

Transcript

**Fifth Meeting of the
Secretary's Advisory Committee on Xenotransplantation,
U.S. Department of Health and Human Services**

Plenary Sessions
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Agenda Item: Xenotransplantation Meeting Updates, News Items, Activity Updates (Part II)

DR. VANDERPOOL: Let's all take our chairs and begin the meeting. Good morning and welcome to all members and all nonvoting agency representatives and members of the public. We didn't announce yesterday that we do have two new non-voting agency representatives that we're very happy to have on our committee, Sherry Hans, who is not with us today, but she is a senior health policy advisor in the Office of the Assistant Secretary of Health, and Ellen Gadbois is the senior policy analyst in the Office of Science and Data Policy in the Office of the Assistant Secretary for Planning and Evaluation, and we are really glad to have you with us, and already have received some very helpful comments from you yesterday.

Also, shortly to be introduced is Howard Zucker, but let's wait for Dr. Zucker for just a moment.

As always, I immensely appreciate the help, not only of all the committee members and of those who are in official positions, but these meetings wouldn't be possible without those who assist us to get here, and to be able to have excellent equipment for recording and for audio equipment, and so I want to especially recognize Joanne Moscow and Barbara McDonald, and Manny Harris and others for their assistance to this group.

For just a very brief time, because of scheduling for Dr. Zucker, I want to ask if any of you have brief announcements of activities that you have done, vis-a-vis the work of this committee, going to conferences, speaking, that are of interest to our group. I mentioned that I would ask this question yesterday. Anyone want to mention meetings you went to, or special conferences, or some participation you had in some activity of import?

DR. SYKES: Well, something I brought up yesterday, I think was the paper of the Ethics Committee of the International Xenotransplantation Association, a committee that I chair, and this paper will be published in March in the "Journal of Xenotransplantation."

DR. VANDERPOOL: Thank you, Megan, that was an excellent report that Megan shared with me on that International Commission, and I believe Mary received it also, if I recall.

DR. KASLOW: I'm sure Carolyn Wilson will mention the FDA workshop several of us attended last fall. I don't think I need to say any more about that, probably.

DR. VANDERPOOL: Excellent, Dan. Any others? I had one of those rare opportunities to go to a miserable place, namely Italy for a week to lecture, and lectured on both the history of xenotransplantation and the regulations of xenotransplantation at a big conference near Turin. I must say that when you lecture on the regulations of xenotransplantation in the United States, you are driven to read the guidance documents like you've never read them before, and so it was a -- It was certainly a learning experience both there and for the purpose of this committee.

Okay. Well, good. We will hope to do this and keep each other apprised of our various activities. Now we are privileged to have from the -- as Deputy Assistant Secretary for Health in the Office of the Public Health and Science Department of Health and Human Services, Dr. Howard Zucker, who will talk to us about DHHS activities regarding xenotourism issues. We are so happy to have you with us, Dr. Zucker.

Agenda Item: DHHS Activities Regarding Xenotourism Issues

DR. ZUCKER: Thank you. Good morning. I thank you for providing me with this opportunity to speak to all of you and to join you in this meeting. On behalf of the Secretary's office, as well as the Assistant

Secretary for Health, I would actually like to express my appreciation and their appreciation for the work of this committee. I learned about the committee about six or eight months ago in discussion regarding some of these issues that have come up. In particular, I would like to thank the chair, Dr. Vanderpool for his work on this, and his able leadership of the committee the last couple of years, and I'd like to thank Dr. Mary Groesch for her excellent work to support all of you as well.

Xenotransplantation is a difficult and complex issue. As everyone in this room recognizes, the work of this rapidly advancing field holds the promise to help alleviate the serious shortages of organs and tissues which we presently face in this country. The subject of organ and tissue shortages is of exceedingly high importance to the Secretary, as probably many of you know from public service announcements, and other meetings and discussions and speeches that the secretary has given.

Of course, one of the shortages, one of the ways to alleviate the shortages is to increase the pool of tissue and organ donors, and this has been one of the messages which the Secretary has put forth. And the Department is working quite hard to advance this, but we have yet to fully achieve the problems that are out there, and to alleviate the shortages of organs.

As a pediatric cardiologist, I am all too well aware first-hand of how painful it is to see patients and parents who are unfortunately suffering from the fact that there are not enough organs out there for their loved one. And to watch these parents and these children go through such troubles and trials waiting for an organ to be available, and sometimes the organs are not available in time.

Xenotransplantation may offer an alternative to this problem, but we really do need to balance the real human interests here represented by the patients against the public health risks of introducing new and dangerous diseases into the general population.

The work of the United States Public Health Service to date to protect all of us from such an occurrence, and also the work of this committee to consider these issues, and provide the Department with sound advice on this issue, I think places the country at the forefront of thinking and planning on the issue of xenotransplantation. Indeed the Department is looking forward to receiving the report that you are presently preparing, as well as to further discussions on this topic.

In fact, the committee has already helped us considerably on the issue of xenotourism. I realize that you will be making recommendations on this issue over the course of the upcoming report. And based on the conversations from the last Secretary's Advisory Committee on Xenotransplantation and subsequent discussions with some of the ex officio members, the Office of the Secretary has already taken steps, begun to address the issue of xenotourism as well.

In December of last year, senior staff in the office, including the Office of Global Health Affairs, met to receive briefings and discuss some of these options. Dr. Megan Sykes represented the views of this committee very ably at that meeting, and it was clear to all of the members of that committee in that room at that time that this is an issue that we need to get ahead of. And although the number of xenotransplantation procedures is currently relatively low, the field has the potential to explode, and we can see these procedures taking place in countries that have not fully addressed many of the public health implications, and have not put safeguards in place, as we have been doing in this country.

So based on our discussions at HHS, we met several weeks ago with the Department of State to look at some of these issues, and try to get ahead of this, rather than to respond to issues. We agreed to work over the next few months to develop and implement both a short-term, as well as a long-term strategy for involving the international committee on xenotourism. Some of the issues that came forth is whether we should address this with other agencies, both not only in the United States, but other health agencies,

including the WHO, and other public health groups on a more of an international forum.

Over the short-term we discussed the possibility of engaging specific countries through our embassies to raise our concerns with their health ministers, and this has been moving forward. Over the long-term, we are considering a number of options, but I think we would agree it would be important for the United States to take a leadership role on this issue at particularly international meetings as they -- as they bring these issues to their governing bodies.

We hope to make progress on this issue over the next year, and I am sure that our office will be happy to keep you informed of anything that comes up regarding decisions that are made, and any of the actions that are taken.

I am glad to actually answer any questions you will have, and to provide you with any other updates that I can give you at this time. As I had mentioned up front, that I will actually have to leave a little bit early. I have a meeting around 9:40. I would like to also add that yesterday, the President had spoken at NIH regarding some of the issues of bioterrorism and bioshield. One of the things he mentioned was about the incredible science and research that we have available in this country, and I think that that really spreads to many issues besides our concerns of bioterrorism. It also spreads to the issue of general science and xenotransplantation, and any of the other areas that we are trying to advance to help public health and science in general. And I think that we should, as a nation, take a lead in this issue, and this will definitely require the collaboration and the efforts of many countries because this is, as we have seen in other issues in the world these days, this is not an issue that is just isolated to the United States, but it shows how health issues really cross all borders and all boundaries. Thank you.

DR. VANDERPOOL: Thank you so very much. Let's have comments from the committee. My one comment at the outset, Dr. Zucker, is that we spoke yesterday about this issue, and about the possibility that this committee should spend part, or perhaps all, of one session exploring the extent of the problem, and gaining a much firmer grasp on what the problem is, and perhaps exploring some possibilities about how it might be addressed. So that is certainly a possibility. If you see that as a significant contribution we can make, we certainly are open to your suggestions about that and your recommendations about that.

DR. ZUCKER: We would feel that as you put together the report, if a part of that report discusses some of your views on these issues, we would definitely want to hear what your perspective of this is, and suggestions of how, from the scientific community, it would be beneficial to move forward on some of these issues, both from a scientific standpoint regarding the xenotourism, but also some of the suggestions you may have regarding a policy or international issues, and then we will incorporate that into our future meetings.

DR. VANDERPOOL: That is good. We almost voted that section out of the report yesterday because of the report is on the state of the science, and we were talking about the need to make a separate contribution, so we'll have to deliberate over what to do about that, because we'd like for it to be of such quality that we've truly done our homework in a very thorough fashion on that particular issue. So we will certainly talk about that today, and maybe we'll have to put together a separate report with all due diligence so that we can address that issue for the Secretary.

Other comments from the committee members? Dr. Salomon and others?

DR. SALOMON: I just had a question. One of the things I'm just clueless about, not really knowing all the ways that your department works, is a critical issue would be to try and define the scope of xenotourism potential right now. We've gone, myself and others on the committee, have gone to, for example, the web sites and discovered some of these boutique programs that are treating autoimmunity

and impotence and other issues, that there is the cerebral spinal cord injuries with shark fetal cells going on. I'm from San Diego, so it's not far away from me. It's just right across the border in Tijuana, and then there are, of course, the more publicized programs such as the one in Mexico that was originally powered by the New Zealand company Diatranz, and later is going forward to do another 25 children with pig islets in Mexico City. But that is more under a formal trial, so those are more than likely to stay above our radar screen and don't worry me quite as much as the pig hepatocytes being injected into the liver in China that was reported in another report without any attribution, so I guess the question comes back to can you help me just understand what could we do as a country to reach out and figure out what the scope of these are, because that has so much to do with trying to decide what to do strategically.

DR. ZUCKER: I think that is a very good point that you raised that there are areas that may be developing some of these issues without our knowing. One of the discussions that took place at, when we spoke with the State Departments, we could reach out to the embassies. Obviously we can't go into the countries, but the embassies have their finger on the pulse of a lot of different issues, and they can hear whether information is being transmitted back to them, that something new is happening in that country, particularly China would be obviously a large country, and would in some ways be a challenge. But there are other countries that may be looking at this as a market, or a potential market, which we may be much more able to find out about. So that is why we reached out to the State Department and international health community, and we will move forward, and as you provide us with some of the science issues, it will be helpful to be able to provide the embassies with exactly what the substance of why this is an issue, and what needs to be done. And that would be very helpful for the committee.

DR. SALOMON: Can I just make a follow-up? So as that would go forward, that made sense to me when I was thinking about it, too, is that the embassies would be our most logical reach into a lot of countries, as you would gather that kind of information, what do you anticipate you would do with it? In other words, how would you evaluate information on a specific program, or come back with new questions to ask? I mean we're not even near trying to track American citizens' activities in those programs. But would you want a group of experts with the Secretary's Advisory Committee? Would this committee be a logical outlet for information like that? Do you have the expertise inside the department to do that?

DR. ZUCKER: We would obviously draw from the expertise from the committee like this to find more about what would need to be done, plus we would draw from the expertise of more of an international community as well, whether to reach out to the World Health Organization or to elsewhere to find out what is going on, because one thing we do not want to do is that we want to be very inclusive on this whole issue, and there are many other places in the world who are also thinking a little bit about this, but obviously we are sort of setting the pace a little bit more, and I think that would be the first -- first step, get the foundation of the science and information, we move forward with that, reach out into the -- the State Department, reach out to the embassies, and also reach out into the community, the larger international health community. And it may be at some point, I can't speak for, obviously, the WHO, and I cannot speak for the State Department on these issues, but at some point we would probably be moving towards them to discuss this on a little bit more of a global front.

DR. VANDERPOOL: As you know, one of the real problems is that the U.S., and certainly the majority of countries in western Europe, to my knowledge, have in place a variety of protective means by which to protect the public from the possibility of xenogeneic infection. And when you have rogue researchers, or even clinics, not just researchers, who turn a blind eye to those protective procedures, then we are all at risk, regardless of how much we protect our patients within the borders of the U.S. I know Dr. Sykes has been working, as you mentioned, at the very outset of our meeting today with the International Xenotransplantation Committee on various matters to -- Megan, do you have comments to make about this particular issue? I know you did represent us well with the agency at one point.

DR. SYKES: Well, the IXA is a professional organization of scientists and other individuals interested in xenotransplantation, and basically the organization has established this Ethics Committee, who -- which I chair, and which has written a position paper that represents the council of the IXA, and represents the views of many members as well. The paper has been passed to the membership, and comments invited, and those taken into account whenever possible. But of course it doesn't represent every member's views. There are always dissenting views. Overall, the position that we took was one of conservativeness and care in moving forward in xenotransplantation. We feel a strong responsibility to make sure as best we can that an infection isn't unleashed upon the human population by -- by this field. And therefore we feel that a very conservative approach is needed, and we took -- We stated our position on issues, in addition to xenotransplantation, such as the need for non-human primate preclinical data to support clinical trials before they go forward.

On the xenotransplantation issue, we took a very similar stance to that, that this committee has taken, that there is a need for international cooperation in the development of regulations that will protect everybody across borders. And we also raised the possibility that perhaps although it wouldn't be necessarily completely effective, that perhaps questioning people re-entering the country after traveling abroad might at least bring to light some xenotransplants that have been performed, and bring these issues to the minds of people who have absolutely no awareness of them when they go and have a xenotransplant at one of these clinics. So we did come up with some practical suggestions that I think this committee should consider, and that I hope the PHS will consider.

DR. VANDERPOOL: Thank you. Other comments from the panel? Dr. Zucker.

DR. ZUCKER: I just want to make one additional comment. I think one of the other things worth mentioning is that some people look at the xenotransplant issue as solid organs, but you have to remember that there is tissues and cells and people may run off to other countries to go after some youth-enhancing cells placed into their body, and not as obvious as a heart, or a lung, or a liver placed in there. That has to be incorporated into the process of looking at this issue.

The other thing is that I guess to every sad event there is always something positive, and we did see this with September 11th, and a lot that came out of that regarding public health, but also I think the international community is also much more aware right now of some of the issues of public health crises, public health issues and infectious diseases across borders, from whether it is mad cow disease and other areas. So they're much more sensitized to these concerns, and it may be an opportune time now when we are dealing with these issues of xenotransplantation to address with the international community, and realize that this is not confined to their country, or from another country's view, confined to a different country and doesn't affect them. So I think that we are at a time now when we can look at those issues as well.

DR. SHAPIRO: I just have one question which may sound like a tangent, but I don't think it is, especially in light of your last comment, that is, if we are looking at how to protect ourselves maximally, I don't think we have to go outside of our borders to come up with concerns. And the current state of public health laws, and we've discussed some on this committee to do something about noncompliant recipients of xenotransplant products, those who don't want to comply with the monitoring, is something that we really can't get our arms around at the moment with our current laws. So would the Secretary also be interested in hearing from us recommendations about possibilities of amending those laws to deal, not only with this infectious risk, but possibly with some of the others that you've just alluded to?

DR. ZUCKER: I think that would be very helpful, and I can say the Secretary is always very interested in hearing anything that involves a way and an effort to improve the public health for the country, so if

you incorporate that into the report, that is absolutely acceptable and useful. Thanks.

DR. VANDERPOOL: This has been immensely important. Thank you so much for being with us, and thanks for all the discussion. We do have significant agenda items for the future. Thanks alot.

DR. ZUCKER: Thank you. Sorry I have to leave.

DR. VANDERPOOL: Now we're privileged to have someone we know well, and someone we respect well, Dr. Carolyn Wilson, to talk about the follow-up on FDA PERV workshop.

Agenda Item: Follow-up on FDA PERV Workshop

DR. WILSON: Thank you, and I wanted to thank Mary Groesch and the members of the committee for inviting me to come here today to provide a summary of what occurred at the workshop that we had in October of last year, to discuss the availability of reagents for assessing seroreactivity against porcine endogenous retrovirus, to just remind the committee briefly this workshop was actually organized in direct response to the discussion of this committee in November of 2001, after we presented data from the clinical experience of screening for retroviruses in the xenotransplantation setting. And in response to the data that were presented, the members expressed concerns about the state of the assays that were being used to detect PERV-specific antibodies, and as an outcome of that discussion, members proposed one option to improve those assays would be to develop a central repository of reagents that would allow for cross-lab comparison.

So with those comments in mind, we organized a workshop with the following goals: To determine what reagents are available for PERV-specific immunoassays, and to determine what assays are available, and to assess those data, with the ultimate goal to develop this public repository of reagents. This would allow for exchange between laboratories, and ideally improve existing assays, leading to enhanced safety evaluation of porcine xenotransplantation clinical trials.

So this workshop was structured essentially in two halves, where the morning consisted of a series of scientific presentations, and I am going to try to quickly just summarize some of the key points that came out of those scientific presentations, and then the afternoon was really the business end of the meeting, where we had a series of three panel discussions focused on three different areas. One was criteria for reagent deposition. The second was to identify current and future needs regarding reagents, and then the final one is how to implement a repository.

So in terms of the scientific presentations, the first two speakers were Walid Heneine and James Brooks from Health Canada. They both spoke about a western blot based assay that is based on use of PERV-infected cell lysate as the antigen for detecting reactivity. The positive controls used in this assay are based on cross-reacting antisera to a related simian Type C retrovirus. Yasuhiro Takeuchi from University College, London, talked about an assay that he has using rabbit antisera raised against recombinant P30 that can be used to attack virus in both western blot and in situ infected cells. He also describes recent data regarding two new molecular clones he's identified using a PCR-based approach.

Dr. Denier from the Robert Koch Institute, talked about a variety of reagents that he's developed, including sucrose purified whole virions, proteins, as well as peptides, that he's used both in western blot and ELISA formats for detecting serologic reactivity. And Gerard Byrne from Nextran Corporation described an ELISA-based assay that they've developed that detects reactivity against the viral capsid P30 protein. In their case, the positive antisera are either rabbit antisera raised against the recombinant protein, or murine monoclonal antibodies.

The last speaker was Dr. Daniel Galbraith from Q1 Biotech. They used a western blot assay against recombinant P30. Their positive control antisera are either rabbit antisera raised against that recombinant protein or monoclonal antibodies. And he used these reagents to do a large-scale study of various human subjects, including normals, transplant recipients, and virally infected subjects. So with that in mind, I wanted to then discuss the consensus points that were reached by the panel discussions, and I wanted to also remember to thank the members of the SACX who participated in the workshop and on those panel discussions as either moderators or participants, because that really helped to provide some continuity between the initial discussion that took place here in the committee, and what went on at the workshop.

So the first panel was composed of Dr. Jon Allan, from the SACX as the moderator, Dan Galbraith, Gerard Byrne and Walid Heneine, and they initially made the point that we shouldn't set a minimum criteria for deposit, because the point here is to make these reagents widely available in order to enhance existing research and encourage new investigators to enter the field. And if we define minimum criteria that would prevent deposit of certain reagents that are available, then this wouldn't really meet those goals. And they also referred us to NIH AIDS repository as a good model for how to develop this kind of approach.

They also recommended developing forms for submission that would allow for standardized requests in terms of the information that we would be asking depositors for certain classes of reagents, although with that in mind, at the time of deposit, maybe not all of these pieces of information would be available. But if they're available, they should be provided. As well as developing a standard material transfer agreement. And again, the NIH AIDS repository has done something in similar in that regard.

And another really important component of that discussion was the concept of developing a web site, where this could be used to share the data that are generated from using reagents obtained from a repository. It was even proposed that that should be a condition of receiving reagents. Relevant protocols, meetings, and abstracts would be posted there. References and links to publications. This could really become a resource for investigators who are working with these reagents and trying to develop these types of assays.

The second panel was moderated by Clive Patience from Immerge Therapeutics and also had a SACX member Dick Kaslow, as well as Joachim Denier and Yasuhiro Takeuchi. They were tasked with trying to assess, okay, here are the reagents we currently have, where are the holes? What additional reagents do we need in order to really enhance existing assays? The first recommendation they came up with is to develop a panel of normal human serum, and they thought about this in one of two ways. One is to either develop a uniform criteria for a panel so that individual investigators can put together their own panels to test reagents and assays against would always do it against the same type of sample: So many normals, so many transplant recipients, so many viral-infected individuals, and so on. Or, we also talked about whether or not we could have actually a much more broader type of panel put together. It was discussed that these types of panels would be useful for a whole variety of assay development for other viral agents, and that there might be an option for NIH, or some other government agency to actually develop a large sample set. Although problems with this approach were raised, such as, you know, how do you assure continued availability, how do you do adequate informed consent, if you are taking these sera to be used for a variety of purposes, and how do you maintain sample integrity. So there wasn't really a consensus reached on which of these two approaches would be the right way to go. They were just both laid out for discussion for consideration.

And then the other really important point that was identified by this panel was to develop positive control antisera. You may have picked up in the scientific discussions in the morning all of the positive control antisera are based on either cross-reactivity to other viruses, or rabbit antisera, or mouse antisera. There is no human anti-PERV antisera that is available. Well, on the one happened that is perhaps the good news,

that we haven't identified any individuals that seem to be infected. It also is the bad news, in that it means we don't know for certain that the assays we are using to screen those subjects could detect a serologic response. So it was really made a high priority to try to identify an anti-PERV serum from a human, perhaps by collecting samples from subjects with high pig exposures with the hopes of identifying somebody that has an antibody response.

Another approach is to develop a humanized mouse monoclonal antibody, and then a variety of additional points were made, such as that we need to do further assay development, all the assays that were presented in the morning were validated for their ability to detect antibody response for the capsid P30 protein, but it was pointed out an antibody response to the envelope protein may also be part of the human response, and we would miss that with the current assays that are in place.

Additional reagents that people thought would be useful to have in the repository are vaccines made in porcine cells, sera from gibbon apes infected with GALV, perhaps again because of cross-reactivity, and a future idea was that as we move forward with these genetically modified pigs, that we may want to consider developing product specific reagents. So, for example, for the alpha-Gal knockout pigs.

And then the final panel was how to implement a repository where Louisa Chapman was the moderator, and we had Charles Buck from the ATCC, Dan Salomon, also a SACX member, and James Brooks. And they put forward the idea that there is really two ways to think about a repository, one is the idea of a central repository, which is really a physical repository, which is what I think most of us are probably used to thinking about, and that is obviously exemplified by the ATCC. The panel suggested this would be a good model for those reagents that are easy to replenish, such as plasmids, cell lines, virus stocks. And then it was suggested for reagents that are more difficult to replenish or replace, that a virtual repository might be a good approach, and that would be consisting of a web site where you would list the reagents, list the contact information, and when an investigator wants to get a reagent, they just directly follow-up on the specific contact. And that they also propose that that web site should maintain a listserv for discussion among people who are getting these reagents, so that it can facilitate exchange of data and experiences.

There is discussion about who and how we would develop such a web site. It was considered that perhaps professional societies who are interested in xenotransplantation would be one place where this could be done. The government could sponsor such a web site, and the ATCC even said that, depending on the scope of the web site, that they may be able to help.

And another point that the panel pointed out was that something to consider for the future is that at some point, once candidates are identified, that the repository would be a place where reference reagents would also be developed and distributed.

So at this point, we now have gathered this information, we are trying to synthesize it. Initial steps that we want to take are to develop a list of currently available reagents, and distribute that among the community to see if we are missing reagents that would be useful to have in the repository. We want to obviously start looking at options for developing this web site. We think it is easier probably to start with a virtual repository, and then eventually move towards the physical central repository.

But essentially the overall goals of developing this repository will be to allow for a uniform experience with these different reagents, and to provide the data to the community prior to scientific publication, because sometimes when all you are doing is assay development, those types of procedures and results don't always get published, because it is not the most exciting science. And so this would provide a mechanism to make sure those data are available to the community who is most interested in knowing about that.

And then finally I just wanted to again thank all the workshop participants, because without the participants contributing their time, data and ideas, you know, we wouldn't have been able to benefit from that discussion. So thank you for your attention.

DR. VANDERPOOL: Thank you so much, Dr. Wilson. I think the State of the Science Report may have a sentence or two to add to its report, in light of the actual decisions and directions this group has taken. Now, at this time, we do have questions for Carolyn.

DR. ALLAN: That was a very nice summary, and since I was at the workshop, I thought it was a great workshop, and I learned a lot from it. The idea of having a repository is a wonderful idea. I had a question. Again, we are focused on PERVs in terms of reagents, and maybe Mike could weigh in on this. Mike could weigh in on this as well, is that there is a number of other viruses that you might want to be concerned about in terms of xenotransplantation, and I wonder whether or not most of those other porcine "pathogens" are -- there are commercial companies that do the diagnostics for it, like circoviruses or porcine respiratory --

DR. SWINDLE: Yeah, there are, and in the case of the corporations, even, that have SPF mini pigs and things like that, those are routine tests that you get monthly health screenings, and a lot of agricultural diagnostic labs have those, so it's not really that much of a big deal.

DR. ALLAN: Including HIPAA, and all these other --

DR. SWINDLE: I'd have to -- There is like a two-page list that I get every month from one of my mini pig suppliers that says what they have been screened for, and it is an unbelievable number of organisms.

DR. ALLAN: So you could limit -- I mean so to have a PERV repository, it doesn't sound to me like you'd need to expand it to other viruses.

DR. WILSON: Well, actually, if I could just add to what Dr. Swindle said, that while there are -- certainly, there is a list of agents that have, you know, commercially available assays that are well-developed and used routinely for agricultural purposes, there are certain viral agents that we have become interested in xenotransplantation that at least, as we are reviewing this information from sponsors, the assays for detection of those viruses is still much more at the investigational stage. And so, for example, the lymphotropic herpes viruses, Hepatitis E virus, circle viruses and so on, these aren't really at that state of the art that they are for the other viral agents. And so I think your suggestion of considering expansion of the repository to include the other investigational assays is a very good one.

DR. ALLAN: Because that way you'd be ahead of the curve, because the other viruses do end up being more of a focus. You'll already have a handle on it, and maybe have reagents available.

DR. WILSON: Uh-huh.

DR. VANDERPOOL: Other comments or questions for Dr. Wilson? Thank you again. We have a place in our schedule for public comments. Is there anyone from the public who would like to make a statement or ask questions? Identify yourself, please.

Agenda Item: Public Comment

MS. CLOSE: Good morning, Mr. Chair, committee and the public, my name is Nicole Close, I am with the EMMES Corporation, and I am the coordinating center director for an initiative called the

Collaborative Islet Transplant Registry. And this goes back to your comments this morning for activities that the committee may want to be aware of, and just briefly, the mission of the Collaborative Islet Transplant Registry is to expedite progress and promote communication from all islet transplant centers in North America through the collection of data and information about donors, islet transplant recipients, and hopefully long-term follow-up of these recipients.

We are currently collecting auto- and allotransplant information, and we are in development of a xenotransplant forum to collect xeno information, and information about recipients and their long-term follow-up. So this is a plan that we are trying to implement. This initiative is funded by NIDDK under Dr. Thomas Eggerman, and Bernhard Hering is our medical director, whom you heard from a little bit yesterday. So I'd like to open it up to the committee, if anybody is interested, in helping us to develop the xenotransplant forum for the recipients, we can get in contact, if you'd like to look over, help draft that. Mary has my contact information. So if you'd like to see that form and help us, we'd be more than willing. I've also talked to Dr. Bloom in the FDA about getting some information and possibly their help in developing this. But we do plan on having annual reports each year. We have been contacted by one of the investigators that is currently doing xenotransplants that was mentioned earlier, and he is very interested in submitting data. So we will hopefully have some xenotransplant information, and if anybody would like more information about CITR, or the Collaborative Islet Transplant Registry, it's www.CITREGISTRY.org, and I'll be around a little bit later if anybody has any questions. Thank you for your time.

DR. VANDERPOOL: Thank you. I think it is excellent to maintain contact with federal agencies so that there can be a symbiotic exchange of information between you. Yes.

DR. HAYWARD: I just had a brief question. I am Anthony Hayward from the National Center for Research Resources. I know that the customs declaration one signs when one comes back into the U.S. asks if one is importing animal tissues. The people coming in with xenotransplant recipients, does anyone know if anyone has yet reported a transplant as yes on that question, and what would happen if they did?

DR. VANDERPOOL: Other comments? Queries?

DR. SALOMON: I think the point Dr. Hayward made is well taken with a sense of humor as well. I certainly would not be in a position to know if anyone reported it. I would imagine that would be quite an interesting set of explanations at customs, and I would like to meet the person stupid enough first to go and do it, but then stupid enough to come in and declare it like that, but that would probably be a scientific report in and of itself, but I think that is exactly the place where something like this would be, wouldn't it? I mean that is -- you know, the little piece of paper you get on the airplane on the way in. But it does point out, kind of what I was asking Dr. Zucker, too, indirectly, that is how you'd keep track of it, what would you do with it? That is going to be something that the committee needs to do, I think first we put it on the department's radar screen, which is, you know, major progress, and but I think it just points out that, you know, completing this whole thing is going to take some effort, and cooperation.

DR. VANDERPOOL: I don't know how many issues there are, but there are a lot that I come away from these meetings thinking this is very newsworthy, but nobody knows about it yet. Yes, Bob.

DR. MENDEZ: It could be at least placed into some sort of a registry that doctors who care for patients who come to them who have had xenotransplants, or who have had any sort of tissue type of xeno tissue implants in foreign countries, that they register them with the public health office, as we have to do with any infectious disease. That would be the most probably logical and easy. Whether or not the doctors would conform to that, as they may or may not do with infectious diseases is another story. But at least it would happen. I know of at least half a dozen physicians already who are taking care of xenograft

patients from foreign countries in the United States, and although this is done by hearsay, such as you and I, there are, I'm sure, there are 50 to a hundred doctors that may be taking care of individuals, whether or not they received xeno tissue implants for rejuvenation or whatever. So I think a public health declaration by a physician might be in order, or something like that.

DR. SYKES: Yeah, I agree that that could be a good starting point, and then the question is how you make the link, and how you get the individual into the system, and who pays for it? I mean I think if a person responds positively to that question, and then upon further questioning is found to have had a xenotransplant abroad, then they need to be informed of their responsibilities as a xenotransplant recipient, which means monitoring. But then to whom do you send their samples? Who pays for it? And all those kinds of things. I think there needs to be some kind of structure in place to make sure that that happens.

DR. MENDEZ: To my knowledge, there isn't any structure now. The couple of patients I have seen and am informed about, they need to be monitored, but there is no place to send them, there is no place that I know of, and no place to inform the agency that they exist.

DR. MICHAELS: I think that is something that we could certainly bring up as a group -- as a committee, that as we have this repository being set up that Carolyn Wilson was describing, and perhaps expanding it a bit, that then the blood could be sent through the County Health Department to the State Health Department, to the Center for Disease Control, and perhaps Louisa could expand on whether that is the appropriate way, or to the repository, you know, however we decide, at least in the short-term.

DR. CHAPMAN: Well, you all probably remember that in an earlier meeting of this committee, I presented some preliminary plans for a national xenotransplantation biological archive, specimen archive, that CDC -- was under development at CDC, that is still under development at CDC. I had hoped to be able to present an update today. But we are -- Our final proposal, our protocol is still in the clearance process. But I think it is far enough along that I feel confident in the near future we will have such an archive. That is an archive for deposition and storage of specimens, in case they are needed in a future public health investigation. It is not a method for sending specimens in to be tested periodically. So the question would be, I guess, if any of the research laboratories that have developed the capacity for such testing would be able to assume that responsibility.

DR. SYKES: At this point, do we know what the tests were? Like a shark transplant?

DR. CHAPMAN: That is correct, in fact, if it is a shark transplant, you wouldn't know what to test for. This is an issue that will need some more thought, and perhaps that would be something to think about. I mean at presently I think what you'd be limited to would be clinical monitoring, the Syndrome X surveillance, looking for unexplained, unusual disease in these patients who have had exposures to we're not certain what, and we don't know what to test for.

DR. SALOMON: My view of this, in terms of trying to put it, I guess what we're all trying to do is come up with someplace to get traction, and then you could kind of go forward, right? And so what we just did now is say, well, let's maybe traction could come through the specimens and through a scientific analysis of the specimens, and then I think we face the reality that at this point we still can't really define what it is we would test so there is really not a lot of traction purely on a scientific point of view. If they were getting pig tissues, thanks to excellent work by Caroline putting together the workshop we just had, you know, we could probably handle pig tissues with some uncertainty, because there is some uncertainty about using animal antibodies as a marker for a human immune response. But anyway, we could start with that. On the other hand, you know, as you say, a lot of this stuff is happening in Mexico, is happening with shark, rabbit, goat tissues. It is really hard to know what the heck they're getting.

The other way to look at this would be in the context of a bioterrorism initiative, which is going to happen in the United States. Really what the idea of the bioterrorism shield is, from my understanding, is the monitoring of this country for unusual patterns of health and disease being reported through emergency rooms and other public health interactions, as well as monitoring as best as possible. I have no idea how that is going to happen, anything that could introduce potentially dangerous reagents into the United States. At this point, I think we finally are getting close enough to where we could find traction locking in with a system like that, without getting, you know, I think we're all uncomfortable with using the T word for -- tourism is fine, but anything else, you know, in discussing this. But I think we could probably interact there, that is my thinking right now, is where we ought to go.

DR. VANDERPOOL: We have Megan and Eda and Tony and Sharon. Yes.

DR. KIELY: I just had a thought, because when we are talking about how people come into the system, like Robert was saying, they come to doctors, they come to emergency rooms, it is somehow picked up that something has occurred, you know, like a transplant, or they had some sort of rejuvenating treatment in the healthcare system, and I am not sure how you determine what is a reportable condition. I mean when we talk about reporting strange diseases, I'll tell you, in the field, doctors aren't really sure sometimes until it's a little late, what is reportable, and what is not, I mean, even, you know, meningitis, sometimes slips past. So there are reportable conditions, however, and I am wondering if there wouldn't be a way -- I know this is done largely at the state level unfortunately, to have xenotransplantation become a reportable condition, per se, and then there would be some state data that could be aggregated, you know, in other ways, or county data that would be aggregated at the state level. So that might be -- I have no idea how to go about that, but it might be something we should look into and see. Dick, do you have --

DR. KASLOW: Louisa, I'm sure can amplify it, but I think the state health officers and other people who kind of make the decisions about what is reportable and what isn't, probably would not be very receptive to having this particular one. It just doesn't fulfill a number of the requirements that -- On the other hand, it is unique, and so it may be worth discussing.

DR. VANDERPOOL: Tony and Eda, do you have a comment?

DR. LUBINIECKI: Once upon a time in the nation's history the U.S. Public Health Service used to be the chief barrier, if you will, to reporting infectious diseases from abroad. The U.S. PHS used to have literally a fleet of little clinics and offices around the country, especially in the major ports. I know up through the '70s, I think that was still in place, but I guess my question would be to my colleagues from the government, how much of that organization is still in place, and if parts of it are, would they be a possible help in this particular problem.

DR. VANDERPOOL: I think we need to move to our -- our reports, because of, you know, certainly this topic will be more pressing as xenotransplantation procedures are going on. Eda, do you want to comment?

DR. BLOOM: Yes.

DR. VANDERPOOL: Yes, please. I thought you were waving me off.

DR. BLOOM: All of you are aware of the National Xenotransplantation Database, which could conceivably be another way to collect this information, and I just wanted to point that out, and also point out that at the current time, the authority that we are using for this database comes from the IND

regulations, and so in order to be able to collect information from folks who are not under IND, for example, folks coming into the U.S. having received whatever, we'd have to figure out another mechanism by which to collect that information. But the database does exist, and it could conceivably be a repository for that.

DR. VANDERPOOL: Okay. I think we should go to our papers, because --

DR. GROESCH: Louisa had a comment.

DR. VANDERPOOL: Okay, Louisa, and we're going to our paper, because, as I said in my comment, in my note, this is an historic meeting if we can do a great deal on our reports. And we are going to have to get with that program, and decide when we are going to have those done, because we are going to get them done. Louisa.

DR. CHAPMAN: I just wanted to follow up on the discussion about whether you could work state by state to make the state of having had a xenotransplant a reportable disease. And I think Richard Kaslow is correct, that it doesn't fit the criteria, and probably the states would not be too receptive to that. However, I do want to remind people, or perhaps inform people, that the state health department really is the first -- if you are following a patient with an unusual health syndrome that you have any reason to wonder or suspect that it might be a sentinel event suggesting a larger public health issue -- the first place to go in exploring that is your state health department. And many of the investigations that CDC does come from calls that either come directly to CDC, and we send them back to the state health department, or come through the state health department to CDC about some unusual health event that causes someone to wonder if it needs a bigger investigation. An example of this is the hantavirus pulmonary syndrome outbreak where the calls that initially seemed to be coming in seemed to be seeing young people dying rapidly of some unexplained pulmonary disease. And is this something that needs a bigger investigation. The same thing happens with some environmental health exposures. Sometimes the decision is to investigate those. Sometimes the decision is that it's not necessary. But that is one safeguard that is in place for physicians when following someone who had a xenotransplant, you are seeing, in your mind, some unexplained physical manifestation, and you are wondering if it needs to be looked at in a more intensive way, that is your first line of discussion and referral, and that always is available to you, and it's always in place.

DR. VANDERPOOL: Okay. Thank you. The meeting places for the respective subcommittees will be across the hall for the State of the Science group, and the informed consent group will stay here, and we'll huddle somewhere in this vast cavern. And it's important to mention the two editorialists, the two people who will help us finish these reports are Deborah Shuman for the informed consent group and Dr. Elaine Richmond for the State of the Science group. Please note that these break-out sessions are open to the public. Also note that we should be back here, if you want to take a break, then it has to occur before we are due back here at 11:15 for discussion.

I also believe that each group should -- 11:50, sorry. And that each group should also bring your estimate of when the report will be completed and ready for the entire committee to look at and offer editorial suggestions. So we have lots to do, and we have some time to do it in. Thanks.

DR. GROESCH: Members, if you could hand in your taxi request forms to me, we'll get going on that.

DR. BLOOM: I just have a quick follow-up to what I said. I don't want anyone to think that the National Xenotransplantation Database is functional yet. I didn't want to leave the public with that. It is still a pilot.

[Breakout Sessions---transcripts are separate from plenary sessions]

Agenda Item: Plenary Progress Reports by Working Groups

DR. VANDERPOOL: I'll take the completion part first. Our group, after identifying about 10 issues and resolving what we thought would be agreeable to the entire committee, eight of those but having two left, decided that we would have a completed manuscript to all of our subcommittee members by April the 1st, and then by June the 1st we would have a document to send out to the entire -- we said that we would have a completed draft that would be changed from all the recommendations we heard that would be sent out to our committee, our subcommittee, April 1st.

DR. GROESCH: Just the working group or the full committee?

DR. VANDERPOOL: The working group. And then the working group would go back and forth with whatever it needed to, so that we would have a draft to the entire committee in light of all the suggestions of the working group by June the 1st. Is that too late? We could move up that schedule. What do you think? Let's move it to April 1st -- I mean, May 1st. What do you think?

DR. SYKES: Well, I would prefer -- I think there's going to be several rounds of changes, so what I had thought was that we could have -- everybody who has agreed to work on various sections could all have their work done and send it to Mary and have that all compiled by the middle of March, sent out to the whole working group, then everybody make comments on that within the ensuing two weeks, get those to Mary, and have those then sent back. And we're probably going to need a conference call at that point, because I think there are still going to be issues to rehash out.

DR. VANDERPOOL: We're talking conference call, too.

DR. SYKES: I think June 1st would be more realistic for completion.

DR. VANDERPOOL: You think June 1st rather than April 1st?

DR. SYKES: No, March 15th for the work that people promised to do, but June 1st for a final document.

DR. VANDERPOOL: A final document sent out to all the committee?

DR. SYKES: Yeah.

DR. VANDERPOOL: So we're agreed, June the 1st will be when both groups have their finished products to be able to send out to the other half of the committee, so each group will be happy with what it has and we'll send out the document for the committee. I think that should mean that by July 1st or before, we should have finished documents. Mary, are you keeping in contact with us as to whether we need to do things sooner than that or not? Okay.

So a quick review of what we went through. We identified 10 different topics that we ought to deal with. Most of you won't be able to make out the scratchings that I made on the flip chart, but the first had to do with the question of ending the study early, making people seem to have to pay out-of-pocket expenses for any cost of a sponsor's pulling out of its responsibilities, its sponsorship of the project. And we changed that where that would be -- it would be possible that people would need to pick up their own health care expenses, but we certainly changed the wording where it wasn't as, quote, Draconian as it was

in our first draft.

Secondly, we scratched family members throughout. We're just going to use the word "intimate contacts," and we clarified by going directly to the guidelines what is required of intimate contacts. And basically it has to do with their being educated and then not giving blood products. We're going to make sure that intimate contacts are not -- the requirements for intimate contacts are not confused with the requirements of recipients themselves, which are very different.

We talked about the need for safety regarding the use of contraception, we talked a good bit about the notion of testing for comprehension, and decided that we can't really test for comprehension. We can press for education -- for the team, the consent person's assuring comprehension as much as possible, but to require comprehension, to test comprehension, we thought for people who were often compromised physically, and even in terms of their strength and rightfulness was asking too much. We had a sentence to the effect that those should ensure, if at all possible, that the patients, respective subjects, did comprehend the information, but not to require testing of it.

We did address the idea of how the consent form that we now have in here, the model consent form, should have a paragraph before it actually -- actually, a paragraph just before the consent form starts to the effect that the consent form that follows would vary differently from consent forms, depending on the nature of the xenotransplant. And we mentioned expressly, for example, those who receive human tissues, human skin cells that have been grown off of mouse layers would likely have sections of the consent form to vary from the one here. So we made sure that those exceptions were recognized.

We also talked at some length about what ought to happen for medical personnel, and again we turned to the guidelines themselves and upheld the guidelines with respect to the need to educate medical personnel, have a program of education for personnel in medical centers where xenotransplantation procedures are being done, and how also these personnel would need to supply sera. Actually, the PHS Guidelines say during the process of 50 years. We say that. But they will have to supply samples.

So we said that they would need to have an educational program, that they would need to give samples, but we again didn't confuse what the medical personnel are required to do with what recipients are required to do.

The next issue that came up here, though, was a new one, and Sharon was really articulate about it and brought it, I think, to clarification; namely that we really haven't addressed anywhere in our document the sort of what we might call U.S. Xenotourism issues, namely what about all the hospitals where xenotransplantation procedures are not being done. That's the greatest number of hospitals. What kind of educational programs should they have? And, of course, there's not a great need for that, given the limited number of xenotransplants that are going on, but we expressly will mention that, and probably in our recommendations, that plans need to be made for the education of medical personnel throughout the United States with respect to special precautions that would need to be taken for those who had been the recipients of xenotransplants.

The two issues we didn't talk about are not minor. One has to do with re-thinking the child exclusions, and the other with the extent to which mentally incapacitated, or at least not fully competent individuals, would need to understand the consent form, and whether exclusionary criteria should be mental capacity. We simply ran out of time on that, and so we'll need a, what do you call it, conference call -- my neurons are slowing down the more I eat. We'll need a conference call about that, and we certainly, with all that we did this morning, including these two issues, will take the full committee's suggestions into consideration and hope to arrive at a document that fully represents everyone in the group.

Any questions from the state of the science members or any comments from the informed consent -- those on the informed consent subcommittee that augment and/or correct what I've summarized?

DR. SYKES: Could you just clarify what changes you made for xenotransplants that were just from cells that had been passaged from mouse feeder layers? How does it differ?

DR. VANDERPOOL: On which issue?

DR. SYKES: You said that you had a different consent for recipients of cells that had been passaged on to the xenogeneic feeder layer.

DR. VANDERPOOL: Actually, on page 18 --

MS. SHAPIRO: In two places. One --

DR. VANDERPOOL: On page eight, at the end of the first paragraph, we took the sentence which begins with "obviously," deleted "obviously" and said, "The actual headings and specific content of a given consent form will vary from this format depending on the particulars of a given xenotransplantation protocol." Now, what was this other sentence we added?

MS. SHAPIRO: For example, all of the consent elements in the following four may not be applicable to an individual such as one who will receive human skin cells grown on mouse feeder layer cells or his intimate contact. That's one place.

And then we were also going to have kind of a disclaimer when we get to the children and the incapacitated adults. This is all still in formation, but to the extent that there may be a xenotransplant that may be appropriate, it may be one like that. And so we kind of allude to that. At least that's what we're thinking now.

DR. VANDERPOOL: In other words, Megan, we just say we're giving you a model consent form, but it doesn't apply to everyone, and we're trying to be specific about the way it doesn't apply.

MS. SHAPIRO: By way of one example.

DR. SYKES: I just wonder if it might be good to add a bit of explanation about what's different about that type of xenotransplant and why there is less concern in certain areas. It's a well characterized feeder cell line that's being done for 20 years or whatever, but I think it might not be transparent to every reader why you're pointing that out. Now, the guidelines are the guidelines.

MS. SHAPIRO: My own reaction to that is that there are pluses and minuses. The plus is that we could really say what we mean. We would need help, I think, from your group to do that well.

The minus is that there may well be other examples, and the more you kind of highlight this one particular situation, there may be the implication that this is the only time when you could do a way with --

DR. SYKES: Maybe it would be better not to point out that particular example, and just say it in a generic way.

DR. VANDERPOOL: One of the problems, Megan, that we did talk about briefly was that, okay, so what on the model consent form we have would we be able to drop for patients with a different population. And to expand on that and give examples of that would require a number of paragraphs to

explain what the exceptions might be.

Furthermore, anyone who receives any xenotransplant product, according to the federal guidelines, according to the guidelines we now have, not the regulations, have to go through everything we have on the consent form. And so I think it would be much more up to the FDA to be able to tell researchers where they could deviate from the guidance that they had been given.

MS. SHAPIRO: Can I ask Megan one question? If we don't include the example, we would be left with the sentence as is, "The actual headings and specific content of a given consent form will vary from this generic format depending on the particulars of a given xenotransplantation protocol."

So do you think it's not helpful to point out one blatant case where it might vary?

DR. SYKES: Yes, I think it's not helpful and confusing, and you're probably better just to leave it with that one sentence.

MS. SHAPIRO: Okay.

DR. VANDERPOOL: Megan and anyone else on the state of science committee, by all means we encourage you -- not just feel free, but we encourage you to send any wording or suggestions you have about our draft and how it should be changed. That's what we're after, something representative of everyone on the committee. We tried, as you can see, the best we could to list and then deal with what we heard as any problems from the committee, but we could have missed something. And if we did, then let us know. Send those to Mary, who will send it on to us.

DR. ALLAN: I don't know how this is going to work, because one of the things you're going to tackle, again, is the incapacitated individuals. And so when you go back and you do your writing and you just have your discussions, when does it get distributed to the whole group? Again, is that like June 1st? Is that when we'll first be able to see it?

DR. VANDERPOOL: That's what we're saying, yes.

DR. ALLAN: That's the first time we'll see it, so it may go back to you again because people are going to have some questions and issues.

DR. VANDERPOOL: It could. What we're going to try to do is take the comments from the entire group and work --

DR. ALLAN: Then that would mean it would be after June 1st?

DR. VANDERPOOL: No. We're going to incorporate in our manuscript whatever changes our subcommittee believes should be made in light of the broader discussion yesterday, and then what we come up with will be sent out June the 1st. And you're exactly right, there may well be some of you who think that we haven't done enough or we haven't said it right, so after June the 1st both of our subgroups may well need to make a few other additional changes. And if so, then we make them and we try to get everything done by -- don't you think July the 4th? I mean, by July the 4th I think we ought to have our reports done. Does that seem sensible?

DR. SYKES: I think so. It means that we will have to give people a deadline for comments after receiving the June 1st document, and I think two weeks is a reasonable time at any stage to give people to give comments.

MR. SWINDLE: Mary, could you clarify something? Because I know there are several of us confused about the term of the committee itself plus the term of the various members on the committee. And I remember that the committee was about to expire by the time we had our first meeting, and then things got fuzzy after then. And I really don't know where we stand.

DR. GROESCH: Well, the charter is only ever signed off on for two-year periods, and the first two years of the charter included time that was spent forming the committee. So by the time that the first charter ended, we had only met, like, once or twice. And that charter was renewed for two more years. The end point of that is July of this year.

And because it's a new committee -- normally members are appointed for four-year terms, but when the committee was first formed, so that in four years everybody doesn't come off and get replaced, we stagger the terms. So we had some one, two, three, and four-year terms, so that every year about a quarter of the committee rotates off. But because of the timing, that we were just starting to develop the reports and it would have been very disruptive to change members midstream, we did get special permission from the department to extend the committee's terms so that we could get our reports done. And we had said at the time a finish date of spring of this year. So right now our members' terms have been extended.

Now, you did ask about the term for the committee. The charter does come up for renewal in July, and at this point we're waiting to hear what the department's wishes are. I know that we've all heard about that the administration has been taking a careful look at all of the advisory committees, making some changes as they desire. Our committee is being reviewed with a lot of the others, so we're waiting to hear what the decisions are, but we don't really know right now.

So I think that we need to certainly get as much done as we can, and as soon as I know something, we'll pass it on to people. But our current members are extended for right now for at least until the end of our charter.

MR. SWINDLE: So the current members and the current committee all expire July 1st?

DR. GROESCH: The charter expires, unless it gets renewed. And we should know soon whether it gets renewed or not.

DR. VANDERPOOL: And Mike, this is pro forma for the charters of such committees. So the fact that we have a sunset clause doesn't mean the sun will rise again, but it means that we're not the exception. We weren't appointed in *propa tieri*, but rather with the sunset clause, and so we'll just hope that it continues.

But I think one of the neat things is that everyone who began on the committee still is on it, and that one of the reasons why I think we all ought to, with all due diligence, complete these reports by the 4th of July is so in case something did happen, we would have legacy in life. I'm not worried about that right now, but who knows. I'm not the one who is on the inside enough to have enough information to get worried one way or the other.

DR. CHAPMAN: I would like to suggest something to consider for your process. As I understand it, the plan now is that by mid March, the rewrites from this section will be finished and sent to Mary to be sent back out to the two separate groups - the informed consent group, the state of the science group - and you have a plan to finalize those two reports by the 1st of June, at which point they'll be sent to the entire committee with a pretty short turnaround time, given that people may be traveling or have other deadlines to put their comments in.

I'm wondering, and this is just a suggestion, that if perhaps when you get the individual rewrites at this point, instead of sending them out to the two subcommittees, you want to send all of them to the entire membership of this committee so that you have the opportunity to get feedback earlier and incorporate that into your second revision prior to June 1st. Just a suggestion.

DR. VANDERPOOL: I like that. In other words, instead of having all the changes made for our committee by April 1st that only go to our committee, send our report to everyone April 1st. I like that. And that way we can be playing with a full deck from there on out and hope to get the changes approved by everyone considerably before the 4th of July.

Does that agree with you-all? When you-all feel comfortable with a draft, your next draft, why not send it to everyone, get the feedback of everyone? We've already heard a lot of comments from each other, so why not start sending things out to the whole committee once the subcommittees get something they feel better about?

DR. SYKES: My only worry about that is that the whole SACX didn't sit in on the working group discussion that we just had, and so some of the changes, you know, if they're seen section by section, they're going to be seen out of context. And I think I would prefer to have a whole document put together by our working group before it goes to the whole SACX.

DR. ALLAN: I would agree with Megan. And the reason for that is if you had sat in on our group discussion, it was brutal in terms of the kind of rewrites we're going to have to do. And so we would hate to take that first draft of rewrites and send it out to the whole committee, when I think it would be better to go back to our working group to get a second go at it before it goes out. So how we do that and what the time frame is, I don't know.

DR. GROESCH: Well, do both groups have to have the very same schedule? You know, maybe if you need to stagger it a bit, that will ease up on the review time for people anyway.

DR. VANDERPOOL: Yeah, we might stagger it more. How many people on the subcommittee for informed consent would be comfortable in sending our April 1st draft out to everyone instead of just our committee members? Any objection to that?

So we'll send our rewrite to everyone, hopefully shortly after April Fool's Day, and when you-all feel comfortable with the more extensive revisions you're requiring of each other - indeed, the brutal revisions - then send it to all of us.

DR. ALLAN: So in terms of what we need to do in our subcommittee or whatever it is, the state of science, when are you comfortable with us getting a rewrite in this next go around? Were you saying March 15th? Is that what you would like?

DR. SYKES: Right.

DR. ALLAN: Okay. So March 15th --

DR. SYKES: Every section.

DR. ALLAN: -- all the sections to the working group.

DR. SYKES: Right.

DR. ALLAN: And then we'll send that out after it's edited, it will go back to our committee members. And then the next time period would be when, to go out to everybody?

DR. SYKES: How about a whole document by April 15th to everybody, and the conference call to discuss that two weeks later. And then we'll have something ready for the whole SACX.

DR. ALLAN: So it will go out to the working group March 15th --

DR. SYKES: Sections March 15th.

DR. ALLAN: Have to come in, and then they go back to the working group the 15th. That's what you're saying, the 15th of April?

DR. SYKES: Distributed March 15th, get your comments to the individual via Mary, say by April 1st, two weeks. And then by April 15th, have your revisions to Mary that she will put together into a single document that will go back to the whole working group, and then we'll all read it and then we'll have a conference call for any final changes. Then we can make those changes and extend it to the whole SACX.

DR. GROESCH: And when do you want to have it out to the whole group?

DR. SYKES: We'll shoot for sometime before June 1st, but June 1st will be the very latest.

DR. VANDERPOOL: I think this is great for us to be agreeing to and committed to these deadlines. I mean, that would be one of the wishes I had for our entire meeting, and it's there. We've done it. So I think we should feel really, really good about that. It's been an incredibly constructive meeting.

In the meanwhile, we've given you an overview of what our committee did together. We sipped tea and ate crumpets while we talked, but I understand you-all used whips and chains. So could you give us an insight as to what happened across the hall?

DR. SYKES: All right. I don't know if we need the board. We tried to go through the whole thing in order, starting with the introduction, and we spent quite a bit of time discussing what we want to be in the introduction, how we want to open the document, and ultimately decided on a definition of xenotransplantation at the very beginning, and a second sentence - two sentences, really - to try to make it understandable to the layperson.

And then we talked a lot about the structure of the section, and we overall liked the structure of the first two sections, but discussed ways to really rewrite them in a more sort of comprehensive and hierarchal way, without so much emphasis on particular examples.

And then we had discussed a framework for the sections, how to lead from current strategies to xenotransplantation and other up and coming strategies such as stem cell transplantation, et cetera, and I think we've come up with a framework for that. So there's quite a bit of work still needed on this section, and I think we have a lot of specific and general suggestions that will be incorporated.

The section on the science of xenotransplantation, we talked about whether or not the section on the scope of xenotransplantation belongs best where it is or at the very beginning of the document, and we decided to leave it where it is, with a distilled version in the very first two sentences at the beginning of our section.

And then the really important change will be the addition of bullet summaries in lay language at the end of each individual section.

then we had a lot of discussion about the section titled Advances and Impediments, because once again, we don't all agree on where to go with this, on how much to recommend to the government or to the Secretary about government infusion of funds into xenotransplantation.

So we went back and forth on that, and I think what came through is that the document as written doesn't make a compelling case for government efforts. And that's not to say that we've all given up on the idea that we should make such recommendations; in fact, I'm going to make an effort at sort of rewriting the points in a way that I hope will be more convincing. And Dan and I, who are not completely in agreement, are going to go back and forth on this section.

It was also pointed out that it's not a forceful -- it's not a meaty section in the sense that our recommendations don't come across strongly, whatever they are, so I think we need to work on that. So I think those were the major issues in this section of the document. You can go for the infectious disease.

DR. ALLAN: The only thing I think was to summarize each section in bullet form.

DR. SYKES: I said that.

DR. ALLAN: You did say that. Okay. And the science writer will work with us on some clarity issues that you guys were worried about in terms of being able to understand the document. At least understand some of it. So hopefully that will get worked through.

The infectious disease risks was fine the way it was, so we're not going to change it. Just kidding. It was excellent. It was the best thing I read. Mary pointed out that there were two or three paragraphs missing from the intro of this section and we lost it and I'll get it back in there. It wasn't deleted for any reason. So we'll work with that. And we need bullets, summarize bullets for each of the sections. There's some discussion that it didn't flow very well or wasn't clear, so we're going to work on that, maybe sentences in each section to help with that.

Another major point was in the section on page 22, porcine infections and potential pathogens for humans, that this section needs a lot of work, and based on the recommendations from the whole committee, that we're going to try and merge the control measures in with diagnostics in the porcine infections. So we're going to try to make this thing work.

We also discussed, which we hadn't discussed before, which is that we needed something to address other species. So we're going to have a new section that's going to address other species and potentially their role in terms of feeder layers, embryonic stem cell, tilapia, other things that we hadn't really even covered, a long with general principles and also the fact that each individual source may have a distinct risk. So we're going to tackle that as well.

The regulatory surveillance end of it, we sort of tabled that yesterday. We started to talk a bit about it this morning, and we decided that it's something that the whole committee is going to have to tackle. So the issue there is probably not going to go into this document in terms of what our recommendations are in terms of any kind of regulatory or surveillance guidance from this committee. I think it's probably something we're going to need to tackle in the future. And we're going to put references in.

DR. SALOMON: It was excellent. No, I mean basically we picked up -- I think the conversation that we had here before the break was superb, and my job is to go back and add some of the recommendations that evolved from Dr. Zucker's comments and the discussion that Dr. Anthony Hayward kind of triggered in us by bringing up some of these issues.

So I'm going to try to put a little more meat into this -- I think overall the theme came out that we feel that, all right, this is an advisory committee, what's the advice. I think maybe there's a little bit more there, but not enough. And that's stuff we'll work on.

DR. VANDERPOOL: Other comments? Sounds like you-all are pressing forward and have a very strong plan of accomplishment in mind.

Well, shall we talk about the subject of future meetings or shall I just close out with some comments?

DR. GROESCH: I think future meetings will be helpful once we know more about the fate of the committee.

DR. VANDERPOOL: I don't like that term. Mary said once we know about our fate we'll be able to talk about future meetings.

Well, this has been an extremely productive meeting. There is a powerful symbiosis between members of this committee and the governing agency. My greatest hope for the meeting was fulfilled, namely that we would end with specific time frames for the completion of these two reports that are going to be real contributions, and I think each will be impressive in its own right.

So with the background of writing poetry and being on the stage a time or two, I wish for each of you the goals that Alfred Lord Tennyson voiced in the last stanza of Ulysses, namely that each of you will be able in your own ways and in your own lives to seek and find and not to yield. Thanks so much.

(Proceedings concluded.)