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PROCEEDINGS

(8:15 AM)

**DR. VANDERPOOL:** Let us begin our meeting. This morning we have two presentations by Lou Marzella and Louisa Chapman after which we will have a brief period of discussion within the Committee and the membership, and we are moving the public comment section up to follow that discussion by the SAC members.

After that we will do two things to end our sessions. First is to talk about the importance, the bearing of what we have learned over the last 2 days and as I mentioned yesterday that will be expanded to include the scientific and clinical dimensions of what we have learned along with ethical, social and legal considerations.

What I want us to do is I will say a couple of things in preparation for that. At this point we will get a flipchart, and what I want to do is go around the room including all the SAC members and ex officio members for each to say something about what you think the import of our discussions are, and as I said, I will make a couple of statements that you might want to work off of, expand, refine, refute or whatever about what we have learned, but I want us to be very candid and open and I am intensely aware of the fact, A, that we haven't had much time for exchange of opinion by Committee members and second that a number of the Committee members who are fully informed and capable of saying all kinds of things on topics that have been discussed have not spoken.

So, we are going to just simply go around the room and talk about that to see where we are on this day, almost day and one-half of discussion and then secondly we need to set the stage for future SAC meetings and deliberations and what responsibilities we have and again, I will initiate that with reflections on what we might and/or should be looking at and thinking about and meeting over in the future, but I want your absolutely candid and open remarks about what you think including again the requests and needs and desires of ex officio members on this Committee who are living with these issues day after day.

So, I look forward to these two discussions, in part brainstorming sessions and I have requested to have a flipchart put back here so we can register some of the points as we go along. So, to proceed right off the bat, our first presentation by Lou Marzella from the Center for Biologics Evaluation and Research of the FDA will be talking about the FDA requirements and recommendations for monitoring xenotransplantation recipients and close contacts.

Lou?

**Agenda Item: Clinical Monitoring in Xenotransplantation: Minimizing the Risk of Transmission of Infectious Agents. FDA Requirements and Recommendations for Monitoring Programs.**

**DR. MARZELLA:** Mr. Chairman, distinguished members of the Panel, ladies and gentlemen, good morning. It is a pleasure for me to be here this morning to talk to you about FDA

requirements for clinical assessments of xenotransplantation recipients and close contacts. My talk will be followed by a presentation by Dr. Louisa Chapman who will further expand on the rationale and specifics of the recommendations. The main concern that prompted the development of specific guidelines for clinical assessments of patients in xenotransplant trials is the risk of xenogeneic infections.

So, the first question to ask is what is the population at risk, and of course, in addition to the patients, the participants in the trial what is unusual with this type of product is that other contact populations are, also, potentially affected and primarily we are thinking about health care providers and recipients' family members and friends and of course, in the worst possible scenario there is, also, the potential for the community at large being affected by the xenotransplant?

So, what are the objectives of the clinical assessments and laboratory testing recommendations that the FDA put forward? Of course, the principal one is to detect the introduction and propagation of xenogeneic infectious agents in the xenotransplantation recipient and the concerns here are with the health and well-being of the recipient of the transplant as well as close contacts and of course the major public health aspect is to be able to in a timely fashion identify and prevent the dissemination of potential xenogeneic infectious agents into the general population.

What are the main components then of this assessment scheme? The emphasis is on lifetime periodic clinical and laboratory testing of xenotransplantation recipients, and there are two aspects to this. One is the archiving of specimens for evaluation for cause if particular concerning events occur, and the other is if you will an active process of assessment.

Another component which is standard for safety evaluation of any product is adverse event reporting and the FDA as you are all aware has specific requirements that mandate reporting of adverse events that occur either in the pre- or postmarketing period, and finally it is, also, important to have a database that is able to track recipients to maintain information on the patient's well-being as well as have a way of linking to the actual specimens that have been archived as well as to be able to link to information about the source animal that provided the xenotransplant.

Now, one of the requirements for ensuring that clinical assessments and testing will be adequate is that the study protocol should in detail list infectious agents and describe the tests and the testing schedule that will be followed. The protocol should, also, show the ability of the test to distinguish between similar agents of human and source animal origin, and I am sure that you have already heard about this particular issue. In addition particularly for uncommon tests the protocol should be able to indicate what the specificity, sensitivity and reproducibility of the test is.

Now, with regard to the collection and analysis of clinical specimens the clinical protocol should demonstrate the availability to the research team, to the study team of a state of the art virology and microbiology laboratory that has the knowledge and experience in isolation particularly of

unusual pathogens. These laboratories should be able to do viral cultures and they should have the capability of, also, developing new assays as required.

So, the testing for infectious agents is focusing primarily on active screening of clinically available specimens and these include serum, peripheral mononuclear cells or other tissues as available because of diagnostic tests and the focus, the initial focus is to focus on infectious agents which are known to be present in xenogeneic products and retroviruses such as PERV have been of particular interest. Another criterion for active screening is to focus on agents that are known to be pathogenic in the source animal and that are specific to the tissue type and to the species of course of the xenotransplant and the third criterion is, also, to focus on agents that are known to be able to infect human cells.

Now, in addition to this active screening if you will there is, also, a recommendation for cause diagnostic testing, and the focus here is to try to delve a little bit more deeply into any unexplained infectious, neoplastic or other syndrome in the xenotransplant patient that could be a clinical manifestation of a xenogeneic infection, particularly a viral one. Relevant to this is, also, the recommendation for the evaluation of health care workers who experience an exposure that might be associated with the risk of transmission of a xenogeneic infectious agent.

With regard to passive screening then for xenotransplantation recipients the focus again is on periodic lifelong collection and archiving of clinical specimens as well as clinical records and key here is the ability to link between specimen archives, clinical records and source animal records. With regard to health care workers the recommendation right now is to obtain at least a plasma specimen which is archived at baseline meaning before the health care worker becomes involved in the care of these particular patients and of course storage and retrieval of personnel records is, also, important.

Now, with regard to the specific specimens that are recommended for archiving for use by public health authorities in the case of suspected occurrences of xenogeneic infection the recommendations are to collect citrated or EDTA anticoagulated plasma, 3 to 5 aliquots, half a ml as well as viable leukocytes, 2 aliquots, 1 times 10 to the 7th cells and specimens, also, that are removed from transplant, from a xenotransplant either post-rejection or post mortem should also be collected and sampled. In case of autopsy, the guidelines recommend an autopsy with a series of samples obtained from the xenotransplant, from major organs either related to the xenotransplant or to an unexplained clinical syndrome. There are specific recommendations to embed samples for histopathologic assessment, snap freezing of samples and cultures also should be performed if necessary.

The guidelines also have specific recommendations about the collection and archiving of clinical specimens and because of the belief that a xenotransplant-related infection would manifest primarily in the acute period, a more concentrated early phase of sampling is required with sampling then becoming progressively less frequent unless indicated. So, pre-transplant it is recommended that two samples 1 month apart be collected, that additional samples be obtained at and shortly after transplant and then post-transplant the recommended frequency would be at 1 and 6 months, then annually for 2 years, then once every 5 years.

Tracking recipients is, also, going to be critical with follow-up clinical assessments and fortunately this is particularly for major life-saving organs this is likely to be relatively easy to accomplish. The important critical information would be the status of the xenotransplant itself, any significant new morbidities, hospitalizations and obviously death reports. With regard to the maintaining of clinical records the recommendation is to maintain records as well as biologic specimens for 50 years and this is based on the latency period of known human, certain human pathogenic persistent viruses as well as precedents established by other health authorities.

Now, if a xenogeneic infectious agent is detected in a clinical sample there should be a plan, a prospective plan for distinguishing infection from a false-positive test. A critical aspect would be of course to determine the infectivity of the agent. Trial should be suspended and all parties notified and the focus then would be to provide acute medical care and counseling of participants and close contacts as well as to take public safety measures as necessary. The specific recommendation if a xenogeneic infection is suspected is to notify FDA immediately, if a non-xenogeneic causative organism is not readily identified and immediately if a potentially xenogeneic causative organism is identified and of course in addition to the FDA there are provisions for notifying other health authorities such as the CDC and others.

In addition to the specific recommendations that were made in the guidelines there are, also, requirements by FDA regulations that have to do with reporting serious and unexpected adverse events. These should be reported as required on a 10-or-15-day basis and in addition the FDA regulations require periodic reports on an annual basis as well as for INDs as well as post-marketing. That is my talk. I will entertain any questions if there are any.

Thank you.

(Applause.)

**DR. VANDERPOOL:** Any questions for Lou?

Dan?

**DR. SALOMON:** So, Lou if an investigator wants to do a trial and comes to the FDA now for the required IND what exactly do they have to give you in documentation to assure you that they have in place a monitoring strategy to give you 50 years of samples?

**DR. MARZELLA:** What we are looking at this point is a description in the protocol. We are looking for standard operating procedures and as far as I know we have not done actual inspections to verify what actual back-up is available. I know that this is a –

**DR. SALOMON:** I am 48 years old, and I hate to admit it, but I just don't think I am going to be here 50 years from now.

**DR. MARZELLA:** One of the possibilities has been that of involving in addition to the principal investigator who may not have an academic half life which may be substantially shorter than 50

years, the thoughts have been to include the actual university or study center and there has, also, been some talk because of obviously the costs involved, also, of trying to obtain funding for a national archiving database, but I am not sure what the latest status of that is, but it certainly is a daunting task. This involves a lot of expense and a lot of follow-up, but I think we are clear that these specimens are necessary for evaluation of an unknown emergency which might occur, but I appreciate the fact that there are big concerns about the costs and about the practicality of being able to carry this out.

**DR. SCHECKLER:** Just to follow up on that, you mentioned that OSHA currently has a requirement that would require records up to 50 years and that there is some biologic plausibility to the 50 years. Would you explore those two hypotheses or underpinnings of the 50-year rule a little bit more for us? What are the specifics?

**DR. MARZELLA:** I cannot speak to the actual clinical –

**DR. CHAPMAN:** I can tell you the reasoning that went into picking 50 years when we determined something. It was the combination of OSHA, I believe OSHA's requirements currently are 30 years of record storage and then the known latency period for known persistent pathogenic human viruses including HTLV-1 which can cause leukemia after a latency of between 40 and 60 years. HIV has a latency of about 10 years, hepatitis B and C which can have latencies measured in decades and those were the things we were looking at in picking 50 years as probably a reasonable period of time that was possible to store and would probably extend long enough to allow persistent latent viruses to begin to manifest clinical symptoms.

**MR. BERGER:** Lou, to add on to Dan's question now I am curious not to the new INDs but the FDA has already approved INDs and monitoring systems are so important. What has been approved so far and what have you required for INDs that are already going on?

**DR. MARZELLA:** All of these recommendations are applied to all the INDs. There are no approved products as of yet, xenogeneic products but there are a number of products under investigation and these guidelines are being taken seriously and are being followed by all the investigators.

**MS. SHAPIRO:** I just have another cost question I guess. You talked about how if something were to happen that medical care should be given to the affected person. Does the investigator, also, have to in a proposal commit to that lifelong care for the infected individual and contacts?

**DR. MARZELLA:** I don't think that -- there is no specific provision for financial responsibility. I think that in the consent form for instance there are general statements about providing for acute care, but we don't have any specific, we haven't specifically thought out about whose financial responsibility it would be. So, whatever guidelines are applicable to other adverse events that occur as a result of other products would probably apply here as well.

**DR. KASLOW:** I am wondering if there are guidelines in place for specific protocols, INDs. Are there forms and protocols and other written information that are in existence that we could

have access to?

**DR. MARZELLA:** Yes.

**MR. FINN:** Hi. I am on the Diacrin study Phase I, and I believe that they agreed to pick up my health costs related to any problems that may show up in the future.

**DR. MARZELLA:** Thank you.

**DR. VANDERPOOL:** Other comments? Just turn on your light and let us discuss without necessarily being recognized from the Chair.

**DR. GROESCH:** I had a question about the follow up on the health care workers. How long are they, well, I assume the responsibility is on their part to inform a physician if they notice any odd symptoms, but how long are they counseled to always think about this and to inform their physician, for the rest of their lives that they were involved?

**DR. MARZELLA:** Exactly, yes. I think that there are no specific recommendations for active follow-up by the health providers. It becomes a matter of education and of the health providers involved.

**DR. LUBINIECKI:** How many INDs have been approved under these guidances?

**DR. MARZELLA:** I need help. Do you know, Dr. Bloom?

**DR. BLOOM:** We have between 30 and 40 INDs. Of those not all of them are active. Some of them have been withdrawn. Some of them may be on clinical hold, but you have to remember the different kinds of xenotransplantation products that we discussed yesterday including the extracorporeal perfusion and including *ex vivo* contact of human cells with animal cells.

**DR. VANDERPOOL:** I have a question regarding the sampling. You said that samples will be taken from health care workers before they perform the xenotransplant procedures and then thereafter. Will samples, also, be taken from close contacts and will that be an ongoing sampling and a banking process, also?

**DR. MARZELLA:** Let me clarify? I think that the recommendation for the health care providers is for a baseline sample so that an acute sample if something is suspected could be obtained and compared to baseline. There are no specific recommendations about close contacts at this point other than involving them in the educational process and in the understanding of the risks.

**DR. VANDERPOOL:** One of my concerns about that, this is an ethical issue, but if one is a health care worker and has some particular form of illness that one wants to keep private then to take these samples raises a question about what if one discovers that there is some disease modality that may be embarrassing or otherwise to the health care workers; what is planned with

respect to any reporting of such information?

**DR. MARZELLA:** I think that this would fall under the usual province of disclosure for specimens that are otherwise routinely obtained for employment purposes, and this is not considered anything unusual in that respect. So, whatever guidelines and law apply to disclosure for that information would, also, be applicable in this case.

**DR. VANDERPOOL:** So, the privacy of health care workers will be assured? Will this be a commitment within the form they sign or their signature to take such a sample?

**DR. MARZELLA:** I must ask for help but the issue of asking for consent from participants, from close contacts was considered and I think ultimately discounted. So, at this moment there is no consent process involved. There is no consent giving by other contacts. There are strong recommendations for education, for awareness but it was felt that the autonomy of the participant in the trial was paramount and that it could not be abridged by having contacts, for instance, participate in the consent process.

**DR. CHAPMAN:** Your concern about the protection of privacy for health care workers with the request for banking baseline serum, this is a practice that is actually fairly commonplace in a number of industries where people are potentially exposed to hazardous substances. It is something that is done habitually at CDC. When you first come a serum sample is banked and for certain people with certain exposures periodically. The consent comes at the point that there is a need to test those specimens, and the consent is for specific testing not broad testing. So, there should not be any risk of abrogation of privacy related to anything other than the specific occupation associated potential exposures.

**MS. SHAPIRO:** But what happens if they refuse consent or if they agree and then there is a need to disclose to their contacts and they don't want that?

**DR. CHAPMAN:** We are in hypothetical grounds of my experience. I am not aware of -- when we have done studies, for example, with people who are occupationally exposed to non-human primates testing for primate viruses the results of those tests when they have been positive are disclosed only to the worker not to the worker's supervisor, health care provider or close contacts. They are advised. They are given our best advice about whom they should share it with, and we make it clear that we are available if they choose to talk to their health care provider or their family members or their close contacts, but the release of information has been between our testing and those employees or the people who were tested and beyond that it is their discretion who they release it to, the same as any other medical testing. Now, I cannot say that that is a standard universally in industry when these things are tested, but I believe it is.

**MS. SHAPIRO:** I would think that if you believed that there were risks to the close contacts and you knew that the person wasn't going to tell you couldn't live with that.

**DR. CHAPMAN:** We don't do that with HIV. I, in fact, by law cannot call up the spouse of someone I see in my clinic and say, "By the way your husband has HIV and I know that he

doesn't plan to tell you."

**DR. SHAPIRO:** And the law certainly is different elsewhere, both statutory and case law which makes it difficult for us.

**DR. VANDERPOOL:** The good news is we are really getting involved in the conversation and we are going to continue this with great fervor very shortly, but the other news is that we do have one more speaker, before we open it up for more extensive discussion and the public's input. This individual is a reservoir of experience and wisdom and knowledge about all kinds of things associated with infectious disease and xenotransplantation, Dr. Louisa Chapman, from the Center for Disease Control and Prevention on considerations in designing and implementing monitoring programs.

**Agenda Item: Considerations in Designing and Implementing Monitoring Programs.**

**DR. CHAPMAN:** Okay, I have an armamentarium up here to ensure I can talk. I want to start by saying that I am going to step back from specifics to sort of very general considerations that you should have in mind when you hear about these monitoring programs and you are trying to assess the significance of them and most of this will be very familiar to the virologists and most of the clinicians in the group.

When you talk about the general approaches to the kind of specific monitoring that Dr. Marzella was talking about you have people who are potentially exposed to something. You don't know what are your options for monitoring, and the first and most basic is simply clinical monitoring of the exposed individual looking for something unusual, a clinical pattern that you wouldn't expect to see. It is a combination of an astute clinician trained with pattern recognition with a patient who shows up with an unusual syndrome and this is the way in which most new diseases are first reported. It is what is called a case report, one report, one patient, an unusual pattern that hasn't been seen before.

The example I am using here was described by George Whipple in 1907. I think he was perhaps still a resident in pathology at the time. The disease is now referred to as Whipple's disease. He did an autopsy on a 36-year-old missionary who had an unusual pattern of migrating arthritis, cough, diarrhea, malabsorption, weight loss and enlarged lymph nodes in the abdominal region and he noted what would have escaped many people was silver staining, great numbers of what appeared to rod-shaped organisms in the mesenteric lymph nodes.

It was almost 100 years later. It was just last year in the year 2000 before this rod-shaped organism was cultured enabling the development of diagnostic tests for this Whipple's syndrome but in the intervening century Whipple's syndrome has been recognized over and over in other patients based on this acute recognition. Now, I should perhaps say that George Whipple was an extremely astute physician. By 1935, he was a Nobel Laureate for work completely unrelated to the disease that bears his name. So, his probability of picking this up might have been a little bit greater than any one of us in this room, no offense to my fellow clinicians.

So, this is the first line of defense. The strength is that it is a passive system. We don't have to go out and look for sick people. Sick people in and present to doctors. Doctors are trained in pattern recognition and pattern recognition doesn't require an ability to test. You don't have to know what you are looking for. You just have to recognize that something in front of you doesn't fit established patterns.

The weaknesses of course are that a new case or a new syndrome is rarely recognized on the basis of one case. It is rarely recognized in the absence of a pathognomonic finding, some finding that is specific for that syndrome and in Whipple's case it was these rod-shaped organisms that were silver stained or some kind of serendipitous clustering as happened with pneumonia among legionnaires in Philadelphia in 1976, when Legionnaire's disease was recognized; PCP pneumonia five gay men in Los Angeles in 1981 first recognition of AIDS; acute HPS in 10 Navajo patients, the significance of them being Navajo is that they all reported to the Indian Health Service the equivalent of one big HMO. They all got consulted on by the same ID group who recognized a pattern of things going on not just a series of individual cases and professional football team A on airline B, this refers to an outbreak that was worked up by the Minnesota State Health Department in 1989, cases of Shigella, diarrhea that resulted from probably contamination of sandwiches put together on the airlines.

Now, food-borne outbreaks are rarely recognized in association with airlines. In fact, they probably happen fairly often. This particular one wound up involving over 200 people on over, I think, 48 airlines, over 28 states, the District of Columbia and four foreign countries, but the only reason it was recognized as part of a syndrome is because the initial outbreak was on a plane that just happened to be transporting a professional football team, and a lot of people who knew about the outbreak may have made money on the bookies on the next game.

So, how does this apply to xenotransplantation? The first line of defense for monitoring here again is the long-term follow-up between the recipients and their individual physicians and a high index of suspicion for clinical syndromes that may not fit previously described cases. Now, the second line of defense is to augment that power of monitoring individuals by monitoring exposed populations and the advantage of looking at populations is it allows you to look at patterns of clinical disease on a population basis, looking for deviations in the pattern of disease distribution in the exposed population compared to unexposed population. The advantage is that this increases the power and the probability to recognize rare events. It is an increased deficiency but it is, also, some increased cost because it requires some monitoring system.

This can be powerful in two ways. The examples I list on the right are things that are recognized by a combination of VAERS [Vaccine Adverse Event Reporting System] surveillance systems for adverse events purported to be associated with vaccines combined with a large linked database system that allows actually testing that hypothesis. This can demonstrate associations as it did with swine flu vaccine and Guillain-Barre's syndrome in 1976, and more recently with rotavirus vaccine and intussusception but an equally important protection is that it can disprove suspected associations and these were publications in 1997 showing that there is not an association between pertussis vaccine and increased rates of insulin-dependent diabetes, in 2000 showing that asthma is not exacerbated in recipients of flu vaccine and in 2001 showing that

measles, mumps and rubella vaccine does not increase the risk for inflammatory bowel disease.

This is just an example of a surveillance system allowing you to monitor populations. The most effective surveillance systems are the simplest ones. This is one that CDC has run for influenza for I don't know how many years, many, many decades. One hundred and twenty-two cities in the report weekly the total number of death certificates filed and the proportion of those that attribute the underlying cause of death to pneumonia or influenza. This is charted against a seasonal baseline that you can see goes up every winter and down every summer of sort of the expected proportion of deaths due to pneumonia and influenza in the absence of a flu outbreak and when it exceeds that expected proportion for 2 weeks in a row CDC officially designates this as an epidemic of deaths attributable to influenza.

The raw numbers behind this are published in the MMWR at least when I was doing flu they were every week. Occasionally we consider discontinuing that and the people who protest in this country are the casket manufacturers because they look at these numbers to determine their goals for the next week, and in fact Spain has a very similar system to this but they go one simpler. They simply chart burials. When the burials go up above a certain amount they declare an epidemic of influenza, and it is just about as accurate.

So, you can have very simple monitoring systems of populations but they can provide some very powerful information. So, how does this apply to xenotransplantation? Our proposal for xenotransplantation is the US National Xenotransplantation Database which is sort of a hybrid system that is intended both to provide surveillance and then to also provide a database against which you can test. It is currently in the pilot stage, and there have been international discussions about the desirability of trying to develop a simpler international surveillance system probably through the WHO. That is still in the discussion stage.

Now, if you know what you are looking for, you are not just looking for something unusual and unknown, you can go to laboratory testing of exposed people and this can be a very powerful augmentation to clinical monitoring or syndromic surveillance of populations but it has some limitations. You must know what you are seeking before you can test for it. Well-validated commercial assays may not exist for what you want to look for. The development of those assays may not be immediately possible. It may be dependent on discovery that hasn't yet occurred and there are some limits of the confidence you can place in the testing results.

One of the moments in my first year of medical school lectures that I remember most clearly is the moment in my microbiology class when it was explained to us that if we were to see a patient who had gonorrhea we could do a bacterial culture and there was an 80 percent probability it would be positive. It was tremendously shocking to me to realize you could go to your doctor. You could be tested and there could be a 20 percent possibility the test wouldn't show what was wrong with you. So, I am going to go through each of these points and I am going to talk in very general terms. I am going to try to cover like about a semester of a public health course in a few minutes here. So, I am not going to go into any of the math, and I am going to ask you to take some things on faith, but if you have questions I will be happy to provide documentation later.

The first principle that you must know what you are seeing, hemorrhagic fever with renal syndrome, Hantaan virus epidemics were recognized in epidemic proportions in UN troops in Korea in the 1950s and they were of great interest to Western military medicine and a huge amount of systematic research went into the cause of this syndrome which actually is described in ancient Chinese texts. For 25 years there was no ability to identify this syndrome other than clinical pattern recognition. There was no test for the syndrome.

In 1975, the Hantaan virus, the causative agent was cultured not from sick individuals or autopsy specimens from humans but from the rodent host and once that was cultured it was possible to develop serologic assays to recognize a broader expanded pattern of the disease and milder cases to recognize cases early on which led to the ability to develop treatment, but there was a huge amount of military interest in ascertaining the cause of this disease for a quarter of a century before the first step was made in ability to diagnose it.

Likewise, 1976, Legionnaire's disease outbreak in Philadelphia infection was suspected at that time. It took only about 6 months to culture the new Legionella bacterium but once they did they could go back and look at two previous outbreaks that CDC had investigated, Pontiac fever in Michigan in 1968 and an outbreak in St. Elizabeths Hospital here in the District in 1965. Unable at the time to ascertain a cause for those once Legionella bacterium was cultured they could go back, apply serologic assays and recognize that Pontiac fever and the St. Elizabeths Hospital outbreak were both variants of Legionella bacteria pneumonia outbreaks at times when testing was not available.

The second problem is even if you know what you are seeking there may not be any well-validated standardized commercial assays available for two reasons, one if it is a new agent there aren't going to be assays developed and two is even for classic, well-known infectious agents of animals there often has not been a profit motivation for the development of standardized assays. So, there often either are not assays available or there are assays available but they aren't as reliable as the ones for human health. When you run into this situation there is a solution which is that you can develop investigational assays as has been done for PERV, but the problem is that that requires a substantial investment of time, money, expertise, and that requires a great deal of motivation and in addition development may be dependent on discovery.

Science is a very powerful tool, but it is not an all-powerful tool. An example of this presently is that we have no test for prion disease. We don't have a serologic test or a blood test you can apply to tell if someone has mad cow disease and there has been again a great deal of effort going into an attempt to develop such assays for many, many years but nobody has succeeded.

Whipple's disease is another place you can look at this process. In 1907, Whipple described the first case. He identified what looked like rod-shaped organisms with silver staining of tissues at autopsy. In 1949, there was a new kind of a stain, PAS stain developed and when that was applied to autopsy specimens from Whipple's case it was recognized that there were these unusual granules and macrophages in that disease. That allowed people to recognize a wider spectrum of disease than had previously been understood to be represented by Whipple's disease.

In 1961, there was another advance, electron microscopy. When this was available they could go back and actually identify these rod-shaped organisms as bacilli and that led to an ability to treat this disease despite the fact that we still didn't know what infectious agent caused it. It was just empiric attempts at using courses of antibiotics with some effect.

In 1992, using genetic techniques, PCR, the bacteria was actually identified by its genetic structure which led again to an ability to test and define a wider range of the disease but it wasn't until the year 2000 that *T-whippelii* was actually cultured allowing the development of serologic assays. Serologic assays are assays that test for antibodies. They test for the host reaction against the infection and it is usually the sort of most basic first line of diagnosis used.

So, my point is the cutting edge of diagnostics is a moving target and further that the starting block at any point in time for different agents differs by agent. HIV was first identified in 1983. PERV was first identified in 1970, and yet in 1996 or 1997, when we became concerned about what the significance of PERV might be for xenotransplantation there were no diagnostic assays available for PERV because there had been no motivation for developing them. There were very sophisticated assays available for HIV because there had been huge motivation for developing them.

Now, this is the part where I am going to skip the math. You have to either take it by faith or ask for documentation later. Okay, so, even if you know what you are looking for and you have well-developed assays there are still some limits of confidence you can put on the results of those testings. Diagnostic tests and results are not absolutely 100 percent guaranteed to give you right or wrong answers for a number of reasons. When you are looking at serologic assays you are looking at antibody reactions of the host against the infection. You can get cross reactivity responses between different organisms and this can be an advantage, and it can be a disadvantage. The completeness of the diagnostic criteria for different assays can vary and that can lead to incomplete testing and confusion, sometimes in the literature a misattribution of causes of disease. The sensitivity and specificity which is sensitivity refers to how likely it is if you have got an infection your test will pick it up. Specificity refers to how likely it is if you don't have the infection your test will not falsely identify you as being infected.

What you ideally want is a test that is 100 percent sensitive and 100 specific, and there has never in the history of mankind been such a test. It is always a trade-off between the two and you always increase one at the expense of the other. The extent of validation, how often has the test been used and how many different sets of hands and against what kinds of specimens and then the predictive value of testing result, this is a hard concept for people, but it is a very important one. No matter how new an investigational your assay or how well developed and how well validated when you apply it to specific individuals in a population how predictive the result of that test is of reality, in other words how likely that a positive test result actually predicts a true infection and not a false signal is going to be dependent on how common the disease is in the population that you are testing and I am going to go through each of these in a little more detail.

Okay, cross reactivity, this refers to the ability for a test designed to pick up antibodies against a specific infectious agent to actually register a false-positive result because of cross reaction with

antibodies raised against something else. This can be an advantage. In 1993, hantavirus pulmonary syndrome outbreak, the first clue that the cause of these mysterious pneumonia deaths was a hantavirus was that the serum from patients reacted in a pattern against serologic assays for a variety of other hantaviruses without quite a typical reaction to any of them, and that led to the molecular testing and the rapid identification of a new hantavirus as the cause of the outbreak. So, there it was a benefit. It can, also, be a disadvantage. For example, it is commonly known clinically that people with certain rheumatologic conditions will have false positive tests for syphilis which can lead to some difficult situations for medical students who don't understand that.

With testing for zoonotic infections antibodies to human herpes simplex viruses can cross react with antibodies to monkey B virus and that can create some difficulty in sorting out the cause of encephalitis in potentially exposed people. So, cross reactivity can be a benefit. It can, also, be a disadvantage, but it can complicate testing. The next issue is the limits of confidence you can place dependent on the completeness of diagnostic criteria. This is always an issue when you are developing investigational assays and when you are hearing about reports of testing done with investigational assays that are not commercial. One of the things you need to have a limit of alertness to is how complete are the criteria; is it based on one criteria, two criteria, three criteria? The medical literature is full of reports that are later retracted, Grave's disease caused by foamy virus infection turns out not to be true. Later people cannot replicate the results based on incomplete criteria.

Now, these are a series of blood samples drawn from a laboratory worker who became infected with simian immunodeficiency virus. These are by date starting at the earliest going to the most recent. These are positive controls. For those of you who aren't familiar with these kinds of tests let me just say that each of these dark bands on this positive control is a potential protein in the simian immunodeficiency virus that the exposed person could react to. Now, how much confidence do we have that this person is actually infected with simian immunodeficiency virus? Well, quite a bit because we have multiple diagnostic criteria.

We have initial reaction to this band that persists over time and grows stronger over time. We have the same thing here. This doesn't really grow stronger over time. It is pretty consistent. Here it grows stronger over time and furthermore as time goes out from the infection we begin to develop reactions to additional proteins that are also consistent or present in the simian immunodeficiency virus. So, we have a great deal of confidence that this is a true positive even though it is an investigational assay because we have got a pattern that persists over time. It grows stronger over time as the person is more exposed and we develop a pattern of reactivity not to one or two proteins but to four separate proteins. They remain specific. They all persist over time, and they all get stronger over time. Often investigations that are reported with serologic assays for new agents depend on reaction to only one or at most two proteins and that has led to some confusion in the literature.

Okay, sensitivity and specificity. Sensitivity again, how likely is this test to recognize a true positive when someone is infected? Specificity, how likely is the test to recognize a true negative; how likely is it to give you a negative result when the person in fact is not infected, and

the thing you need to understand about these is that there is always a trade-off between. You increase one at the expense of the other and how this is dealt with in actual practice I am using an example of HIV where it was terribly important to pick up infected people but also terribly important not to falsely label people with this devastating disease. The way that has worked out is they use two different tests, an ELISA and a Western blot. The ELISA is a very, very sensitive test and the first time they run it it is probably going to capture everybody who is truly infected, but it is also going to give you a positive result on a whole lot of people who are not infected.

So, the standard of testing is you test with an ELISA and you pick up everybody who is infected and a whole bunch more people. You test again with an ELISA. The probability that people who aren't infected will repeatedly be positive on an ELISA is smaller. So, you eliminate some of your people there who are not truly infected but you are still going to have a whole lot of people with serially positive ELISAs who don't have HIV. Then you follow that up with a Western blot test which is a very specific test, but a more time consuming and expensive test that weeds out most of your false positives and what you are left with is a group of people who tested positive to ELISA once, positive to ELISA a second time, positive to a Western blot. Most of those people will truly have HIV infection, but if you apply this series of testing to a series of nurseries you are going to turn up if you test enough people some positive reactions in people who are not infected with HIV. There is just no absolutely completely 100 percent sensitive and specific testing regimen in the history of mankind.

Okay, the question of validation which the FDA referred to, what this really refers to is how often has this test been used in how many different sets of hands and against what different kinds of controls, and I put here a comparison between standard commercial assays and investigational assays. Commercial assays have usually been tested against true positives and true negative controls by which I mean they have been tested against people who actually have the infection and are known to have the infection and people who actually don't have the infection. Investigational assays that is not always possible. PERV, for example, they are usually tested against the best positive and negative controls available but those are often somewhat artificial. For PERV for example the positive controls are not serum from infected people because we don't have any. They are the closest thing that can be concocted in the laboratory to that. Standard commercial assays have been tested against multiple thousands of individuals minimally. Investigational assays have usually been tested against tens to hundreds to maybe thousands of individuals. Standard commercial assays have been tested in multiple laboratories by multiple people for reproducibility. Investigational assays have usually been tested in the creator's lab and in their technicians' hands. Sometimes they have been tested in a couple of labs, but you don't have as much information about how likely the reliability of the test will vary when you put it in different labs. Standard commercial assays have usually been tested against large numbers of unscreened populations and investigational assays have usually been tested against screened populations, volunteers, for example, who are usually not representative of the general public and blood donors.

An easy way to get a couple of thousand serum to test your investigational assay against is to get serum that a blood bank has saved on people who have donated blood and it is separate from the

individuals. You don't need to get informed consent. You cannot link it to anyone, and you can test your assay against a couple of thousand people. The problem is before you become a blood donor you have been tested by ELISA for HTLV, for HIV, for hepatitis B, for a variety of other tests, and there are a number of people who will not be infected with HIV or HTLV or hepatitis B but will have false positive tests on the ELISAs and the policy of the blood banks is their job is not to diagnose infection. Their job is to provide the safest possible blood supply at the lowest possible cost. So, their policy is if you have repeated positive ELISAs for HIV, for example or HTLV they don't accept your blood.

Now, you can have repeat positive ELISAs for a variety of reasons and when I was working in flu one year as I was about to go to bed at night the 11 o'clock news leader came up, and it said, "Flash, news at eleven, flu vaccine causes HIV in blood donors." I thought I had better stay up and see what this is about. Well, what this was all about when all was said and done was that a new ELISA had been introduced to the market. In the investigational stage it had been tested against a select number of people and had performed very well, but when you put it into general use in the population anybody who had a new high level of antibodies had a probability of getting a false positive reaction on that ELISA and when you go to donate blood they ask you if you have been sick recently. If the answer is yes, you don't donate. They screen out most reasons for having new high levels of antibodies. They don't screen you out if you have had a flu vaccine, and flu vaccines are given between September and November of every year. So, here in the fall this new assay was introduced at the time that a large number of blood donors had recently gotten flu vaccine. It resulted in a rash of false positive ELISAs, scare headlines on the evening news and literally shut down the AIDS hotline at CDC, we had so many calls we couldn't respond to.

Now, I have lost my slide. Okay, so my point is that even these commercial assays as carefully tested are not foolproof. Most of the reports you are hearing about are using investigational assays. So, you have got to have a little higher index of suspicion that something may be wrong or that you have got to be careful in accepting the interpretation of the results.

The last point I want to make is something called the predictive value of test results and by that I simply mean if you get a positive test result does that predict the actual presence of disease or if you get a negative test result does that predict the absence of disease or infection and this is something separate from the quality of the assay and no matter how good the assay is this is always influenced by how likely it is that the condition you are testing for is present in the population that you are testing. It is extremely important. It is poorly understood. It is rarely remembered and it can lead to a lot of misery.

The likelihood that a positive test result is in fact a true positive indicating the infection you are looking for instead of a false signal is dependent on how likely it is in the first place that that individual has a disease not on the quality of the test and this is what lies behind my statement earlier that if you take enough nunneries and you test everybody for HIV you are going to get some positive test results in people who are not infected. This leads to two widely accepted sort of precepts that all medical students hear in medical school. One is when the test result conflicts with your clinical judgment, trust your clinical judgment not the test result and the second is the general principle in public health that in general you don't screen large populations of people for

diseases they are unlikely to have because not only is it not cost effective but you are more likely to do harm than good because you are more likely to turn up positive test results that do not indicate the real presence of disease than you are to turn up real instances of disease.

This is something you need to keep in mind again when you hear about studies looking for PERV infection in exposed individuals. The paper published in Science in 1999, by Kaz Paradis where 160 patients were tested by multiple testing modalities and multiple labs has gotten a lot of discussion, and they were all investigational assays. There were some incomplete signals in there and there has been a lot of appropriate concern that the investigators and I was one of them may have falsely interpreted those incomplete signals as negative tests when in fact infection may have been present.

That is an appropriate concern because what we don't want to do is overlook a PERV infection, but when you are entertaining those concerns yourself the principle you need to keep in mind is when you are testing people for an infection that has never been shown to be present in a human being and is therefore very unlikely you have always got to remember that it is more likely that you will have a positive signal that is false than that you will have a positive signal that indicates disease. So, you have got to be equally careful in your interpretation of the testing in both directions.

So, how does this apply to the xeno situation? Let us look at PERV assays. They are all investigational and this is advantageous in that the serologic assays all exploit this concept of cross reactivity. The one we developed at CDC that Paul Sandstrom developed actually is based on gibbon ape leukemia virus antigens rather than PERV. So, that is advantageous but what that also says is there is a greater possibility that you have got a less exact signal there, that you may pick up positive serology for something other than PERV infection.

The complete list of the diagnostic criteria is incomplete. Usually they test against one or two antigens as opposed to the pattern of four or more that I showed you. Sensitivity and specificity in the few assays that have been head-to-head tested in a blinded fashion against each other seems to be about equal despite pretty large differences in the approaches and the ways these are developed. The extent of validation for any of them is very limited. They have been tested against at best hundreds of samples usually in the hands only of the investigator who developed them and always against artificial positive controls and usually against blood donors who again are a screened population who are less likely to show cross reactive results, and the predictive value of a positive test result again if PERV infection exists it is extraordinarily rare even among exposed populations. So, you always have to bear in mind that a positive result may be more likely to be a false positive than a true positive. That doesn't mean you discount it, but it means you have to be very rigorous in what you demand of the investigator before you accept that you have demonstrated an infection.

So, to summarize there are multiple potential approaches to monitoring exposed people. There is clinical monitoring of individuals, surveillance of exposed populations and laboratory testing for specific agents. Each of these has strengths and weaknesses. None of them are foolproof and collectively they are more powerful than any individual approach.

(Applause.)

**DR. VANDERPOOL:** Okay, discussion and questions for Louisa Chapman. Feel free to join in without recognition from the Chair.

**DR. LUBINIECKI:** Have any populations been screened by any of the existing assays, so for example if you look at pig farmers and other people with extensive contact with porcine populations do you see antibodies to PERV in those populations?

**DR. CHAPMAN:** In terms of validating the assays the ones we developed at CDC have been screened against a couple hundred and in some cases a couple of thousand blood donors. So, again we are screening against a population that has already had all the people likely to do false positive serologic results screened out, but that is the basis for the published reports of sensitivity and specificity. In terms of not validating the assays but just testing them against large populations of potentially exposed people I am aware that Jonathan Hibbs and Dave Pursey when they were at Mayo developed a large study trying to look at people involved in the swine industry. I don't know if that has ever been published.

**DR. SALOMON:** No, in fact I was just going to comment that that was announced in the press by Hormel at the time of the large swine convention in Minnesota, and I thought it was great that they were going to cooperate and it was a perfect thing for the swine industry to collaborate on, but it has never been published, and I checked just recently with Nextran which was involved in that study and they also informed me that it hadn't been published, but you know sometimes it gets published somewhere in a journal that we don't read. So, if somebody in the audience knows about it being published, I am not aware. There is a study going on right now that I am participating in Spain by Raphael Monet at La Curinya(?) Hospital and they are looking at a whole group of Spanish swine workers right now, but there are not results yet, but it is interesting. It is something you really would have thought would have been done a couple of years ago.

**DR. VANDERPOOL:** So, Dr. Chapman, you covered your bases so well you don't have further queries, but I am sure other issues will be raised that you can comment on. Let us now move to public discussion and questions and comments. Does anyone wish to come to the mike and address the Committee or make whatever statements or observations you might wish? Please identify yourself when you do so?

If not let us move to the discussion of two important issues, one the import of what we have discovered in our meeting thus far and then also an identification of issues that need to be discussed and worked on in future meetings.

**Agenda Item: Committee Discussion: Infectious Disease Risks in Xenotransplantation - Ethical, Social, Legal Considerations.**

I want this discussion not only to include the SAC Committee members of both official and ex officio but also the speakers. If the speakers who are not on the Committee are here, Brian Mahy

or others, feel free, also, to participate in this discussion. I will move a flipchart up there in case I need to use it as we go along and then make a few comments and open our discussion up.

Since this may go unsaid if we get in the warmth if not the heat of discussion, I want to commend all those who have made this meeting possible and we all owe a great debt of gratitude to all these persons, Margaret and others at the desk and certainly Manny Harris for his outstanding work and rescuing operations with respect to the speaker system. I actually wrote a letter commending Manny for his work last meeting and he knows that letter will stay in his folder and I have, also, heard at least two other members of the Committee commending him. So, for all those support staff and certainly Manny we want to congratulate you and thank you.

(Applause.)

DR. VANDERPOOL: Now, the question I have to ask first is open ended and that is what have we learned from these meetings and what are its implications. Two of the charges to the SACX Committee, original charges consist of one and three, advice to the Department of Health and Human Services on the current state of knowledge regarding xenotransplantation and advise the department on the potential for transmission of infectious diseases as a consequence of xenotransplantation.

Now, those are two clear mandates we have to offer this kind of advice, and it appears to me that we are on the way to being able to put together some kind of a statement that should go to the department and perhaps also to the public. We may not be there yet in terms of our feeling that we need further work on this, but the reason why I think that such advice is important is because of all the misinformation we have. As we know PERV has been linked to AIDS time and time again and there have been worries that a new infectious disease pandemic will be set in place and so on.

Now, what implications do we have in these meetings to be able to make statements that are considered, that are accurate, that are nevertheless tentative and subject to change regarding infectious disease potential for xenotransplantation? I foresee the need for a subcommittee of our group to begin to work with Mary Groesch as she pulls together this meeting and puts the various parts of the meeting into perspective so that we can at least make a statement as to where we see things are, where we see things at the present. Maybe some of us are still exceedingly worried. Maybe some of us think that the issues have been overstated and made too alarming in the press and that we can begin to not only inform the department but, also, begin to inform the public about a more accurate and considered evaluation of the issues we have been discussing.

So, it seems to me that one of the imports of this meeting is to be able to think of making this statement. Mary Groesch has reminded me that we may wish to have further discussion before we are ready to make such a statement, but I do think that we should live up to that mandate, advise the department on the potential for transmission of infectious disease. As we can tell by the report review these guidelines that have been set in place assume that this is of considerable concern, if not danger and therefore all of these various steps must be taken and put in place including monitoring and sampling and so on.

I am not saying that we would want to load back any of that at this point, but I think that this Committee has the wisdom and the savvy and we have listened for 2 days to be able to begin to formulate something that will be at least a standard at this time or a statement at this time that will give a considered judgment on the infectious disease potential, but we may before we are ready to make such a statement want to hear more, maybe from other parties who are more alarmed than the persons we have heard during these meetings.

I see that statement or some considered statement by this Committee some analysis, some document however brief as also important for the education of the public and so at least that is one of the challenges I see from this meeting and whatever we state will be significant for issues involving informed consent of recipients and certainly issues regarding testing and monitoring and so on.

So, that is my original statement but since we have not heard from everyone else who may have all kinds of other takes on what we have been listening it to, let us open it up for discussion, and what I would like to do is to start with Lou. Lou, you may have said your piece and come around the table. We are very happy to have Kathy with us today and you weren't here to hear all of yesterday but let us just go around the room and each person say something. Don't think that what you say is the last word because you may come back with several other words, but I would like to go all the way around the room and see what various others of you have to say or perhaps to make no comment at this point.

Lou, let us begin with you.

**DR. MARZELLA:** I don't have anything to add to the original comments.

**DR. CRONE:** I think having missed yesterday's I am obviously going to be playing catch-up on reading all the presentations, but one of the things that struck me was in the press recently there was some statement about the meetings about xenotransplants in Europe and how they had really sort of expressed a lot of doubt about xenotransplant being a possibility because of the risk of infectious disease and it sounds like from what was presented that perhaps one of the things that could be done is to really help clarify and help maybe quell fears about what is real and what is sort of more just continued sort of fright.

**DR. VANDERPOOL:** Excellent. We talked very briefly about that yesterday, but you make the point. You are making this in a very pointed fashion and I hope these words are being captured because I am not going to try to put all this on the flipchart, but there is a lot of misinformation and there was a statement by the UK advisory committee that expressed real concern and disappointment and certain drug companies are pulling back from doing research because of the alarm and concern that they have and so I think that is an excellent point to make at this time.

Bill?

**DR. SCHECKLER:** I listened with great interest to all of the virologic, particularly data yesterday and the concern that I would like to express relates to the 50-year rule which I don't

think is either feasible or realistic, and I think it is a huge barrier to any advances in the field of xenotransplantation. As I understand it the prions and retroviruses in the viral focus from pigs is the real focus of what we are talking about and that the porcine source of cells and potentially organs is what the focus of much of the research has been, certainly what we have heard presented and offers the most promise to patients.

So, what has happened is we have developed a great deal more information about prions and even the possibility of developing porcine herds that are free of prions that can infect human cells which is wonderful. The retroviruses otherwise are not a major issue and we have a long list of porcine infections. I am concerned about two things, one the health care worker exposure and the necessity to maintain a huge amount of information on health care workers for a long time which is not done really in anything else. I think, Louisa I heard you say that OSHA which is never a model I like to use in health care ever has a 30-year rule for some kinds of toxic exposures. You mentioned the HTLV, the worst case scenario with that and I think the 50-year rule. I have been at the same hospital for 31 years, expect to be there for a few more years, but I just don't see that as something that is doable. It is potentially doable as far as the patients that receive transplants are concerned and maintaining some type of serum bank and specimen bank at a place like the CDC or the FDA which is the only thing that makes sense to me.

Currently in health care worker practices we require immunizations. We follow up sharp injuries, particularly look at source patients for the blood products. We do PPDs on people that are exposed to TB and by the way we found that one of the PPD products gives us a large number of false positives periodically. We had a whole group of those recently at St. Mary's when one product turned out to be cheaper than the other product and our buying group bought the cheaper product and we had seven false positives in a row, and that caused as you well know a great deal of mischief, and then we follow workers for routine care in injuries in Workman's Comp but there is a lot of turnover in health care and there are lots of people that are exposed. I mentioned the rabies case yesterday, and we have 54 different employees that had some type of contact with that patient that we found out about 3 weeks later when we found out that the patient did indeed have a case of rabies and trying to maintain records of everybody that might have some contact with xenotransplantation patient other than what is recorded in the chart would be a very difficult thing to do. So, what it seems to me the 50-year rule is coming from is a worst case scenario and because of all of the concern in the press much of it is as you know the press is particularly interested in horror stories and that is what they want to report. That is where we are going with this, and I am concerned that as a great deal of information has been developed about porcine infections and we have learned a lot in the last 5 years that some of these regulations, rules, requirements, guidelines, whatever you want to call them will have a chilling effect on the industry and will make it financially impossible to do much of this work or if not impossible will make the actual application of this so expensive that it will be limited to only a few patients and those that can afford it or have health insurance that can afford it, and I don't think that is the purpose of all of this is to find ways to make a real health difference in the country, and so I am attacking the 50-year rule the best way I know how to do it.

**DR. VANDERPOOL:** Vigorously stated, Bill, the idea of this having a chilling effect. Let us continue around the room unless there are immediate strong responses to anyone's statement in

which we can discuss that briefly but let us make sure we can get all the way around the group before about 11 o'clock, when we need to shift to the business in the future.

Any brief comments to Bill?

I will just comment historically that one of the documents that I worked with in great detail and have written a number of articles about and actually presented a commissioned paper to the National Bioethics Advisory Commission on is the Belmont report, and the Belmont report shows all the signs of being formulated at a particular historical time in a particular historical place. I think some of the regulations do reflect historical time and place. Part of the challenge for this committee is to think to what degree do the historical concerns, at the time these were drawn up, still hold, and to what degree might they not.

**DR. KING:** I think our discussions both this morning and yesterday related to monitoring, as well as the possible transmission of infectious disease with xenotransplantation, those are all highly dependent upon one thing, and that is patient adherence or compliance. If patients do not adhere to follow up, then obviously our ability to monitor and to detect possible infectious disease transmission is non-existent. When we look at the adherence literature and the non-adherence literature, we know that is extremely problematic across all treatment regimens and within the general population as a whole.

The other problem with non-adherence is that it is not individually predictive, in the sense that we are not able to look at demographic and social factors and say, this individual is likely to be non-adherent because of these factors. You may find one study that says age is related, and then you may find 12 other studies that say it is not. So, it is very difficult to predict adherence.

We do know that looking at behavioral and some environmental factors, that there have been correlations. Just a few that I will toss out that I think relate to what we are talking about, in terms of long term follow up, we know that chronic conditions versus acute are much more likely to result in non-adherence. Obviously, if we are talking about a 50-year follow up, we are talking about long term chronic types of follow up and issues. We also know, then, looking at adherence, that people are more likely to become non-adherent as they begin to feel better. Obviously, in looking at xenotransplantation, our goal is to have people improve in their health and their quality of life. So, hopefully they will feel better. We know that can fall into non-adherence issues as well.

Obviously, non-adherence is not just an issue for xenotransplantation. It is for allotransplantation as well. With allotransplantation, we run only the risk of rejecting a transplant, which is crucial, but in this case we are running that risk as well as running a public health risk. I would just caution us that, in talking about all the infectious disease transmission possibilities, we have to look at adherence as the first step. If people are not going to come so that we can follow them, we will never know whether these diseases exist or not.

**DR. VANDERPOOL:** Dr. Collins, do you have comments?

**DR. COLLINS:** Thanks, Dr. Vanderpool. I just want to make a couple of comments. We didn't talk about this during this meeting, but we will, I am sure, in the future. I still have a concern about physiology and physiologic function. When Dr. Reemtsma(?) did his studies in the 1960s, he did note that, although the chimpanzee kidneys worked, the patient still had an electrolyte imbalance. I know Dr. Hume did a transplant in the 1960s also, chimpanzee into human, and I think in that 24 hour period, that kidney made about 15 gallons of urine, and that patient died of electrolyte imbalance. So, even a transplant as simple as a kidney transplant can be associated with some physiologic dysfunction in a different host. We know that islets will work, because porcine insulin has been used for years. A big transplant like liver will not make the thousands of proteins necessary for human existence. So, that is a concern that I have. I think that long-term studies will be necessary. Hyperacute rejection is not an issue. That is a low hurdle. Acute vascular rejection, which we discussed last time, is certainly still the Achilles heel.

The second point I would like to make relates to Dr. Michaels' talk yesterday and immunosuppression. CMV is one of the successes in allotransplantation. Prophylaxis and preemptive therapies are available. Fortunately, because of work such as hers, that is not an issue in our transplant patients. I think as we talk about bridging a bigger species barrier, we have to be concerned about the level of immunosuppression we use. Perhaps too much immunosuppression will make us more prone to those porcine infections. Maybe the work that Dr. Sykes does in xenotolerance may be something that we can hear about and discuss, maybe using less immunosuppression. Those are my issues. Thank you.

**DR. VANDERPOOL:** Comments on Dr. Collins' statements? Okay, Dr. Russow.

**DR. RUSSOW:** Part of this probably belongs in the next session on setting the stage for the future. So, I will just mention some things that I think need to be addressed, or ought to be addressed, in future meetings. Almost all of the speakers and many of the comments used the term risk. There are certainly specialists in both the fields of risk assessment and risk/benefit analysis, which are, in fact, two separate fields. I think that we need to be more careful, or we need to investigate further -- let me put it that way -- what somebody who specializes in one or both of those fields would have to say about how we ought to think of risks and how we ought to think of benefits. Dr. Vanderpool mentioned, in one of his comments yesterday, he pointed out the difference between scientific and social risks. I think that is a wonderful first step, but I think all of that needs to be looked at in more depth. I can elaborate on that now or save it for later.

**DR. VANDERPOOL:** I would like to hear you elaborate on it a little bit more now.

**DR. RUSSOW:** First of all, as I said, the notion of risk sort of has developed in a professional academic arena that I think has a lot to contribute to our deliberations here. Secondly, from an ethical and social perspective, risk/benefit analysis is not equivalent to a utilitarian perspective which balances, not risks, but harms in general. Some of them are risks, potential harms, some of them are known harms versus benefits, and again, potential benefits and real benefits. So, it gets more complicated than just talking about a risk/benefit analysis. Of course, there are more considerations from an ethical perspective.

Dr. Vanderpool mentioned the Belmont Report, which clearly takes a different perspective, not just benefits versus harms, but talks about certain kinds of respect that we owe to other human beings, particularly patients, respect for their autonomy, letting them make decisions based on their best understanding of the situation, while, of course, it is the investigators or the doctors who are responsible for making sure that they are well informed. Considerations of privacy also stem from this idea of respect, and those are things that we have to think about, both in terms of benefits and harms.

The other sort of harm that hasn't been discussed this time, although it was a bit last time, is where do animals fit into this. We know that they are going to be harmed in some way or other, in many different ways other than just sacrificing one animal for one organ or one bit of tissue. That needs to be addressed. I am not saying it is the most important. I would claim that it is not, but it is a background factor that needs to be included in deliberations.

Sort of related to that point, particularly the point about autonomy and respect, one thing that I have encountered quite often, not just in this committee but in other scientific committees, is the belief that when the public gets worried about something, that we can say, definitively, they ought not to be worried about, so Dr. Salomon's example yesterday of the pig heart valve. Basically, the problem is, if they understood good science, they wouldn't be worried about these things. So, the real solution for this is for the scientific community to educate the general public. That is certainly sometimes true. In fact, it is always true to some extent. I think that fails, again, to respect the autonomy of people and the fact that risk assessment depends on a multiple factorial consideration, not just what is the scientific basis for quantifying the risk. Social attitudes, cultural attitudes and so on play a large role in determining what people even count as a risk, and how they might count it. There are all sorts of examples of that, in which the judgement about risk or benefit is at odds with the actual statistical correlations, but are reliably correlated with other factors.

Again, that is where we need to look more at the sort of background of risk assessment and so on. We shouldn't just jump to the conclusion that all of the public concerns could be fixed if they just knew more about how science works. We have to be careful about that, because those judgements about concerns might be legitimate and not just ignorance of science, including, among other things in the general public, often skepticism about science, not how much it can do but how much it can be trusted. I guess I would like to see those issues addressed in sort of a separate forum or at least one of the future meetings.

**DR. VANDERPOOL:** Excellent points. Michael?

**DR. SWINDLE:** I would just like to comment on, having been involved in this since the first Institute of Medicine meeting, I think the attitude has changed, as was pointed out, I think, by Marian yesterday. There was, if not a prevailing, at least a widespread attitude in 1995 that you could pick up a pig off the farm on the way to the hospital in the morning and put the organ in, in the afternoon. I think that at least those perceptions and standards have changed for scientific reasons.

What I would like to see us do -- and I will go ahead and address the future conference -- I do think it is time to make some sort of an infectious disease statement. What I would like to see is your appointed subcommittee come up with some draft statements and then discuss that at the next meeting. I would like us to not fall into essentially a public relations type of trap. I will use as an example, currently, when you fly back from Europe, USDA employees spray the soles of your feet with a disinfectant, to show that they are doing something to keep foot and mouth disease out of the United States, which is totally ludicrous. It is a public relations move. I would like for us to stick to practicalities and realities when we are dealing with those things. Thank you.

**DR. VANDERPOOL:** Very good point. You are for making an infectious disease statement. Avoid a public relations trap. Do that perhaps as a working group in the committee, bring a draft document to us, for reflection, analysis and refinement. Robyn.

**DR. SHAPIRO:** I feel particularly unprepared to answer your question about whether we are ready or not to talk about the true nature of the infectious disease risk. I do have a suggestion and a question. I think that obviously that question is important, but I think that we should do more, and I think we should wait to talk about that until we look at the implications about whatever that message may be. It is critical to all the rest of the stuff, which is equally important, I think. I am left with this day and a half with many, if not all, of the same issues that we talked about that I brought up, I think, last meeting, in terms of important legal and ethical implications.

Consent obviously is critical of the person, the context, of the community, and interspersed with all that is the tension between privacy and duty to disclose, and we got into that some today. Closely related to that, with the same kind of attention, is the monitoring including, but not limited to, the 50-year thing. Who should be, why should they be, how should they be? Closely related to that -- and Karren talked about this some -- the public health response for the non-compliance. What are we going to do? We should anticipate that. We should have recommendations about that. It will happen.

Closely related to that -- these are all closely related -- liability concerns. When and if this happens, what are we going to do about the lawsuits that will be brought. Health care workers and workers comp issues, what are we thinking about their own exposure, or how do we suggest that we as a country respond to all that. All of this flows from what I picked up which is that, while the risk or the possible harm, or whatever terminology we might want to ultimately use, it is not zero. It is not risk free. Nothing is. For me, with my lawyer's mind, we have to think about these issues.

Then finally, the international component of all this. Since the viruses, if they are out there, will not respect geographic boundaries, how are we going to suggest that we collaborate with and cooperate with the rest of the world in addressing all the issues that I talked about so far. My suggestion would be to, through work groups or whatever, to begin to look at those as well, so that when we come out with something, it is more comprehensive than simply we think, and we don't know for sure, but we think at the moment that this is the nature of the risks out there. My question is, since I am still somewhat unclear, although I have these suggestions about what we

should be doing, these 30 or 40 protocols, are we not supposed to be weighing in on those as well?

**DR. VANDERPOOL:** When we get to the discussion of future meetings, we need to talk about questions of spending some time on informed consent and what all that would involve, international cooperation. I have several topics to suggest and then work off of, and certainly other issues as well.

**DR. SHAPIRO:** I mean these protocols that have been acted on.

**DR. VANDERPOOL:** One of the key issues that we have -- and this also comes from -- I am speaking ahead of time also -- but one of our commissions is to review current and proposed xenotransplantation clinical trials.

**DR. SHAPIRO:** Right, so we have not been asked to do that.

**DR. VANDERPOOL:** We have been asked to do it, but we haven't done it.

**DR. SHAPIRO:** Has it been put on your desk?

**DR. VANDERPOOL:** That may be the next meeting. We need to know what the knowledge base is, and that may call for closed committee meetings with respect to certain proprietary interests.

**DR. SHAPIRO:** I would like to see those, those that are already in play.

**DR. VANDERPOOL:** Absolutely. Robyn, I have a question for you as a lawyer, in the light of this discussion. How far do we have to go and what all do we have to consider in order to decrease liability for some untoward infection that might occur. Is what we are doing now and what we will continue to do about these issues, does that help cover the bases for possibly being liable or putting health care workers at risk, legal risk, with respect to xenotransplant procedures?

**DR. SHAPIRO:** Are you asking about the liability exposure of this committee and of us as individuals in coming up with recommendations? I didn't think my role was to serve as counsel for the committee, necessarily. I don't want that job.

**DR. VANDERPOOL:** We can be sued, according to the plaintiff's attorney, who have decided that something has gone wrong in a clinical trial. Robyn, you might disagree. Right now, the plaintiff lawyers who find something that goes wrong in a clinical trial sue the doctor, all the health care workers, the entire IRB along with the university, the president and the deans. I am on an IRB that has \$50,000 worth of coverage that is not even going to scratch what the attorneys are going to come after.

**DR. SHAPIRO:** That is why, you know, when I was talking last meeting about models like the court of claims model, to think about in terms of suggestions for what we will have in place to

respond to that. I think it is something that we should think about, but hopefully not liability exposure as committee members. But what kind of insurance do we have?

**DR. VANDERPOOL:** Yes, we won't focus on that. Yes, what kind of insurance do we have? Alan.

**MR. BERGER:** I will try and just address the comments from this meeting. Actually, the first one about educating the public, I have been interviewed by the press over the years and made public comments myself. I really do monitor what the press is saying and I come from an exactly opposite point of view. I think the press has been overly positive about xenotransplantation. I don't really see any major public concerns. I am going to stop on that one.

To get to the infectious disease, I don't think we are even in the ballpark of making any kind of a statement as a committee. It seems like what was presented yesterday was just some very early indicators. The major study is still from 1999 that Louisa pointed out is very limited and certainly has maybe some serious flaws.

The issue that was brought out about public fears of the unknown, there is an unknown here. I mean, there are viruses that we know in animals that we are not sure what might happen besides new viruses that might appear from time to time. That is real. The unknown is real. Infectious disease can't be separated, which was pointed out earlier, from the monitoring of infectious disease. I have great respect for Louisa Chapman, but the surveillance system just does not appear to me to be able to do its job because it needs to, on a voluntary basis, try to monitor close contacts or people who have a life style that they may not want to follow this particular system. On top of that, which was pointed out before -- Dan brought it up at the last meeting -- no matter what is done in the United States, you may have rogue operations outside the United States, where people can travel and enter the United States that can be a real risk factor.

On the international end, which was also pointed out, it does seem to me that we need as a committee to be cooperating even more in terms of what study groups are doing in other countries. Louisa mentioned it, too. I don't think we can do a surveillance monitoring system unless it is an international system. The U.S. system alone doesn't seem to be able to make it to me.

One other point. It does seem that, before we make any statements as a committee -- I know this was brought up before and it is on our future agenda -- we really need to look at what the alternatives are to xenotransplantation, because there is a lot of other research going out. It seems to me that if we want to make a statement as a committee, I think what the United Kingdom has done -- and they have been very thoughtful in making their statement -- is where this committee should be.

**DR. CRONE:** I think one of the comments, I don't think anybody has said that there aren't unknowns. When you deal with any new technology, there are going to be unknowns. The concern that I have is that the statement made by this committee could potentially have a fair amount of weight. I have concern with how the press did cover the United Kingdom. It was a

statement that was very clearly made in the press, in the Post, as if, well, this is just dead in the water. I have to think about, you know, one of the things that struck me the last time we had a meeting was really what Jim Finn said, about his situation and what has happened with him. I am concerned that we consider what our role is as a committee. We do have to be cautious. We also can either make this into an impossibility or make this into, is there a possibility and, if so, what do we need to do to make it a possibility.

All these other things that people are raising, that is fine, but I am also saying, look, you have to look at patients. There is never going to be a time that we are going to get into a situation where there are going to be no risks. Transplant as a whole, the development of organ transplantation has had risks. There continue to be risks and there is never going to be a time. I know with xeno there are going to be even more concerns. I think we can either sort of follow and really make a lot of -- I am concerned about whether or not we make things go a step further and whether or not it is something we can really do or we end up shooting it.

**DR. VANDERPOOL:** So, whatever statement we would make would make would be contingent on what we know at this time in this place, and do we need to know more in order to develop a statement. It seems to me we could begin a draft statement and perhaps hear other alternative points of view and do our homework as much as possible. The statement would be, it seems to me that the committee, in part, exists to be able to address the issues over time, to help shape opinion over time occur in that overall opinion. Okay, Dan?

**DR. SALOMON:** I think one of the things that has been frustrating to me over the last 10 years has been, although I make my career in biotechnology, my interests are in cell transplantation and gene therapy and xenotransplantation. What is so obvious to all of us is that the impact of successful gene therapy, successful xenotransplantation and successful applications of biotechnology is just compelling. Yet, we really haven't done as well as we all had hoped, as fast as we all had hoped. I am not overly bothered by that. I am frustrated, perhaps, but I think we have to take a view right now of sort of where xenotransplantation is today and be rather pragmatic about it, and make decisions about where this committee goes based on sort of where xenotransplantation is today. Perhaps in a way it is freed at the moment of a lot of the hype that had bogged xenotransplantation down for the last five years.

Let me make a couple quick comments. One, risk benefit ratio. There is no risk benefit ratio here because there is no benefit yet. The problem really was because of an overstated sense of benefit, we focused on risk. Risk was very clearly and quickly articulated. Benefit didn't follow and we ended up in sort of a negative spiral, if you will, for a couple of years, where the risk arguments dominated the field, which I don't think had a positive effect on the work going on in laboratories to move the benefit forward. I think if you want to take a pragmatic view of where the field is today, we need to think about sort of where the next advances in the technology and the science are, that are going to start to contribute to the benefit side of it.

Point number two, infection disease risks. I certainly don't think that we ought to be talking about pronouncements on infectious disease risk. I believe it is too preliminary. However, I do agree that the committee should probably make some sort of statement, pragmatic, reasonable

and balanced, about where the infectious disease risk is today, to at least begin to try to set a framework for where we are going tomorrow. I certainly, as involved in it as I am, don't feel that I am certain what the infectious disease risk is today. I think we need to look at what xeno is today. It is not vascularized organ allografts or xenografts. It is just not. It may be soon, and that would be great, but it is not. What we need to think about is, what is in the context of the 35 or 40 FDA INDs to give the committee really a working idea of what xeno is today. Xeno today is cell transplantation. Xeno today is biologics that are made in contact with animal cells. Again, if we want to inform the directions of the committee, we ought to say, where is xeno today. Let's focus on it.

Fourth, I think we need to realize that there has been a change because of the disappointments in the last five years. Biotech and pharma aren't steering it quite as directly, albeit they are always going to be in the background. There is going to be a greater and greater need for individual investigators, and we are back to investigator-sponsored research, and I don't think that is a bad thing. We probably got ahead of the game for whatever reasons -- we can talk about that in a historical conversation, but the reality today is that a lot of the work is going to come back to individual laboratories doing good basic research. We need to make sure that we don't do anything and that we work together to lower barriers, to facilitate the sort of cutting edge research that is going to be required to add the benefit part to this risk benefit ratio.

Just a simple thing here, I mentioned it yesterday and the theme has been picked up by a couple of us already, I just can't get past the monitoring barrier if we are going to be doing clinical trials in academic centers. I think we need some help. I am not trying to say that it is a simple equation because the responsibility of the government is to protect the people. If you need 50-year follow up, then we need to take that seriously, too. Just because I want to do a research project and I don't have funding for 50-year follow up or I won't be alive 50 years from now isn't necessarily the arguments that says there shouldn't be 50 year follow ups, and we need to deal with that.

Lastly, I actually think that the danger for xenotransplantation is higher than ever now. It is really easy to see the big ships. It is easy to see Baxter and Novartis coming through the water. The waves are easy to follow. Right now what is going on is that 40 miles from where I live there are two xenotransplants in Tijuana that are doing xenotransplantation. I got email last week from a group in China asking me to help them do PERV assays because they want to do pig liver transplants.

I think we have got to come back to where Robyn was talking about. I mentioned it the last time, and Alan. This international thing is really, really critical. If we are supposed to be protecting the public and we are supposed to be making comments about where we think the dangers are, well, then, I would like to go on record as saying I think the danger is all around us.

**DR. VANDERPOOL:** Okay, Dick?

**DR. KASLOW:** I think I would like to make a comment and then perhaps raise some questions. The first comment, I suppose, is just an extension of what has already been said with regard to

examining the protocols in place now, not just the protocols for the whole xenotransplantation process, but maybe more specifically we could begin by focusing on the protocols in place for monitoring the follow up, the concern that people have about this 50-year rule. Let's take a good, hard look at the concrete instruments that have been prepared for that process. While it may be disconcerting and a great concern about whether we can really do it, it would certainly be unwise for us to assume there is a feasible system in place right now, when in fact there is really no system or no feasibility to it. I think we ought to take a look at those and see what we think of those as models or inappropriate efforts.

As for my questions, I guess I would pose them more as the lessons that we have learned from allotransplantation. I think Marian's presentation yesterday really highlighted it for me, and that is that we have known, of course, about all the infectious disease risks from transplantation in the setting of immunosuppression done for many years now. What can we learn from that. What do we know, first of all, about how allotransplantation really differs. It is one thing, as Dan said, to talk about transplantation of whole profused organs. When we are talking about cells or other components being used for this whole process, I think the boundaries start to blur a bit. What do we know about what happens with blood transfusions. We don't really, I think, fully understand what the whole process is, or at least I don't, what the whole process is for screening in the same human allotransplantations as compared to the xenotransplantations.

How do we decide that we are going to exclude people who have traveled to Great Britain in the last decade or so, but not necessarily exclude pig farmers or cow farmers from donating blood. I am not aware of any recommendation to do that right now. What are the risks? What do we know about transmission of infectious agents as a result of transfusion? We certainly know about it in unfortunate detail with regard to HIV, but what do we know about other agents that may have been transmitted by transfusion. How do transfusions and organ transplantations, allotransplantations, differ with regard to the risk of transmission than xenotransplantation. How do those risks change? What are we doing to monitor how those risks change? AIDS, again, brought that into all too high relief over the last 20 years. It may be also, I think, that some sort of more practical issues ought to be addressed with regard to sentinel systems.

The suggestion that there has been a study done by Novartis about which nobody seems to know the results is a little disturbing to me. It would be nice to know if we could have some contact with them and with your studies, obviously, as they proceed, and learn a little bit more about what the risks are to people who ought to represent sentinel populations for this kind of thing. I guess to close on a lighter note, I wonder if the equivalent sentinel population to nuns, when it comes to STDs, might be orthodox Jews for monitoring whether or not there has been transmission from humans to pig, as a negative control, at least.

**DR. VANDERPOOL:** Mary, do you have some comments?

**DR. GROESCH:** A comment about some of the discussion about whether the group would like to, at some point in the future, make a statement about the infectious disease risks. I think a number of people have pointed out that we have had some very good overview presentations today, but I assume you would want to go more in depth with presentations in order to talk about

a statement about it. One thing to keep in mind is that we could certainly put together a workshop that would look at this more in depth to provide a foundation for something like that.

Also, we have had some discussion about not only talking about what the risks are, but I think also how these risks are communicated, how they are communicated to potential recipients, and how they might be communicated to close contacts, might be useful, that this group could provide some guidance on that.

Also, the long-term follow up, to look more in depth at the requirements for it. Do we want to recommend any changes or supportive statements about it. What are the mechanisms for it, and how the need for it is communicated to both the potential recipients and their contacts.

**DR. SYKES:** I would like to mainly expand on some of the comments that have been made. First of all, I agree with Mary that it would be very helpful for us to hear in more depth about some of the studies that we haven't heard about. I think there is additional work in the area of CMV transmission that we ought to hear about, and these additional epidemiological studies of people exposed to pigs in their work. I think having done that, we should try to come up with some kind of statement. That statement ought to include suggestions regarding areas of research that should be done that haven't been done, that could help to position us better to assess risks.

My second point is also sort of following the forward looking tone of Catherine and Dan's comments. We have been talking about infectious diseases these last two days, but I would like to remind everyone that, as Marian pointed out in her talk yesterday, most of the human beings who have had organ xenotransplants died of infectious complications that were common opportunistic infections that affect the immunosuppressed patient. The reason for this is that the amount of immunosuppression that would be needed to maintain a xenograft, at this point in our science, is going to be inordinate. We are nowhere near being able to do organ xenotransplantation because there are so many immunologic barriers to xenograft, that if you were to use non-immunosuppressive drugs, as are used in allotransplantation, you would need far too much. The opportunistic infection risk would be unacceptable. For this reason, some of us believe that tolerance, altering the immune system so that it tolerates the xenograft is essential, and will be essential before we can do organ xenografts.

I think this committee needs to be made more aware of those immunologic barriers, especially if we are going to be assessing FDA protocols. I think we need to -- part of that assessment should include potential benefit, and I think right now the state of the art is such that, as Dan points out, there is very little benefit to be had from solid organ xenografts. I think those are my major comments. Thank you.

**DR. ALLAN:** I will just reiterate what some others have said and that is, personally, I don't think we are ready for any type of statement regarding infectious disease risk. I also think that it is not even necessary. I think the media -- if we are targeting the media, I don't think that is probably appropriate to begin with. I think that the facts stand for themselves. We hear stuff today and it seems optimistic that PERV may not be the kind of problem that we originally thought. Tomorrow it may be something else. I don't really think we should be in a position to

make that kind of statement, whatever it might be. I think we need to stick to the facts. It is constantly evolving, just like everything is constantly evolving. If we make a statement tomorrow, then next week there is a new virus. I just would be a little bit concerned about making types of statements like that.

The other thing is the INDs. That is critical. Thirty or 40 INDs are already approved. Certainly a lot of it is probably the 3T3 cell type of thing, but I think without us being able to look at that, I don't think we can even function as a committee. So, I think that is really critical. Parasitologists, bacteriologists, oncologist, I think the committee member that has additional expertise would be nice.

The other thing is the 50-year long term, that has been talked about. I think the infectious disease risks, this is just a practical thing, and what I am hearing is just money. I don't think most people on the committee would argue that it is something we shouldn't do. I think it just ends up being about money. You don't expect everybody is going to follow this program, but if you just get a certain -- it is all about statistics. It is all about the math, which is that you will only get a subpopulation of people you can actually end up following. Even that subpopulation is going to be important enough that, if there is an infectious disease and it is transmissible to contacts, that you probably get that information. I am just supportive of that type of approach, but I don't know. Again, the money issue is probably going to be important. I am done.

**DR. MICHAELS:** I, too, would like to concur with comments made by the other speakers who have gone before me. I just add on my own sort of editorial comments. I do feel somewhat that we are acting a little bit in a vacuum without having a little more information on the 30 to 40 protocols that have been approved. As others have stated, I would like to have more information. From that, I think we might be able to get more data to at least make comments or, if not a statement specifically on the infectious diseases, at least be able to comment in a more educated fashion about the approach in the protocol for monitoring for the risk of infections.

The 50-year rule, I guess, is for the archiving. The patients, as I understand it, are supposed to be followed life long, if possible. As an advisory committee, perhaps we would decide that, while this is biologically plausible, that we would advise that perhaps the Public Health Service be able to be the repository for those archives and have funding to support that. A lot of this goes over to the next part for setting the stage, but everyone else is doing that as well. So, I concur that I would like to hear more about the immunologic barriers and where we are today and where we are moving in that, in terms of some didactic information for us, and the consent process.

The only other comment I had in terms of the health care workers -- this has certainly been contentious among animal care workers and among health care workers in a number of institutions, and some have moved, rather than doing up front archiving, to do archiving at the time of having an exposure, be it a splash two, a mucus membrane, or a needle stick or a blood exposure, and have the baseline drawn there. So, it wouldn't be quite as cumbersome a number of people to follow, and that might be something that we could consider as well.

**DR. LUBINIECKI:** There are several concepts that I have seen over the last 25 years or so with

other biological products that I think apply to xeno. The first is that fear is a poor basis for public policy. In contrast, good science and relevant data are a far better way to create public policy. As a couple of examples, in 1975 there was tremendous concern over work on recombinant DNA technology. In the extreme form, there was one town in the northeast of the United States that actually banned recombinant DNA research. Overseas, there were several countries that banned recombinant DNA research in *e. coli* and other microbial organisms, out of fear of the unknown, basically. Shortly thereafter, the Federal Government established, under the leadership of NIH, the recombinant DNA advisory committee. This committee looked at the facts, looked at the issues, gathered some data and eventually created some guidelines which were modified, reviewed, expanded over the years and eventually, after about 10 years, there was judged to be enough data to relax virtually all of the guidelines. Again, it was based on good science and getting the data.

A little bit later in the early 1980s, similar things happened with the use of recombinant technology in mammalian cells of continuous capability meaning, in essence, we were practicing recombinant DNA in tumor cells or cells that were capable of forming tumors. This ran sort of contrary to a several-decades-old ban by the scientific, medical and regulatory community on the use of tumor cells to prepare biological products. It was clear that, if we were going to have the benefits of hybridoma technology and recombinant technology, we had to basically get the facts, address the issues. To be sure, endogenous retroviruses were one of the major issues that were a part of that family of concerns. Again, with about five years of concerted work, the data base was eventually generated to say that, with the data and with rational ways of designing control systems, it was possible to allow the benefit of these products to be realized.

Between these two examples, there are now nearly 60 products, therapeutic products and other products for *in vivo* use in humans on the market in the United States. What this experience has taught me is that basically the way to perhaps deal with xeno is to identify the issues, get the facts and then establish public standards, and then everyone agrees to work to those standards. If we do that, I think there is a very high likelihood that these risks can be managed.

The second piece of advice that I would provide is that the time to organize the fire brigade is before the fire starts. If we wait until, heaven forbid, there is perhaps the realization of one of these theoretical risks from infectious diseases associated with xeno, there is the chance that it will burn out of hand. So, even though it is not very likely, it is something that needs to be considered. Another way of looking at this is that the probability of a nuclear reactor melting down, that the impact is very great. It is a situation that everyone should take very seriously.

Among the things that I would see as important in this regard is that we certainly need a strong surveillance system, both for the investigational products as well as eventually for the marketed products, such as that organized by the FDA and described previously. These systems are organized by the FDA and actually run, in part, by the manufacturers and the government. We also need the availability of the relevant laboratories with scientific experts and with sample collection as has been mentioned. It is absolutely essential that the government, through CBER and CDC, maintain this tradition of maintaining these laboratories, such that they can be used at a moment's notice in the event that a fire does break out.

Then a third one is to make key reagents available. I think we have heard some very great breakthroughs in the last couple days in the virology of porcines and xenotransplantation. It strikes me that there are probably only a few laboratories in the world right now that are capable of doing these pieces of work. If we expect it to be applied to minimize the risks associated with this, the techniques have to be widely available, and especially the reagents. The specialized reagents have to be widely available and, if necessary, the government should help in that regard as well, as it has historically in other similar efforts. There was a large resource reagent program run by the NCI in the 1960s and 1970s as part of the viral oncology program, which produced in the long run many great advances. If xenotransplantation goes forward, I think these must be in place in order to help monitor the safety and be prepared for whatever comes out of it. Thank you.

**DR. KIELY:** Last evening, when Dr. Vanderpool asked us to think about the scientific, social, ethical and legal concerns related to xeno, I thought, well, what do I know about the science. I am a general internist and I have heard all this science in the last two meetings, actually. What I started to really think about and be concerned about was something that I was glad to hear Dan Salomon, who has certainly been in this longer than I have, to say the least, had similar concerns, and that is ideas about where is xeno now. Where are we at this point in time. Are there, in fact, critical gaps in our knowledge that are limiting us from getting from where we are to where we need to be, for example, what Megan was talking about in terms of immune tolerance. Tied to that is just a global concern. Is there adequate funding. Where is the balance of this work being done.

We have heard from private industry. We understand there are other studies going on. Where is the balance of this. Who is setting the agenda. One of the things that we would like to believe is that the market sets the agenda. In other words, the market will drive this. The most promising research will go forward. I am not so sure about that in the case of xeno. So, I just put out as a broad concern that what is the federal role concerning xeno. I have always felt that the federal role is where there is market failure. Dr. Salomon was talking, is that a potential that we are facing, given the news from Europe, given the concerns in general. That is just a broad concern. Basically, should we be focusing on promising areas in xenotransplantation as opposed to just having a very broad agenda which isn't, I guess you could say, very -- it doesn't set a great environment for scientists, particularly for investigator-initiated research projects.

The ethical concerns that I was thinking about, I have a sense now that there has been very serious and very careful thoughtful attention to the issues of monitoring, surveillance, consent to some degree. My concerns regarding the ethical implications of xenotransplantation is really how flexible and responsive the system of checks and balances is. This is reflected in several other comments some of the other committee members have made. How flexible is the system as it relates to recipients, what Karren was talking about. You know, folks feel better, they are far away from their transplant. How frequently do they want to bring this up, and enter into the health care system. The great unknown, to me, and I brought it up yesterday, I believe, is what is going on in the world. Now, as we move from being a very responsive committee, sort of thinking about what we now know, what we can act on, and becoming a more proactive committee, what do we need to know and must act on, I think we probably have to straddle both

of those reactive and responsive as well as proactive spheres, as this committee evolves. One of the things I thought that we might consider would be developing a central contact place for clinicians who have concerns about xenotransplantation. If that already exists, I don't know that. Again, there will be issues that come up and people will wonder where to turn.

Finally, socially, Dr. Vanderpool had mentioned that our goal is to improve the health of Americans. I feel in that regard we have really two responsibilities. One is education, which I think the lay press and Saturday Night Live has actually done some service, in getting word out that these things are taking place. More responsible education, whose responsibility is that? Is that the providers? Is that industry? Is that the government? How will that be shared? How will that be managed.

Finally, equity. I think we already know there is a lot of data regarding minority group rates of receiving transplants and other life saving and life altering treatments. I think we always need to consider that this new research would be available to those groups. Then, too, we have a large group of individuals who are uninsured in this country and we need to focus on them as well, and recognize that those individuals might benefit from these treatments, should they become available. Thank you.

**DR. MENDEZ:** I have certainly enjoyed the presentations and I think everything that all the speakers have said so far is quite relevant. As a clinician, I found these past two days very interesting with regard to the infectious disease aspects and the regulatory aspects of our system. I have to -- although we have, I think, come a long way in learning a great deal about the virology of xenotransplants, I still feel a little bit uneasy about making any significant statements to the press or to anyone with regard to either our affirmation of the minimal risk involved or the significance of the risk involved. I think we probably need a little bit more information with regard to this.

With regard to risks, however, and infections, I don't think we will ever come to an equilibrium that is acceptable to all. There is always going to be a significant risk to some and an insignificant risk to others. I do feel, however, from the information that I gleaned over the last two days, that there are areas that we can promote and go forward with, such as creating a PERV-free swine herd. I believe very strongly in what Marian has said and what others have said with regard to allograft infections and the need for substantial immunosuppression in the xenograft setting. From that standpoint, I think we should move toward a situation in which we develop tolerance in the xenograft or develop a chimeric type of state. I don't think we are anywhere close to being able to use xenograft organs without massive immunosuppressive medications. For those of us who have been in the field 30 years and saw where infectious diseases was the culprit and the cause of mortality in the early part of transplantation due to our lack of sophisticated immunosuppressive medications, and have seen that fade away as we have developed more sophisticated immunosuppression medications and have also been able to, through infectious disease advances, been able to conquer some of these infectious situations.

The second -- so, from that standpoint, my feelings are that we are not quite ready to go public with a significant statement of one or the other but rather, perhaps, a statement as to where the field is at the present time. With regard to regulatory considerations, I am quite impressed by

what we have in place, but I would like to try to put it perhaps into a more historical perspective of what we should do with regard to the regulatory aspects of the xenograft. When you look back at the past 20th century and you look at the advances that occurred, the incredible advances that occurred in medicine and in science, it was with some degree of regulation, but yet, you have to give the scientists a leeway to be able to prod ahead his ideas and his theories in order to make advances. You can't stifle them with the handcuffs of significant regulatory rules and regulations. I think the ones that have been placed are excellent and are very good. I am actually, I should say, a little bit impressed by the flexibility that has been shown by our regulatory agencies with regard to this. I think we have to watch this very closely and always allow our scientists some degree of headway.

As I thought back over 30 years of transplants and the advances that were made, they were all made by very bold individuals and they were all made against the general consensus of what was the standard of therapy or the standard of treatment for patients at that particular time. Thus, I do think we have to allow our scientists to take that bold step, on occasion.

Thirdly, with regard to the international cooperation, it is quite apparent to me that they are going to far outstrip us, simply because of their lack of regulatory abilities. As much as I would like to fantasize that we could have an international cooperative agreement with other countries, I think it is perhaps a little bit more fantasy. I think we ought to try to strive for it, but I don't think we are going to be able to control it any greater than we are going to be able to control hoof and mouth disease by spraying the feet of people coming into the country.

The other aspect I think we have to look at is where does xenograft transplantation stand in the face of the future of alternatives to xenograft transplantation. There are significantly excellent other alternatives to xenograft transplantation that are going to occur. You can just take one example of diabetes. If we are -- and which we are going to try to do in the future -- try to access all organ donors, not just those suitable for whole donor, but all donors for islet cells, if we are able to develop some sort of stem cell therapy from young adolescents who die, or from tissues of adults, if we are able to develop artificial means of diabetic control, we are going to eliminate 25 percent of those individuals who require transplantation. With changes in organ donation and improvements, we may get to the point of even being able to perhaps balance to some degree, or at least make less urgent, the need for xenograft transplantation. The thing that we haven't talked about at all, however, is the benefit of xenograft transplantation to someone. I think that unfortunately we have so little, almost anecdotal evidence, of what the effects and risks have been with xenograft transplants into humans. Dan's presentation yesterday, I think, was quite excellent in pointing out what has been done and what needs to be done.

You only have to sit next to a person who is dying, and who is going to be dead in the next 18 to 20 hours, to realize that they will do just about anything to stay alive, especially if they have families that are dependent upon them. I think that these benefits perhaps outweigh many of the very carefully restrictive activities that we are going about, or perhaps the pace that we are going about in trying to bring this modality of therapy to those individuals who die every day. I think it was mentioned like 17,000 people died on the list last year waiting for an allograft. I am sure any one of them would have been very happy to have accepted, at any risk, a xenograft of some sort.

I think we have to put into perspective the benefits that would benefit society. I think that is about all I had to say.

**DR. VANDERPOOL:** Thank you, Bob. Jim?

**DR. FINN:** I am not a scientist or any kind of researcher. I can give the patient's angle on this important story. As a patient, I had to agree to several things, such as no blood or organ donations, taking basic AIDS-like precautions for my health care workers and emergency room attendants, whenever I was in for anything like a bad cat scratch the other day. The patient has to sign away quite a few rights, has to allow various things to happen, such as ongoing testing and monitoring until the day I die. That is not much of a problem for me. It is a small price to pay for the benefits I have received out of this therapy. I am tested every six months for the first four years after the procedure. Then it is once a year -- it is coming up in September -- for the rest of my life. They do a blood draw and I believe an MRI and electrocardiogram is required also.

I have been interviewed extensively by the media, both print and broadcast. The Frontline piece ran about three months ago back in March. A lot of viewers wrote in about the program after it aired, and they are running two to one against xenotransplantation. The principal reasons are -- and they are pretty much split down the middle -- are animal rights and fear of infection. The program, this was what was commented on. I think we need to educate the public about the risks and the benefits of xenotransplantation. Practical Science did an article on me, TLC, and Sixty Minutes have also interviewed me. Most of them were very positive, especially the TLC interview was a very positive piece. They showed me driving around town in my old sports car. Basically, what I got out of this was a second chance at life, and a chance to help the rest of mankind. That is kind of my contribution. Thank you.

**DR. VANDERPOOL:** Thank you, Jim. We are supposed to be through in about 12 minutes. I think we will need to go over a little bit. I think we probably need to disband by 11:30.

We have the ex officio members to go. I think what we may end up having to do, obviously we are not going to have time to go all the way around the room and ask what the future meetings should be. I think what we can do is take a quick vote on some of the highest of priorities that have been mentioned and at least have a sense of the meeting on some of the things, the several things we have talked about. Let's proceed now with Louisa Chapman and Dan and Lily and others about some of their concerns.

**DR. CHAPMAN:** Listening to the committee talk, from the perspective of my agency, I think there was something very instructive in Dr. Lubiniecki's presentation when he started talking about the early phases in the development of biologics as therapeutic products in the 1950s, when there was a lot of enthusiasm about the recognition about the fact that we could take viruses that we wanted to protect people about, inject them into monkey kidney cells, and develop vaccines to protect people, coupled with the naivete, or perhaps given the state of virology at the time it is more appropriate to say an ignorance of the fact that there could be viruses that we didn't want in those same monkey cells that we would inadvertently expose people to.

He described a progression of the state of biologics from a state of a lot of very risky procedures out of ignorance to a state of progressive science and study and development of better measures of safety to a field that, at this time, actually operates with a very high degree of safety. That wasn't described quite as clearly with allotransplantation, but those of us familiar with the field know that it went through the same progress, from an early stage where people enthusiastically transplanted kidneys and, along with them, cancer and infectious diseases, to a state now where we have well developed screening programs that cannot completely eliminate, but largely eradicate, these risks.

I think that is a view through which perhaps it would be useful for this committee to look at the government guidances and the PHS guideline and also the FDA guidances that are developed. Recognize that when we began trying to formulate those in 1995, we were at that same stage with xenotransplantation. People were unaware that there might be any problem with taking pigs off a farm and putting them into people within a couple of hours without screening. There were proposals to try to capture baboons in North Africa, with an unawareness of the potential for infection in any baboon to transfer to humans, and of geographic diseases that you can introduce and may be not familiar with, when you start bringing living organisms from one part of the world to another. It was in that state that those of us in the government began trying to develop rational guidelines. If, as a southerner, I can maybe be excused for using a Biblical analogy, you know, the world was without shape and form, and darkness was upon the face of the earth. We worked with largely the tools of reason by analogy from previous experience and stringent scientific reasoning largely in the absence of data directly applicable to the situation, to try to develop reasoned public policy, the process which are the guidelines and guidances that you have before you today, and I hope you will become very familiar with those, because it is against that base that you need to be advising us. That process highlighted areas in which questions were framed and science could begin to be done to address those questions, and that has been a moving target since.

Some of the issues, like the 50-year rule, when that was formulated, it was the best rule we could formulate at the time, and our expectation was that that recommendation may change over time, either by a recognition that it needed to be extended, or that at some point it might be appropriate to foreshorten it or eliminate it altogether. My response to a lot of the thoughts here is that these are good things and our expectation is that you will look at the policy, the best public policy we have been able to develop to date. You will consider it against a rapidly evolving scientific data base, and you will respond with the best advice you can give us, about where we may need to reconsider that policy in the light of available science, or push the science to give us more information on which to base our public policy.

**DR. VANDERPOOL:** Thank you. That is in keeping with one of our charges, which is recommend to the department, as needed, changes in the PHS guidelines on infectious disease issues. That would include other documents also. Dan?

**DR. ROTROSEN:** I would like to emphasize the point that has already been made, that it is really going to be critical for the committee to hear about the 30 to 40 approved INDs. To do so in detail and in a setting where the committee can at least hear about these protocols in closed

session, we ought to think about ways to do that as part of a combined open session discussion so the public can get some information about these, but also to allow the committee members to hear about them in closed session and to ask some tough questions and get very clear answers to them. I think there might be quite a bit to be learned from that. For example, what kinds of unanticipated problems have come up in those trials. How have they been dealt with. How good has adherence been. What measures have been taken to improve compliance if there have been problems. Things like that, the committee really needs to make informed judgements.

At the same time, I think the committee needs to be aware that the national portfolio of research in this area isn't much larger. NIH funds probably not three dozen, but maybe six or seven dozen research project grants on xenotransplantation. The total dollar investment probably is considerably smaller than the industry investment in these clinical trials. None of the NIH-funded research currently is in the clinical trials sphere. It is all bench research at a preclinical level. When the portfolio is that small, that is a relatively small portfolio for a \$22 billion ship. The importance becomes even greater to the advancement of science and public trust in science, when there is a path forward for continuous and stable federally-funded research.

It is a big concern to me that, as you have heard from Bob and others, that most of the kind of paradigm-breaking advances have been made by creative individuals working with federal support, generally not industry support. It is a concern that ongoing activity is difficult to support when researchers perceive that their career paths are constrained by external factors. It is going to be very important for this committee, even though it is not within its mission statement, to provide some assurances that research in this area will have stable funding, despite the ups and downs of industry support.

One other unrelated point that I would like to make is that we have heard quite a bit about the need for a data base, and I won't argue about the duration, 50 years or whatever, for that. It might be helpful to have some analysis from the CDC or the FDA or on the committee's part as a whole, in detail, what should such a data base look like and what would it cost. I think Jon Allan is absolutely right. This is largely a cost issue and we do support other transplantation data bases at NIH and elsewhere, that are not all that expensive. It would be interesting to know what the projected costs of this data base are over many years.

**DR. VANDERPOOL:** Thank you, Dan. Lily?

**MS. ENGSTROM:** One of the disadvantages of being at the end of the line is that most everybody has said what you want to say. I want to make two general comments. I want to harken back to what you, Dan, said earlier, and let me paraphrase you. You said, well, cost benefit, what are we talking about. There is no benefit here right now. I think you put your finger on it. We are talking about potential, potential in two areas, potential of the risk of transmission of disease -- we don't know whether that is actually going to occur -- and the potential for benefit in terms of alleviating pain and suffering and improving the lives of patients.

So, if we, I think, as a society want to look at xeno, I think we need to look at it from two points of view, and I am echoing something that has been said over again, and I capture for myself as

we are being driven by two things. One force is the need to protect the health and safety of individuals who might be potential recipients of xenotransplantation products. On the other hand, the second drive is that we should not stifle any means that would actually bring about the promise that could, in fact, improve the health of these people. I won't say that balance, you know, balance you assume they are absolutely equal. So, I won't use that word. But at some point in time, I think we need to look at, if there is potential risk and there are potential benefits, how do we proceed in a way that allows us to actually minimize one and maximize the other to the extent possible, because there are lots of unknowns right now.

I think that science -- this is reflecting a personal belief on my part -- I think science should pursue and pursue responsibly all the avenues that have potential promise. When we are talking about xeno, we definitely have to make risk part of that equation. I have heard several people around the table saying some a little more pro, some a little more con, but the point is I think everyone recognizes that if, in fact, the field is going to go forward, Dan just finished telling you that our portfolio is actually quite small, it is all in the preclinical area, so most of this work is being done by industry. I think we have got to be able to pursue xeno in a way that doesn't bring everything to a halt either. If there is something promising there, let's take a look at it. Maybe at the end of the day we will find out, hey, this isn't going to work. Like a lot of other things that are out there on our radar screen now, this is only one, and I stress only one, potential area.

The second comment I want to make has to do with process. This committee meets four times a year, which means an interval of three months between each meeting. For the work of this committee to move forward, one of the things I would like the committee to seriously consider -- and I think this has also been brought up at least by a few speakers around the table -- is whether or not you would want to organize working groups on specific arenas, topics or issues, whereby a smaller group, perhaps supplemented by outside technical experts, if you feel that is necessary and appropriate, to help pull together the issues, tease out the things that are pertinent, come back to the parent committee as a whole, to present certain issues that the parent committee said, this is worth studying, this is what SACX should be addressing. So, in between the four meetings we have, you know, the work of this committee is moving forward. If we depend only on the four meetings a year, it is going to be a little difficult for you to get where you want to be on that kind of schedule.

**DR. SIEGEL:** A couple of things I want to comment on. One is the issue of long-term follow up, as Marian correctly clarified in our guidance, the HHS and FDA guidance. The 50 years refers to archiving of specimens and the guidance regarding patient follow up is specimens every five years and follow up for lifetime, which of course, can be longer than 50 years although in many of the patient populations we are looking at, it is not likely to be. That is important, because I think there are separate issues that might determine the duration of follow up. The duration that you want to follow a patient depends on the duration of risk, and I will come back to that in just a second.

The duration of archiving is very different. Conceivably, 30 or 40 years from now, we could come up with a concern that maybe there is a certain type of infection or a certain type of risk.

I can tell you, when those concerns arise, you might be very glad that you have the specimens to go back and address that. A perfect case in point is that FDA requirements and HHS guidance required archiving of specimens pre and collection of specimens post-treatment going back a number of years prior to the discovery that PERV could infect humans.

I think a critical piece of dealing with that concern -- and you have heard some of the data that came from Russian studies -- but there is a lot of additional data that you haven't heard that came from studies by sponsors of xenotransplantation trials in this country, all of whom had banked such specimens, and all of whom were required to develop serologic and PCR assays and to go back and look at those specimens. If those specimens hadn't been collected, we would have been in a quandary as to whether to generate them by doing more human studies, and placing new patients at unknown risks -- the risks are still unknown, but the risks are significantly better bounded by the data that was able to be generated from archived specimens. So, I think there is an important lesson there.

As has been noted, long-term follow up is an issue that can and should be revisited. In fact, Dan alluded to the fact that we are revisiting it in the area of gene therapy, and it is important to point out that there is a lot of relevance and connection. One of the principal vectors used in gene therapy experiments has been retroviral vectors, raising many of the same concerns. Other vectors are used as well. In the last couple of years, we have increasingly identified that the standards that we set a few years ago may not be optimal ones, perhaps too stringent for retroviral vectors, perhaps not stringent enough for other vectors. We have had two discussions with the biologic response modifiers advisory committee already. We will have an additional one in October.

Our FDA experts, including clinical experts and retroviral and other biologic experts, including Dr. Wilson, whose work in this area and xenotransplantation, you have heard references, have been working on risk assessments focusing on what are the diseases of concerns, chronic neurologic diseases, cancers, what are the likely time frames, what are the best ways to screen for them. We will be having further discussions with that committee, as I said, in October. Those will be public. You would all be invited. We would like to -- and I assume we will at some future date -- revisit those issues in the context of this committee, particularly with the interest in this committee in having that done. We would certainly welcome your input.

The second issue is the issue of international surveillance and monitoring. There was one statement that sounded to me -- I may not have got it quite right -- that this shouldn't be done nationally; it needs to be done internationally. Of course, there is a truth that it needs to be done internationally but it shouldn't be, I think, taken from that, that we should not do it nationally. The WHO has expressed a lot of interest in international monitoring, at least in their early statements to HHS agencies they have indicated that the right approach, or the approach they are looking at, is to have national systems, and then have a WHO coordination set the standards for those systems, try to allow cross-talk. I think from a pragmatic point of view, to try to set up de novo an international system is probably not realistic. It should also be noted that this committee and the HHS agencies can, in fact, to the extent that we do move ahead of some other countries, set important precedents and set important example. That has already occurred in

xenotransplantation. Dr. Bloom, whom you know, from FDA and other from FDA and others in CDC and NIH have been involved in international discussions. I think that where we have set standards for how things should be done they have been considered very seriously. And in many cases used as important starting points for international efforts. So I would urge, while we recognize the need for internationality, I would urge this committee to not necessarily use that as a reason to wait, whether it is for surveillance systems or for guidance and standards development.

A brief comment – I think it was Dan’s comment or someone’s – about the field not moving along as well as we had hoped. I would simply say that I consider myself extraordinarily privileged over the last few years to be in a rather unique seat for observing the development of new biotechnology modalities. There is not a one of them, not a one of even the most successful modalities we have seen, that have moved along as well as people hoped. It seems to be the nature of this field that we have exciting new technologies, they get hyped, people expect in two or three years we will have miracle cures, we don’t, people get depressed, funding dries up. Then for those therapies – we don’t know yet for this one – but for those therapies that are useful, they rise up and take a place in the armamentarium. We have seen that happen with monoclonal antibodies, which took about twenty years before they started becoming important in the clinical armamentarium. Interferons were hyped and then panned and now have an important role, as has happened with many other modalities.

Regarding RDNA modalities, particularly in the area of sepsis, the whole industry grew and fell on sepsis trials. Recent reports suggest that there may in fact be new approaches to sepsis that are promising under development. Gene therapy remains to be seen. But suffice it to say it is not uncommon to see that. I think you don’t want to go too far with either the highs or the lows when you are dealing with a technology. Laboratory advances may move along pretty quickly in some areas, but development for something in the clinic is fraught with unexpected findings. You don’t know all the variables and you never move as quickly as many people would anticipate.

Finally I would just like to highlight my perspective that our society has had the wisdom to create an infrastructure that actually allows this field to move forward in a way that does appropriately protect the public and protect patients, while still allowing research to advance appropriately. This committee is an important part of that infrastructure and that the guidance and advice from this committee and from the public is critical to that. But that we have particularly, and this may sound somewhat self-serving, within Health and Human Services, a rather unique resource.

I know the FDA angle. The FDA is far larger than similar authorities overseas and one of the only, if not the only, that reviews protocols in advance for investigational agents, and stops them. That increased oversight allows more flexibility, the type of flexibility that some of you have called for. Furthermore, we are staffed with laboratory-based scientists, such as Dr. Wilson, Dr. Conn, who asked questions from the audience, retrovirologists, as well as clinical development experts such as Dr. Marzella, Dr. Bloom, a laboratory-based scientist. I can say, having had to make important decisions about PRV trials and stopped them, or having been part of the team making those decisions, that those are very critical resources to have available, the types of

expertise in how to assess how soon can a PCR be developed, how soon an serological tests be developed, what is reasonable for safety here? What exactly are the risks?

But not only in house to have committees such as this, the Biologic Response Modifiers Committee, to allow not only expert input but public input, something that advisory committees in many other parts of the world don't accomplish. And also to have what I think is extraordinary cooperation that has existed within HHS in this area between NIH and the CDC, with their wealth of expertise and resources and the PERV setting again is an outstanding example of that in terms of the studies that were done, the assay development, not to mention in that case the cooperation of scientists in industry as well. So there is an infrastructure here that can, I think, allow progress with appropriate oversight. I look forward tremendously to further input in this committee in terms of how best to do that.

**DR. VANDERPOOL:** Thank you, Jay, particularly for the perspective of the ups and downs of cutting edge research. We need to end our discussion here within four or five minutes so we can take a vote on the predominant issues we would want to look at in future meetings. Dr. St. Martin?

**DR. ST. MARTIN:** It has been stated by several committee members already that, in order to paint a clear picture of the potential of xenotransplantation, there should be greater availability about clinical trials. I would emphasize the nature of clinical trials. We should all keep in mind the scope of xenotransplantation products. Some may have greater potential for clinical use in the near future than others, and differential risks. So there is a need for information on the successes and failures of clinical trials, presented in accurate ways and in ways that are not misleading to the public and in ways that do not require an extensive scientific background to interpret.

**DR. VANDERPOOL:** Thank you. Brian?

**DR. MAHY:** Yes. I think we have been discussing the infectious disease risks the last couple of days. I have been extremely encouraged by what I have heard. I think the major problem in relation to this has been the issue regarding retrovirus, and particularly PERV, and the possibilities of having a pig herd that was completely free of this. It seems to be around the corner and I think it is very encouraging.

I have heard nothing in the last couple of days to indicate what I would regard as a true public health risk, which is the possibility of a new spreading infection developing from the act of transplantation. We have examples, the best one in nature, which I described, was the one done in Malaysia when 280 people became infected with a virus directly from pigs, which was lethal in nearly 40 percent of the cases, and not a single health care worker or anybody involved in dealing with these patients acquired the infection. I think we have heard really very little here to indicate there is a major public health risk in terms of a spreading infection coming from someone who has received a xenotransplantation.

The work that has been done, especially with retroviruses, have obviously leaped ahead by leaps

and bounds and I think they have been done mainly on the basis that this committee has been formed and these issues have been raised. We do need to be very careful to continue monitoring the situation, to continue to improve these methods, and also to be aware of new agents which will continually appear, as they appear, so we have these techniques available. But given that, I think the committee has done extremely well.

**DR. VANDERPOOL:** Thank you. Dr. Eda Bloom.

**DR. BLOOM:** Thank you. I will make this very brief. I actually didn't intend to make any comments, but I moved to the table when it became clear to me that I needed to clarify a couple of comments that I had made earlier. One is in regard to the 30 to 40 investigationals in a transplantation INDs that we have. I tried to say, and I think it is worth reiterating, probably half of those are not ongoing for some reason. Of the ones that are ongoing, the committee heard last time about an extracorporeal liver perfusion device and about neuronal cells being implanted, and about a product in which cancer patients' lymphocytes are exposed *ex vivo* to cells from *Drosophila* – those are fruit flies. Those really are very, very highly representative of those that are ongoing.

The other correction that I wanted to make is that FDA does not approve these ongoing trials. There is no stamp of this is okay to go. But what it is is that it allows them to proceed. If something goes wrong they are not allowed to proceed. So the word approval may sound small, but it gives a sense of – I don't know – a stamp of approval that is really not applicable to any investigational drug, perhaps to other investigational devices, but not to any investigational drug.

The other thing I wanted to comment on actually, the idea of the different spectrums of xenotransplantation products and the idea of the fifty-year recommendation applying not necessarily to the surveillance of the patient, but to archiving of samples and of records. In fact, the samples that are recommended from the health care workers include only baseline samples. Those are pretty much collected in health care workers anyway. This would just be collecting a little bit more for xenotransplantation.

**Agenda Item: Setting the Stage for Future SACX Deliberations.**

**DR. VANDERPOOL:** Okay, it is vote time. I have a couple of announcements to make before vote time. One is, obviously several of you have voiced concerns about what is happening at the international level. One of the things we started talking about yesterday was, at the very least we need to have a central person to whom information about national meetings on xenotransplantation are held. That person I wish to anoint and appoint as Mary Groesch. Any of you in the audience or anyone here who knows of important national or international meeting, let Mary know.

Secondly, someone on this committee should be going to those meetings. I know, in talking to several of you, that you have been going to some of these meetings. But we need to have a representation there and we need to begin build some connections between the people there.

Third, we need, I think, at every meeting, to have brief reports from the SACX members who have attended various international meetings so that we will begin to have a feel for what is going on and begin to establish some knowledge in association with them. That is the least we can do. We may not yet be able to spend an entire session on international issues. I don't think we can afford to do that right now, but we can do that. Can we all agree that that is what we should do? Have Mary as a central focus point. Someone on the committee – anyone volunteering to Mary and willing to go. Any of you already invited to these meeting, give a brief report of what occurs there. One of the things you can do – you can't speak obviously for the entire committee, but you can help educate the meeting as we had from Canada yesterday, the US has this active committee and about some of these issues.

Secondly, what I am hearing, which is a highlight on my ideas for future meetings, is we need very much to be able to hear about and review the current and proposed xenotransplantation clinical trials. That will have to be in part closed meetings, as someone has pointed out.

Everyone in favor of our having a focus on current research, the problems that are being faced, the changes that are being made, and so on – everyone in favor of our having a meeting on those issues about our current research in both pre-clinical and clinical – we can have a review of preclinical, but focus on clinical issues – everyone in favor of having that raise your hand.

I think we are unanimous on that.

**DR. MICHAELS:** The ones that have stopped – that had some humans that had undergone procedures in the IND even if they are not ongoing right now would be willing to give us information on what happened wrong, what problems were unexpected, that might be helpful.

**DR. VANDERPOOL:** Absolutely. I talked both with Jim and Louisa about the trial with Parkinson's disease. We can raise all kinds of questions – were there enough patients? Even if a minority are affected positively should these trials be ended now or should they go on? So absolutely, we need to know what trials are needed, why they were ended and whether they are still yet promising.

**DR. BERGER:** One question. There are some guidelines that are floating out there about public disclosure. Some of that information. I would just like an update on where that is?

**DR. VANDERPOOL:** We don't have time to do an update, but to set up that meeting –

**DR. SIEGEL:** I can do twenty seconds on that. In January we published a proposed rule that would allow for substantial public disclosure of the essence of what is submitted to the FDA in INDs for xenotransplantation and gene therapy. It was out for a public comment period for a couple of months. That period has completed. Extensive commentary was received and it is currently in review in the Agency. At some point, after review, we will have a rule or a revised proposal or we will withdraw the proposal or whatever, depending on our assessment of the commentary.

**DR. VANDERPOOL:** Thanks. I read those proposals very carefully and I think they are very important. There would be some issues that could not be discussed in public, but for the most part these are to be public and I think that is excellent.

Third, I was accosted - that is obviously far too strong – I was invited and encouraged to come to meet with the people from various federal agencies here and one of their requests, and I endorse what Lilly said, was that we develop two or three working groups on a couple of issues, two or three issues, and we could have four working groups on only two issues. The two could eat and drink together. Actually we need some working groups and one of the requests we had was for the working group in this committee to work on guidelines for consent forms related, informed consent for recipients, related to xenotransplanted organs. I think that is really important. The guidelines would not have to be a consent form, though perhaps an example could be given, but would have to do with guidelines concerning who would be on the local committee. It could have a topical outline with a brief description of what needs to be under that outline, of the issues that need to be included in all consent forms. One of the headaches the agencies have had is to hammer out and debate and come back on what the consent forms ought to include. We have on this committee lawyers, ethicists, policy makers, people who are aware of psychological and social issues – we need a subcommittee that can work up a draft of the informed consent guideline for recipients.

Third, this group encouraged that a committee of this group talk about and at least address the question of “third party consent.” Now third party consent is a twenty-five cent word meaning contacts and health care workers and maybe communities. It may not be feasible to have consent. Maybe what we would come up with is we need certain bodies of information given to these parties. But we need to address that issue. We need to take it on. Encouraged by the ex officio members, every one of these statements, both informed consent guidelines and anything dealing with wrestling over whether we do or don’t need third part information, needs to consider all the federal documents that have been well thought out and addressed as issues. If you need other information we can gather that for you. For example, Charlie McCarthy has done an interesting article on informed consent for xenotransplantation. That has been addressed in the IOM report of 1996 and so on. So there are federal documents and there are other documents that could be used to bring those together.

I do think we need to continue to stay abreast of what the federal guidelines are. So I back what has already been said – read them, read them, read them. I think some of the committee members have worked carefully with them; other perhaps have not.

Other issues. In future meeting we should look at whether children should be used – not used – should be subjects of xenotransplantation. There is a debate on reasons why they should or shouldn’t. I don’t set that out as a priority. But I think the two priorities for future meeting involve first off, knowing what is happening in ongoing proposed and ended research protocols. I think we need to ask this question about what this group should like to do. Would you like to suspend any further investigation of infectious disease until after we have that meeting? Would you rather go in further depth on infectious disease and hope to be able to write up some kind of segment?

Those who would rather delay infectious disease until after we deal with all the protocols, raise your hand.

Those who would rather pursue infectious disease issues further and seek some kind of a statement regarding advice to the Secretary and perhaps the public, raise your hand.

Okay, so I think we are about split on that.

**DR. SALOMON:** Can I ask for clarification on that? What I am concerned about is I don't – personal opinion – I don't think we are ready to make a statement that this is it. However, I think if you put it as this is where the state of the art is in infectious disease, with all of the appropriate qualifications, so that the Secretary would get a clean statement after a given date that we sign off on it, that this is where it is at.

**DR. VANDERPOOL:** Dan, that is what we are all talking about. When we say statement, we are not talking about ex cathedra pronouncements. We are talking about a description of where we are with respect to infectious disease issues.

**DR. SALOMON:** Then I would vote that we could do that. I don't think we need to spend hours more educating everyone on this committee to where xeno infection is. I think we have spent a lot of time on it.

**DR. VANDERPOOL:** I tend to agree with that. As is often the case, I tend to agree with you heartily because there are obviously people on this committee who are superbly trained in these issues. We have access to the federal agencies and to friends and colleagues and to bring together a draft description of where we are would be, I think, of value both to the Department and to the public. So everyone in favor of our moving in that direction, of doing a descriptive statement of where we are at the present time in infectious disease concerns, raise your hand.

(There was a show of hands.)

**DR. VANDERPOOL:** I think we have unanimity on that. I think what we need to do, Mary, is secure the enthusiastic volunteerism of the people on this group, all of whom are busy obviously, for one group to bring together a draft of an informed consent guideline, and another bring together a draft concerning where we are in terms of infectious disease. I think we are agreed on that. So the meetings to come probably would be to focus on the present research that is being done in this area so we can come right up to speed on that and within that meeting I think we could have a session or two on the informed consent draft, as well as a session or two on the descriptive statement that we could sign off on.

Obviously we don't all have to sign off on a descriptive statement – we could say the majority of the committee, or we could even give the numbers on the committee who agree with it and those who dissent. Dissenter could possibly put together why you dissent. But I think that is excellent.

**Agenda Item: Closing Remarks.**

This has been great and thanks so much for your incredible patience in our going over time and your incredible contributions. I was extremely impressed, as I thought I would be, at the various statements that everyone made. We have a highly expert and diverse group of thinkers. I thank you personally and as chair of the committee for what we have accomplished in this day and a half.

(Whereupon, at 11:38 a.m., the meeting adjourned.)