to see tens if not hundreds of thousands of patients receive xenotransplant products, the blood-monitoring system proposed in the guidelines is insufficient and will quickly become unmanageable. It will be impractical, for example, to allow medical directors to determine an individual's health status on a case-by-case basis if xenotransplantation is practiced on a larger scale. Nonbinding

guidelines are simply not going to protect the public health.

A better plan would be to require the introduction of legislation to establish a computerized surveillance system which would include a national name-based registry listing the names and addresses of all xenograft patients in the U.S., and, ideally, also abroad because viruses don't respect national boundaries, and the hospital personnel that may attend him or her. Such a system would always be vulnerable to hackers I think it's important to note. There was a program on ABC News recently which talked about how hackers could shut down the Internet in 30 minutes.

Similar though less elaborate registries already exist to track individuals infected with HIV, and Washington and Texas have implemented name-based HIV reporting to enable public-health follow- up. The CDC has concluded, in a report issued last month,

that name-based methods for collecting and reporting this information are really the best ways to monitor people with AIDS.

These registries, however, are plagued by legal problems, raising substantive Fifth and Fourteenth Amendment due-process issues about individuals' right to privacy and liberty. There have been numerous legal articles written about the complexity and problems that such name-based registries raise.

In light of experiences with AIDS and CJD, however, the establishment of such a registry, with all its social intrusions, would perhaps provide the only hope of trying to prevent blood donations from xenograft recipients and their close contacts.

If we are unwilling to enforce such a surveillance system through legislation, then we must acknowledge that xenotransplantation poses unacceptable risks to the blood supply and to the public health,

and I'll just leave it for that right now.

DR. AUCHINCLOSS: Thank you very much. An important part of today's conversation has to do with a somewhat expanded definition of xenotransplantation compared to what were working with say two or three years ago, and then the notion that with an expanded definition there might be a stratification of risks. Do your comments apply to all of xenotransplantation as we were discussing it today?

MS. FANO: We'd have to go back and rethink that, but clearly based on what was said today, those are concerns that trouble this panel. So, it seems like you guys have to figure out what your real definition of xenotransplantation is, and it seems like it's constantly changing. So, that is a troubling issue from our perspective.

DR. VANDERPOOL: Could you identify yourself again? Could you wait one second? I have a question to ask.

MS. FANO: I'm Alix Fano, the director of the Campaign for Responsible Transplantation.

DR. VANDERPOOL: I would just note for the record that your concerns and critique of xenotransplantation are a good bit like those of Margaret Clark who wrote an extensive article in the recent of issue of the *Journal of Law, Medicine, and Ethics,* and I wrote a critique analysis of her positions. So, for the sake of the group, you can see the issues joined in those two articles. If you haven't seen that exchange, I would encourage you to see the exchange.

MS. FANO: I've seen it. Thank you.

DR. VANDERPOOL: Because I think a number of the assumptions you set forth are generalized and problematic, and a number of your primary ethical concerns are all right in a world where people aren't suffering for loss of organs.

DR. AUCHINCLOSS: I'm going to push this on because we're going to start falling further and further behind.

MS. FANO: There are alternatives to xenotransplantation that are not being explored.

DR. AUCHINCLOSS: We're going to start this afternoon's portion now with the presentation from the FDA by Eda Bloom.

DR. BLOOM: A lot of what I have to say actually was covered in part by Dr. Dayton's talk earlier, so I'll gloss over what I think is redundant.

First, I'd like to give a very, very, very brief background of where we've come from to be where we are at. The first FDA announcement that xenotransplantation in any form was regulated by the agency came in 1993 with the publication of the application of current statutory authorities to human somatic self-therapy products and gene therapy products wherein we mentioned

that xenogenetic cells would be regulated.

For a xenograft product or a xenotransplantation product IND submitted to FDA came in 1984, and immediately raised some concerns within the agency and in fact within the whole Public Health Service as well as the public for the transmission of xenogeneic infectious diseases to patients and potential possible subsequent transmission to close contacts and to the public.

That was followed by a whole series of meetings and consultations and resulted in the issuance by the Public Health Service of the draft guideline in 1996 on infectious disease issues in xenotransplantation. For those of you who want to know when the revised version is coming out, it's coming out.

There was another series of public meetings held by the Public Health Service including FDA and NIH, and just this past year, as has been alluded to, we issued the

guidance for industry on the use of nonhuman primate xenografts, and then the more recent guidance document on blood donor deferral has been discussed.

Andy showed these definitions. I don't believe we need to spend a lot of time, but I do believe it's worth showing them again because, again, the expanded definition which was first published in April of last year, however, which had been spoken about in public meetings prior to that point, is the human body fluids, cells, tissues, or organs, this is part B, that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs, are considered xenotransplantation.

The product is just the live cells, tissues, or organs used in xenotransplantation, and this is intentionally crafted to include both the human cells that may be administered after *ex vivo* contact with animal cells, or the animal cells, and so forth.

The rationale for the expanded definition has already been discussed. Because of certain *ex vivo* exposures of which we were aware including extracorporeal perfusion which could have been taken care of in itself by just saying and extracorporeal perfusion, but also there is the instance of coculture for example with the early embryonic development on primate feeder cells.

The definition also includes all nonhuman animals because cross-species infectivity of viruses are not always predictable, and this is another issue that we'll revisit in the second part of this afternoon's discussion.

Implications from the definition are that xenotransplantation encompasses a diverse range of products. Valuable information and guidance for sponsors of such products has been provided in the Public Health Service guidelines and the revised one

when published, and the FDA guidance documents. FDA must consider, however, the particulars of any given application and the proposals of its sponsor which may differ from this suggested in the guideline and may be equivalent or perhaps even better than what the guideline has suggested, and we must determine whether these suggestions adequately address the applicable laws and regulations, including those intended to address safety.

I also wanted to make the point that continued public discussion of these risks will be an ongoing issue and of these definitions.

We wanted to first discuss Epicel as a xenotransplantation product, and you heard before lunch a nice description of the product; that Epicel is a human autologous skin cell keratinocyte product that has been expanded on irradiated feeder layers of murine fibroblast 3T3 cells from NIH 3T3.

It's a long-established and well-characterized cell line and maintained using a cell bank system.

Now, we'd like for you to consider the recommendations made in the Public Health Service guideline and the FDA guidances, and we request input from the committee on what would constitute acceptable and appropriate approaches to addressing the risk of transmission of infectious agents by this particular product, and this will be our first set of questions.

However, first I wanted to give a brief review of the recommendations, so that, although, we've recently discussed the blood-deferral document, just for the sake of being able to consider the questions, a brief review of the 1996 Public Health Service guideline because that's the one that's out there currently. These will not cover the all of the recommendations in the guideline and will gloss over or abbreviate, although I

think you'll find that, Dr. Vanderpool, I'm not very succinct, so maybe you'll like these.

We recommend that regarding herd and colony surveillance that the source animals used to produce xenotransplantation products should be from closed herds or colonies with documented health-surveillance programs and appropriate staff to person these colonies.

The colony should have standard operating procedures that govern such broad range of issues as animal admissions, movement through the facility, disease monitoring, isolation, cleaning, disinfecting, source and delivery of feed and water, measures to exclude arthropods and other animals that could transmit new diseases, animal transportation during which an animal conceivably could be infected, dead animal disposition, and criteria for screening and surveillance of the humans

entering, and permanent individual animal identification.

Again, regarding the herd colony and surveillance program, the veterinary care should include traditional physical exams and standard laboratory tests, but also should include monitoring for infectious agents that may not be clinically apparent. Such monitoring should include collecting of blood samples and testing of such blood samples, and archiving of such blood samples. We also have recommended the use of sentinel animals.

Again, regarding the source animal, animals need to be individually qualified, individually screened. They should come from documented lineage and from closed herds or colonies maintained using the appropriate barriers and means to minimize exposure. It's recommended that source animals be quarantined for at least three weeks prior to their use; that appropriate physical exams and tests take place during that quarantine.

Again, the transportation of animals or products should maintain appropriate protection.

We also recommend source animal archives and records that can be a linked records system documenting the use of the source animal and including all the animal health records. The archive should contain also banking of source animal biologic specimens that should be accessible and linkable both to the source animal and to the recipient's health records, so that it would be easy enough to link a xenotransplantation product recipient with a source animal.

Now, regarding screening of the product, we've made a few recommendations regarding pre-clinical studies and assay validation. In pre-clinical studies, some of them, not all of them, they should be aimed at characterizing potential for pathogenicity of microbial agents identified in the product including endogenous retroviruses.

As always with all products, assays need to have well-documented specificity, sensitivity, and reproducibility, and these would be whether they're performed on the herd, colony, or xenotransplantation product.

Again regarding the product, there are recommendations that have been made regarding screening for infectious agents. The assays and programs appropriate for species and clinical application should be employed. Samples of the product should be tested, that's of the final product as much as possible. Aseptic conditions for procurement and processing need to be employed. We recommend that tests include cocultivation assays to detect viruses that may not be detected by other assays.

We recommend a necropsy at the time of euthanizing the source animal which may or may not be at the time that the product is obtained, and such necropsy should include gross histopathological and microbiological

evaluation.

The nonhuman cells should be archived, that is, an aliquot of the product used to product each lot of the product. I say this because, again, we have products that may be xenotransplantation products comprised of human cells, but this is the animal component. If it's not possible to archive an aliquot of the product itself, a proxy of the product may be used.

In cases where human cells, tissues, or organs have had *ex vivo* contact, both the animal cells, tissues, and organs need to be archived as well as the final product which would be the human cells.

Regarding recipient education and surveillance, we had some discussion this morning about recipient education vis-a-vis the guidance for blood donating and deferral. The informed consent should comply with applicable statute as always, but should also add the potential risk of infection from

zoonotic agents, the potential risk of transmission of unknown xenogeneic infectious agents, and the uncertainty of the course of such infections, so that the potential recipient is informed of these.

In addition, they should be informed of the potential for transmission to others, and information regarding use of barriers during sexual intercourse.

Any need for isolation or specialized precautions need to be described in the informed consent along with a description of life-long surveillance and reporting of serious or unexplained illnesses to their physician, so that there is guidance upon which to educate the recipient on these issues, as well as that they should be indefinitely deferred from donating blood and tissues for use in humans.

Again regarding the recipient education and surveillance, the 1996 guideline makes explicit and specific

recommendations regarding clinical and laboratory surveillance, an active laboratory surveillance program, and with special attention to acute infectious episodes. It also mentions behavioral modifications such that the recipient and close contacts need to be informed regarding the possibility of risk from xenogeneic infections.

The 1996 guideline didn't place the responsibility I believe so much on any one person at that point, but there has been significant public discussion beyond that guideline. Education should address behaviors known to transmit infectious agents and methods to minimize the risks.

Archives and a database need to be established for the recipient as well as for the source of the xenotransplantation product, and a very specific schedule of pre- and post-transplant collection of biological specimens was recommended in the guideline.

The guideline also mentioned a

database which maintains records with the ability to link information. I should add that there have been actually presentations publicly that there such a database in existence in pilot form at this point. The development of this database is very central to the development of the xenotransplantation regulatory environment.

Public Health Service and FDA made recommendations regarding, again, recipient education surveillance regarding hospital infection and control and health care workers. Use of standard precautions and education of health care workers and surveillance of health care workers were all recommended.

This is just an extraordinary brief summary of what you've spent most of this morning on regarding blood-donor deferral. The xenotransplantation product recipient should be indefinitely intimate. I didn't have the chance to change the slide.

Contacts should also be indefinitely deferred if activities could result in exchanges of body fluids. We had, but I probably should cross that out, about the health care workers regarding indefinite deferral for percutaneous exposure. That exceptions may be granted by FDA especially for well-characterized cell lines or exposure across a barrier.

The firs set of questions that we wanted to address are now in regard to Epicel, and as you have heard, Epicel is one xenotransplantation product that is currently under review by FDA. It is an autologous human cellular skin replacement product in which the human cells have been expanded on a mass feeder cell layer. The agency will request input from the committee regarding what would constitute acceptable and appropriate approaches to addressing the risk of transmission of infectious agents by this product.

Considering the general recommendations made in the draft guideline which I have just summarized, and also considering the specific case of Epicel, we'd like for you to discuss the following specific recommendations proposed by CBER at FDA and whether you agree with the proposed FDA approach.

DR. AUCHINCLOSS: Eda?

DR. BLOOM: Yes?

DR. AUCHINCLOSS: I think I would like to use this if it's all right with you unless you have a conclusion built into this, if we just go ahead and start addressing these questions one by one as they come up. Is that all right with you?

DR. BLOOM: That's absolutely fine, and this will be the first one.

DR. AUCHINCLOSS: Good.

DR. BLOOM: So, shall I sit, and you can change them as you wish.

DR. AUCHINCLOSS: So, I think that

the most efficient way to do this will in fact be to go through the FDA questions in sequence, but I think there are some additional points that may come up as we do that. Then part 2 or Question 2 seeks to generalize beyond the Epicel case to look for principles that we think are important.

But let's start with Question 1.a, regarding the animal procurement sources and source facility control, FDA believes that this category of safeguards need not be applied to Epicel, and I would agree. Discussion on that point from the committee, that when dealing with this kind of cell line, and this is again a general principle, that the source is really trivially important; the issue is the degree of characterization. Any other comments to be made there?

Now, I don't believe we're in a voting situation here are we? You don't need a show of hands at this point which would

ballots things up.

DR. SIEGEL: You may vote whenever you wish, but we're not dealing with regulations or formulating a regulation. We're dealing with getting. So, if there's consensus we have the advice we need. So, we're not specifically requesting votes on any of these. Even if there's not consensus, we'll be getting the advice we need. The votes I think are not specifically going to add --

DR. AUCHINCLOSS: I understand. When it's close it may be useful to have some show of hands, but I get the idea.

So, let's go then to 1.b regarding pre-procedure screening of the xenotransplantation product for infectious agents. FDA has requested tests of the non-irradiated and irradiated murine cell line. Well, that strikes me as fine, and I guess it should be irradiated and non-irradiated, but what tests was more

important than anything else. So, what tests?

DR. BLOOM: I was just going to say to perhaps shorten it we had requested cocultivation assays.

DR. ONIONS: Yes. I think wanted to make a kind of extension. I'll stick to that.

DR. AUCHINCLOSS: I'm sorry, Dr. Onions. The point you were making was that cocultivation should be one of them?

DR. ONIONS: Yes. Definitely, yes.

DR. AUCHINCLOSS: Okay. Dr. Coffin?

DR. COFFIN: I would just like to make a general point, and I don't think we need to consider it specifically here, but a general point that I think the retrovirology tests in here are a little bit old-time retrovirology. I think, the FDA needs in general to consider updating the tests to more modern technology involving things like

PERV assays and PCRS-based assays and so on, and to get the vendors that sell these tests to the companies to develop them because I think it's just not the way to do it.

I think the PERV people have sort of led the way in a lot of this, and we could take some guidance from what's been going on there.

DR. ONIONS: I think in fairness in defense I absolutely agree with that. I think a PERV assay should not be cocultivation. I think in fairness to the strategy as I understand it, some of this testing was done historically quite a long time ago. It's just that our standards have perhaps changed, and I think all we're saying is that for a product now coming towards testing it should incorporate these kinds of approaches.

DR. BLOOM: Do you think that needs to be done in the case of Epicel?

DR. ONIONS: I think it would be

advisable to do that, yes, because in a sense what you've got here is something rather different than a product coming off the cell lines we've discussed this intimate contact with human cells, and therefore I think it would be prudent to take those more stringent assays that both John and I are suggesting.

DR. SIEGEL: I should note that there is a lot of activity in FDA labs in our labs at CBER as well as in industry in looking at PERV assays for retroviral as long as you're talking about supplementing them on more traditional tests we'd be quite comfortable.

The issue as to whether they're adequately validated to replace certain other types are issues that we have under investigation.

DR. COFFIN: Clearly a research program is desirable to get this in the correct place.

DR. KASLOW: I guess you could go a

little bit further, potentially, in saying that not just for retroviruses or viruses per se, but for other organisms and agents there are a whole new battery of tests coming on line, representational difference analysis and other sophisticated tests that may be used to identify nonculturable bacteria and other agents, and the question the FDA ought to address is at what point do we need to start incorporating those tests as a general rule.

I don't have any comment about Epicel per se. I think it depends on the literature on that cell line as to what the likelihood is.

DR. AUCHINCLOSS: Dr. Salomon wants to make a comment, and I'll come back to Dr. Onions.

DR. SALOMON: I just wanted to pick up and make a specific recommendation based on the discussion that we had. So, what's missing here I believe is evidence that there

isn't actually a xenotransplantation going on of the cells that are being used in the feeder layer. So, to be specific, I think that there has to be, in addition to screening for infectious agents, it has to be clarified whether, A, the procedures that the company or producer has used to inactivate, kill, prevent replication, et cetera, of the feeder cell line are actually indeed doing so and to what extent that is. Is it 99 percent which still means you have one percent competent cells, et cetera.

Secondly, that the product itself is or is not free of the cell line from the feeder line. Three, kind of related to both is, if it's not free, is it just that there's DNA contamination which isn't irrelevant actually because a lot of viruses and other things can be transmitted by naked DNA potentially, or RNA, I suppose. Or is it just actually even there and alive, so, three things.

DR. AUCHINCLOSS: Dr. Onions?

DR. ONIONS: I just wanted to sort of extend the point, I think it was very important that the procedures used in preparing the product are actually tested. In other words, not just testing a cell line, but testing in this case the fact that the cells were irradiated because that can affect certainly endogenous retrovirus production.

But it's also worth bearing in mind that certain other latent viruses can be affected by a number of procedures and one of those procedures could be the actual interaction between a human cell and the cell line through circovirus and so on. I'll use the example again, for instance, the circovirus CCPK 15 is not normally expressed but can be induced by a variety of different insults to that cell.

So, those kinds of interactions may also be important for us to see that, in fact, at least a final product had been

tested. Perhaps in part of these testing procedures you should at least consider validating a final product initially and perhaps when any key reagent is changed. For instance, if you change a batch of SES that might be carried over in a procedure or it's used to stabilize the product at the end, perhaps you should then test as a kind of validation procedure just a small part of a lot -- that change. So, those are the things that I would perhaps put some emphasis on.

DR. AUCHINCLOSS: I agree with everything that I have heard, but I want to put out a comment and see whether the committee would agree with it. Perhaps there's a 3T3 cell there in the final product or some of them, but this form of xenotransplantation that we're talking about where the real product is in coculture *ex vivo* and the goes into a human being strikes me as vastly different from xenotransplantation that we ordinarily talk

about where there is immunosuppression involved.

Now, I understand that some of these recipients may be immunocompromised, burn patients, et cetera, but I still suspect that those 3T3 cells, the five of them that go with the product, are there for about 24 hours and gone.

DR. SALOMON: That's fine. That's a reasonable statement. I'm not sure of that, by the way, but it's possible. But my point is the same. We're looking for general precepts of what should be demanded or not, and I'd like to know. Then if that were true, if I knew there were competent replication, competent 3T3 cells, in the final product then I would ask perhaps for skin biopsies at three months and six months to look for microchimerism for malspecific DNA sequences. Something very simple like that.

It turns out, John, that in the

experience with transplantation chimerism that peripheral blood is pretty poor after about seven to ten days, but that skin biopsies and, well, of course, you can't do liver biopsies, have been much, much, much more sensitive, that's my only point, because dendritic cells are important in that.

DR. COFFIN: Kind of going back and cutting into this burned skin, I think it will raise a lot of resistance.

DR. AUCHINCLOSS: I want to bring this up another level again. Xenotransplantation creates risk for some very special reasons that are different from the ordinary environmental exposure to animal products and tissues. The hundreds of times that a mouse has bitten me over the course of my career has exposed me to lots -- if a 3T3 cell got into me, it wouldn't bother me one iota.

So, I think that we're getting a little carried away about the exposure to

these cell lines even if it occurred that might come through the *ex vivo* cultivation process.

DR. SALOMON: I guess all I'm saying is you're implying that I would take a position that if I was told there was 3T3 cells that were living in this product that I would say that you can't use this product, and I'm not. However, you're putting it in a place where there's been a full-thickness skin burn and you're transplanting it there, and I don't think the immune system is working all that well on that site in patients with a 70 percent total body burn and a mortality of 50 percent or greater.

DR. AUCHINCLOSS: I would still suggest to you that in the ordinary course of nature there has been more exposure of mouse tissue to humans in various immunocompromised ways than will ever come up with through xenotransplantation.

DR. SALOMON: Fine. Then just do

those things with your eyes open. That's all.

DR. AUCHINCLOSS: The FDA's statement is correct, and we accept it, and we've amplified it by talking somewhat about additional tests that might be appropriate. The part 1.b goes further and says archived samples of xenotransplantation final product and nonhuman cells, tissues, or organs involved in manufacture, FDA requests the retention of samples of murine cells and the final patient product be archived. Dr. Onions, this is essentially what you said, is that correct, that you want final product? Well, you want it tested. They're saying archived. You want it tested periodically?

DR. ONIONS: Yes. My working suggestion is that when critical factors are changed in the manufacturing procedure. Clearly, when you first start doing it you want to validate the final product. But when

you change a critical factor in the manufacture, that might be a lot of a particular reagent, that you then validate the final product. Perhaps presumptively with that it would be advisable to store material if you ever got a question that you need to go back and independently check it. So, that would be sensible.

DR. AUCHINCLOSS: I guess I did have question. In a certain sense, archiving final product sounded like it could be extraordinarily cumbersome. Does this mean that there are 552 samples that you wish were archived of Epicel? I guess that is what you mean.

DR. BLOOM: That's what it means, yes. Actually, the nature of the product is that it's a cell layer which would make it a little bit difficult to obtain a little portion of the cell layer without disrupting the cell layer. So, it would have to be taken a little bit before the final product,

and they could do that. But yes, and I think that they actually have a number of stored vials of cells as they're proliferating along the way. So, it's not one or three vials additional. It's probably not an enormous amount.

DR. NOGUCHI: Also just as a biological product principle fairly standard because very often you may have a contamination problem and you want to go back and see is it the product, is it the hospital, and so forth. So, it's not too uncommon. The fact that it is a cell layer a little bit uncommon, but archiving in that sense is pretty usual.

DR. AUCHINCLOSS: It is usual and not cumbersome. So, anybody want to say that this is unnecessary on our committee, or should we push forward and suggest that archiving of final product is appropriate? Yes, Dr. Vanderpool?

DR. VANDERPOOL: If indeed the

pre-tests and post-tests are done and there's no evidence of xenotransplanted activity, why would you need to archive? I mean, it seems to me that the answer to this question over archive activity could be answered, and the extent to which archival work would have to be done, would be in part on what the pre and post-testing might show. I mean, this not be a xenotransplanted product by the time they get through with all they've done, and plus irradiation. It may not be. So, why archive that under xenotransplanted rules?

DR. AUCHINCLOSS: I think you're coming to the heart of the question: Do we really think we really have a xenotransplant when the cell line has been characterized in the manner in which we're talking about getting it characterized? I think that will emerge a little bit further in these several questions where it becomes operational.

But archiving is such an ordinary thing that I guess I was sort of saying to

myself that's not the place where you'd start quibbling. Archiving sounds reasonable. It's going t come up again. Your question?

DR. ROSE: Harold, the other thing is you don't know what you don't know is the point.

DR. VANDERPOOL: What I'm saying, in the light of the earlier discussion over hey we need some better pre-testing and we need some post-testing, and if the company would indicate that none of those gives any evidence of live xenotransplanted cell activity, then I think we're home free on this. I don't want to say this should discourage archival work. Seems to me that could be done anyway, but maybe not archival, maybe I'm not clear on this, but archive every patient, every procedure when it's done? I don't know how extensive the archival work would need to be.

DR. AUCHINCLOSS: Go ahead.

DR. SIEGEL: Just to address that,

even if the cells are completely gone we can show that it's still possible the issue was infected with something that we don't know about, and I think it would be very important to have a way to trace it back later on, if something came up.

DR. AUCHINCLOSS: Dr. Hollinger?

DR. HOLLINGER: It also depends a little bit about what they're talking about or what they're putting under a xenotransplantation final product or the other things, because I think that if they're going to use something like fetal bovine serum in the product, then, that, at least somewhere along the line, has to be tested or at least made certain that it doesn't have any viruses in it as well.

So, it's not just necessarily the final product. If it's a serum-free medium, then that's not an issue. But if it's going to have serum in it, then that has to be looked at somewhere.

DR. ONIONS: I'd just like to get back to this issue of testing lots of final product because clearly you can't do this on very patient this is a time-limited procedure. You've got to go back into the patient. I want to make clear that I didn't mean that every new sample had to be tested. I did not mean that. What I meant was that, actually using serum is quite a good example where, for instance, we now have concerns about new agents that I don't think were included in that testing strategy, things like the bovine parvovirus where that virus certainly can infect human cells and may be a true zoonotic virus.

So, where you change lots of materials, you test the fetal serum, but you probably also ought to test the final product that's been produced with that using epithelium cells that you may have banked from a donor, or that you can use in this kind of validation procedure. That's really

what I was trying to get at.

DR. AUCHINCLOSS: Any other comments about arching samples? Now, Questions C, D, and E are variations on a theme, and I'm going to suggest that we turn to 1.e as the next question. The only reason that I'm going to turn to 1.e is that it's the blood-donor question, and since we spent the morning there we'll feel very comfortable that we know that we're talking about.

So, 1.e is FDA recommends that information on blood-donor deferral be made available to the recipient and requests the committee's opinion on whether deferral should be recommended for, number one, xenotransplantation product recipient.

Now, specifically this is Epicel. Tested in the way that we've seen so far, perhaps one could add further tested more with coculture and as modern techniques become available. Do you believe, as the FDA recommends here, that the person who got

Epicel should be told that they had a xenotransplant and they should never be a blood donor again?

DR. ONIONS: I think I would be content for deferral is not necessary provided these additional upgraded types of modern testing are put in place. I think that would be acceptable. That's my viewpoint.

DR. AUCHINCLOSS: I'd really like to get input on this from around the table from anybody who thinks they have expertise. I think it's a critically important question. Is this so well characterized that for all intents and purposes they didn't have a xenotransplant, which is what I think we're saying here?

DR. ONIONS: I should also say that I agree with Dr. Salomon. I think he's made a very good point that really we don't quite know that the final product is and it would be better to have better characterization of

the final product in terms of cells, I mean, I understand that facts work is being done, but I think I share Dr. Salomon's concerns about the limitations of that.

DR. AUCHINCLOSS: Jonathan?

DR. ALLAN: I'm a little stuck in the middle on that question because even if you do all these tests and whatever, there's always a possibility of something that will be discovered ten years from now that's a new class of agent that was transmitted in this or whatever. So, I'm sort of straddling the fence on it myself in terms of whether to do it or not.

I think a lot of people are sitting here with the same sort of attitude. I'm not quite sure. But in the end, I think you can err on safety and just say deferral for these recipients as you have listed would be the simplest way to handle it. That way you eliminate any possibility.

DR. AUCHINCLOSS: It's not simple,

obviously. It's possible. Again, it goes back to scope and scale of the morning, where at this point what we'd be saying if the answer to this is no, they haven't had a xenotransplant, then the people who are being blood deferred are the 50, who had a different kind of xenotransplant and their intimate contacts the way we talked about this morning.

But if you say yes here, then their blood pool and the plasma derivatives that we were talking about this morning are subject to recall for all 552 people if ever were blood donors in the past.

DR. COFFIN: Hugh, but I think there's a distinction here that if I hear John right and David and Dan, since you're not sure what the final product is, then the question is the central one you got to, is this xenotransplant; is the cell line characterized enough to get to the central meat of what you're getting at.

DR. AUCHINCLOSS: As I was making clear or not making clear a little time ago, even if the 3T3 cells are there, I'm not worried about that as a way of transmitting new viruses or agents to the human population that would not occur in nature anyway, or could not occur in nature anyway. We get exposed you and I to mouse or to pig or to a whole variety of animal viruses and tissues in a whole variety of ways.

Xenotransplantation we've always agreed is a unique situation. I think that the risk here in the *ex vivo* culture is only to the degree that the agent goes from the mouse cell to the human cell, and then with the human cell back into the body. So, I'm not worried about the final product in that sense. I'm worried about this conceivable risk of transfer *ex vivo*.

DR. COFFIN: I completely agree with what you just said. What I'm torn the same way that John and I think David is sort

of the risk-benefit. I mean, the risk is extremely small, but on the other hand, the benefit of allowing these people to donate blood I think is also very small in societal terms.

DR. AUCHINCLOSS: Couldn't agree more.

DR. COFFIN: How is the balance, and I don't know actually. I haven't decided.

DR. AUCHINCLOSS: Dr. Dayton?

DR. DAYTON: From a practical standpoint to throw this into the argument, this is probably a group that would be very effectively deferred by education and by the information they're going to receive during the treatment. So, I think in this case deferral is certainly enforceable, if that makes the decision any easier.

DR. ALLAN: This is a little sticky too, but I mean, I guess the concern here is that you're going to have to go back and pull

plasma, and if that's not a concern then like you said, I think the consent and just talking to the patients would ensure the safety. So, I don't see a problem. Especially the way John mentioned it too, which is that it's not going to be that significant in terms of affecting the blood supply to defer these patients from donating blood. So, why not do it.

DR. HOLLINGER: I have two comments. One is that we're not talking about a large volume of patients necessarily unless the indications for use are expanded to include much small burns. Secondly, regarding the point Dr. Dayton made is that we don't necessarily have a good educational pool particularly in the case of young children with extensive burn injuries, who as they become older perhaps their parents have died and they're not aware of what they went through.

I even have a number of adult

patients who we will graft, and because they tend to be relatively unconscious during the grafting procedures, even months later all they know is they got grafts, but they don't know much else about what happened during their hospital stay. That's good, and it's bad.

DR. ROSE: But I'm going to throw it I think the way that Hugh was getting at it which is the Epicel is being used as a test case, i.e., you could say it's the best possible scenario. You have a well-characterized cell line.

So, whether you're dealing with 50 patients or 500 patients, a decision here has an effect of setting a bar for people doing blood donation, and if this doesn't meet the criteria, what are you going to set as the criteria to allow people to do blood donation. Am I correct, Hugh? That's where the discussion is coming from.

DR. AUCHINCLOSS: So, you that one

look it in one of two ways. You could ask the practical question, we know how Epicel was tested over the past five to ten years, and it's been out there and it's on people who were not cancelled, and so now there's a practical question, is if you say yes to this that they should have been deferred and they weren't, then you'd better start checking plasma derivatives that exist right now. So, that's one level of practical question, and it could easily be that one would come to the decision that that was not necessary even though you wish it hadn't gotten to this position.

Then you can ask the second question which is let's assume that the best testing that we can imagine is now in place in the future and that the situation changes. Now it becomes easy to give the patient education, but the question is, is it necessary or useful and it won't be just for these the next 552 patients, it will be for a

large number of patients presumably who have similar kinds of *ex vivo* contact under the best possible circumstances.

So, the committee members can try to address both of those. Do we have to go back on what's happened before? Supposing the best that you could ask for is being done in the future, do they have to be deferred, all of them?

DR. ONIONS: I just want to make clear that my comments were on the basis of your first question. That is, I had assumed that there may be the possibility that you would have to go back and trace people and possibly pull plasma. So, my statement was really colored by that position. So, if you are asking the second question, and that is that should you defer patients now, if this is a new situation, then I think I would be more inclined to Jonathan's position and say, well, this is not, I assume, going to dramatically affect the availability of

plasma in the United States, and it's just a simple act of prudence to suggest that they don't donate, and I think that it's not a major issue.

So, if you're asking the second question, I would be in favor of deferral, but I thought we were primarily asking the retrospective question.

DR. SIEGEL: The question on the paper is about deferral. I presume this committee believes that you can associate the answer to a question about deferral from a question about withdrawal given that I believe this morning you suggested that close contact should be deferred but that shouldn't be a basis for withdrawal of pooled plasma. So, I think there is some recognition here that it's not necessarily the same question. Right?

DR. AUCHINCLOSS: So, I think I heard that the committee, and this is broad because not everybody has spoken, but I think

I heard that prudence, as in the future, no matter how good your characterized, contact with a xenotransplant in this form is grounds for the recipient being deferred. You didn't like that? Yes, Louise?

DR. CHAPMAN: I have a question for the FDA. At the beginning of this you talked about, and some of the things said earlier about agreeing with the concept that for these sorts of exposures it might be appropriate for FDA to make deferral decisions on a case-by-case basis for the individual products.

So, I'm a little unclear here about whether in this discussion you want the advisers to be having this discussion thinking about this product as one of those case-by-case deferral decisions, or this product, with recommendations they made now, being generalizable.

DR. SIEGEL: Both. I think the committee said we should look at these on a

case-by-case basis. The second part of questions on this topic are going to ask the committee to talk about generalizable principles. For example, is it that we don't need it deferred when it's a well-characterized cell line as some have suggested, or is it as Hugh has suggested we don't need to defer when it's not as highly immunosuppressed donor, what are the principles.

But in trying to discuss the general principles in the past we have found that each product presents itself with a mixture of issues regarding not only how well-characterized it is, but what species it came from, how much the exposure is, are there cells transferred. All the issues that have come out.

So, what we would like would be what do you think we should do on this particular product, but I think all the discussion of that and the later discussion

will help us make decisions on other products as well.

DR. AUCHINCLOSS: I think what I heard was that for this particular product don't go back and deal with things in the past, but in the future treat them as if, up your standards with some new assays, including coculture, and in the future those recipients of Epicel should be deferred as blood donors.

Now, personally I don't happen to agree with that, but I think that's what I heard from the committee. I think that it is possible to create a well enough characterized cell line that those patients would not have to be deferred, but I can't claim any great expertise on this. So, that should be a very small opinion.

DR. DAYTON: I'm not a lawyer, but I think I'm becoming one, but I guess but disassociating withdrawn and deferral as we have done for the intimate contacts might be

sticky in terms of liability or medical-legal implications. But again, I'm not a lawyer, but I know that this is a worry for us.

DR. AUCHINCLOSS: It's illogical in a certain sense, but it's not fully illogical because it is a cost-benefit analysis. To go back retrospectively and say oh, oh, we let them be donors and that's contaminated your plasma products out there, that's very costly. But it's not costly to turn them in the future and say don't be donors. That has no impact on the future blood supply. I think we all agree on that. So, while it's illogical, it's not unreasonable.

MR. LAWRENCE: Lawyers don't understand this any better than anybody else. How about political problems?

DR. MICKELSON: A lot of things change when you have to go into court and they read every way you dotted the I or crossed the T. But I was wondering in this situation we're unable to arrive at any kind

of agreement that some risk must be acceptable. There has to be a level of characterization at which we can be satisfied. Risk will never be zero. NIH 3T3 cells, assuming that all those tests are carried out and turned out in a way that the results would support the fact that there's some minimal level of contamination that's below a level of detection with this cell line, we can't find it, it could be there, we're never going to find a way to answer risks that we can't identify.

It's sort a part of being alive. I mean, my gosh, we can eat peanut butter with little parts of insects in it and stuff like that, and it's good for you. It's extra protein.

I just feel that, in this particular instance, I think the suggestions of characterization of the product are certainly excellent suggestions, but to then talk about these patients, the people that

would receive this, as requiring deferral, you will never get that patient population out of that category if we accept at this stage that the theoretical risk is so high that we can never answer the question that there is some unknown agent in that particular product.

That's always going to be an issue so that none of these categories of people will ever be able to be moved out of deferral categories unless we begin to have some concept that there is an acceptable risk here. I guess that's just a personal opinion, but there has to be some recognition that that happens, but that the use of this product and the positive aspects of it far outweigh this.

I would be very uncomfortable with voting to defer because to me the characterization is not xenotransplantation.

MR. LAWRENCE: I would just remind everyone that there is a certain amount of

risk inherent in transplanting human organs. As a recipient I can tell you, and I said this at a previous meeting of this committee, we're prepared to accept a certain amount of risk as long as it's a reasonable risk and everybody has done the best they can and the risk can be fairly well articulated and it's at a rationally low level.

DR. AUCHINCLOSS: Like remember the difference here. I think we're willing to accept a lot of risk for the individual recipient. The question is what risk are you willing to subject the population at large to. That's the public health issue. Dr. Onions?

DR. ONIONS: I think the problem here is that we've really got two separate risks haven't we? That there's the risk of an extremely improbable event of an agent getting into the blood supply and then being amplified through the blood supply. That's a very improbable event, but with potentially

disastrous consequences. So, that's one element, and it's the element that drives Jonathan to take a precautionary view that go for deferral.

The other risk is that if you apply this not just to this product but to many products, then you have the risk of jeopardizing the size of the blood supply and these interlinked but actually separate risks, and the problem seems to me that I am on the side of precaution when it's not going to affect the blood supply because why take that risk when it's not going to have any adverse impact.

The problem arises when those number of treatments begin to affect the blood supply. In effect you then alter your risk-benefit ratio, and that seems to me the problem. But even doing it on a case-by-case basis is not entirely satisfactory because it turns on the total number of products out there. But you may have to ameliorate and

have to alter your views with time.

DR. AUCHINCLOSS: Dr. Vanderpool?

DR. VANDERPOOL: You asked for experts in the field. That's why I haven't spoken up to this time. From the standpoint of common sense, we told the FDA we would give them their ability to make judgments and it strikes me that in this case one should defer until they do the most recent pre- and post-tests. But if those recent pre- and post-tests end up being nothing, quit having the people deferred.

DR. AUCHINCLOSS: So, it's a temporary deferral, but when the tests are done, they will show that they didn't have a xenotransplant.

DR. VANDERPOOL: Deferring deferral, right. Then if those tests are all made when they presented all their testing, we saw nothing but negatives. No evidence. No evidence of this. No evidence of that. If they can say the same types of things,

if this is a unique product, then 500 donors, we can do without them.

DR. SIEGEL: The reason you are being presented this as a test case is because in fact there is a need for general principles because we are making decisions about a whole family of products. As discussed earlier, not at the present time a large family, so you might argue with the 700, or whatever so far, and with however many more each year, 100 or 200, that you could just say defer everybody and wouldn't lose a large number of donors.

On the other hand, there's a reasonable expectation that if one or another of these therapies proves effective and apparently safe for a substantially sized population that it may not be, and it hopefully wouldn't be the very distant future before we could be seeing much larger numbers. So, I think that has to be borne in mind.