DR. McCULLOUGH: Yes.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: Yes.

DR. FREAS: Dr. Linden?

DR. LINDEN: Yes.

DR. FREAS: Our industry rep?

DR. PETTEWAY: Yes.

DR. BOLTON: Now, I'd like you to note that I specifically left out the single donor processing because I would like to consider that separately. I believe that we can take a more definitive vote on that and I would suggest that the committee recommends that at this time single-donor aseptic processing be the default standard, if you will, and that pooled processing only be considered under a special application to the FDA.

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: Yes.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: Yes.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: Yes.

DR. FREAS: Dr. Bailar?

SPEAKER: Yes.

DR. FREAS: Dr. Pardo?

DR. PARDO: Yes.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: Yes.

DR. FREAS: Dr. Doppelt?

DR. DOPPELT: Yes.

DR. FREAS: Dr. Bolton?

DR. BOLTON: Yes.

DR. FREAS: Ms. Knowles?

MS. KNOWLES: Yes.

DR. FREAS: Dr. Belay?

DR. BELAY: Yes.

DR. FREAS: Dr. Priola?

DR. PRIOLA: Yes.

DR. FREAS: Dr. McCullough?

DR. McCULLOUGH: Yes.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: Yes.

DR. FREAS: Dr. Linden?

DR. LINDEN: Yes, provided it's not too restrictive.

DR. FREAS: And our industry opinion?

DR. PETTEWAY: Yes.

DR. BOLTON: We now come to Question 2. Believe it or not, we're only to Question 2. This is going to take I think some discussion but perhaps not very long to vote. Ruth?

DR. SOLOMON: Question 2, "Please comment on the design of a satisfactory TSE agent clearance study for HCT/Ps in terms of the following criteria: (A) suitable TSE agent strain and animal model (B) accept measurement of abnormal forms of prion protein alone or require infectivity assays (C) accept substantial reduction or require complete elimination of detectable prion protein and/or infectivity (D) accept a single validated method or require that more

than one validated method for eliminating TSE agents be included in the study.

DR. BOLTON: Before I open this up for discussion this is not so much a voting issue but a recommendation and I think that we have heard in Dr. Rowher's presentation today as well as in several presentations in the past that in each case of these questions it really depends on the specific tissue that you're looking at and the specific process.

So we could spend from here until next Sunday discussing each possibility but I think it's not really worthwhile. It is clear that there is a variety of suitable agent strains and animal models to be used, each depending, as Dr. Rowher suggested, on what tissue you're looking at, what process you're looking at.

Either looking at PRP scrapie as a physical marker and/or infectivity as a biological marker can be acceptable or not

acceptable depending on which approach one is using and et cetera. The reduction in titer that's required, again, varies on the type of spiking, the source of the spiking, the type of process, the expected bioload in the tissue, and clearly it would be desirable to have more than one validated method but in some cases a single validated method may be all that's possible.

So, having said that and given my own opinion on all of those, I'll open it for discussion to get any other information and opinions so that we can communicate those to the FDA.

Yes, Steve and then Sue.

DR. DeARMOND: These are not yes and no answers. There's no way we can do that. These are Blue Book answers. We all should have been handed out our little essay books because the --

DR. BOLTON: Well, this is your chance. It says to please comment on. So

you can --

DR. DeARMOND: Yes, please comment on suitable TSE agent strains. Of course, every strain has really markedly different properties. A new variant CJD and CJD are really markedly different and they really require different animal models. The bovinized transgenic mouse does beautiful with variant CJD and the humanized ones don't do very well at all and the ones that respond to CJD itself are quite variable. From the MHU2M model to the HUPRP model they all have different properties and each one of them may be valid under different conditions.

An overexpression of those may, as Paul Brown brought up, create false positivities. On the other hand they create short incubation times so that you can get answers quicker. So this is a very complicated question with many answers to it.

And there are two components, strain and the model. It's not answerable at this stage without a blue book.

DR. BOLTON: Sue?

DR. PRIOLA: David, I completely agreed with what you said to introduce this and I'd just like to add that at least on part B, which is the only one that I feel comfortable even making some proclamation on, and that's that given what Bob Rowher has shown us that there should be a requirement, no matter what is decided, depending upon what tissue you're looking at, what your requirements are, that infectivity should always be assayed for because to my knowledge I've never seen any convincing evidence that you can correlate lack of PRP-SC with lack of infectivity or correlate level of PRP-SC with level of infectivity. So at least in that Part B infectivity remains the gold standard and should always be.

DR. DeARMOND: Could I comment on that?

DR. BOLTON: Yes.

DR. DeARMOND: There's no question. Infectivity is the ultimate gold standard. The problem is with low titer infectivity on an instrument or in a tissue or one of these processes it could take a year and a half to two years to 500, 600 days in a mouse model to get an answer, which is beyond what most people will wait for, which is why that would be the last resort.

If the PRP model, if the PRP measurements, which can be done in the order of 24 hours, are negative, if the titre is so low that PRP scrapie doesn't even show up in it, then I think you go to the next model.

DR. PRIOLA: Just real quick. That's right where Part C would come in. That's part of your blue book thing. You'd

have to make the decision what constitutes an acceptable or not level of infectivity and what would be a cutoff point for an experiment like that.

I'm just saying that infectivity I think should be given heavier weight always than PRPSC.

DR. BOLTON: Steve?

DR. PETTEWAY: I think maybe an analogy to some of the things that we've done with plasma, for instance, that it's really going to end up being a combination of things because you're looking at more than one parameter showing that any of this inactivation or removal that removes infectivity is important.

Showing that it's valid and reproducible is also important and that may not be feasible with infectivity. So demonstrating you have a correlation between the process's ability to remove prions in infectivity and in using the prions to

demonstrate reproducibility makes a lot of sense.

So I think that requiring that there are validation studies to demonstrate reduction and then leaving the details of that to whoever is doing the studies to produce a valid study based on what's available makes the most sense rather than trying to dictate it up front.

DR. BOLTON: Additional thought and discussion? John?

DR. BAILAR: Is anything known about the infective dose of these things? Is one prion as bad as 100,000 or whatever?

DR. DeARMOND: It's something like 5,000 PRP molecules for one infectious unit, something like that or 50,000.

DR. BOLTON: It depends again on the model but it's somewhere between 10,000 and a million depending on -- I mean, this is, again, it's as complicated an issue as you can get. It's different if you look at

mouse versus hamster.

DR. DeARMOND: And strains within those are all different.

DR. BOLTON: That's right so it's very complicated and how you relate that to one infectious dose in humans is completely unknown. We did not how many PRP molecules are equivalent to one infectious dose in humans and, of course, it also depends on the route of inoculation and everything else.

DR. DeARMOND: And, of course, the other complication now is we have this soluble protease-sensitive PRP scrapie, which seems to be in some strains of an agent 50 percent or more of the total PRP scrapie. So it's getting to be more complicated and the assays that are being developed now look at both the protease-sensitive or the soluble PRP scrapie plus the protease-resistant PRP scrapie. You get curves that define different strains of

agent based on their being able to separate the two.

DR. BOLTON: Other comments? We're not going to vote on anything here. If there's anything regarding this particular issue that you want to communicate to the FDA now is a good time to do it.

MS. KNOWLES: Just from my experience with the BPAC Committee there have been many times when actually there have been people internally at FDA who have developed algorithms that then they brought to the committee for review and suggestions and comments and maybe that's something to think about with this particular issue, too.

DR. BOLTON: Dr. Gambetti?

DR. GAMBETTI: I think what I would include in the recommendation is that really, as was said already, one has to use probably a different method according to the situation. So I think we all agree that it

would be nice to have. There should be some clearance study. But they may not be one study, and there is no way to decide at this point. One has to compromise time versus sensitivity of the test and that has to be open according to the system.

So this would be a recommendation. These tests are needed. These questions actually are a little bit ahead of the time. That is the problem. But there has to be flexibility on which one to use according to the situation.

DR. BOLTON: Yes, I agree. I think that's basically what Steve was saying as well.

DR. PETTEWAY: Just one more follow-up. I don't think that the committee or even the FDA and certainly I would not have predicted the method that Regeneration Technologies is using to get into the bone, to extract what's in the bone, the pressure. I mean, I think it's important to allow

industry to use some of the mother of invention philosophy, which is require that the clearance or removal is demonstrated but leave it up to the people that know the specifics to invent methods to do it, not limit them.

DR. BOLTON: With the assumption that they're going to run that by the FDA before they start their studies and they're going to get some agreement that that's going to be acceptable once it's done because nobody's going to launch into one of these several hundred thousand dollar or million dollar clearance studies without knowing that the end result is somehow going to be acceptable to the FDA.

DR. PETTEWAY: Just to comment on that just again from all of our experience in the plasma industry we did that up front and the FDA was very open, very receptive, and very helpful in all of the studies in designing the studies as we went through

this. I'm sure they would be the same in this regard.

DR. BOLTON: Absolutely. Now, what I would like to do is take a break for 15 minutes if it's --

MR. PARDO: Before you move on to the next subject I have not heard an answer to this question. Does the committee now support the FDA additional donor questionnaire for tissues related to travel? Previously this committee had voted against it.

Several of the presenters talked about the impact on the industry, and yet it is almost 6:00, and I still don't know the answer. Thank you.

DR. BOLTON: I don't believe that was on our agenda to consider this morning, today at least. It was whether we support the European travel restrictions for tissue donors, right? Jay, I think it's on the agenda for tomorrow.

DR. EPSTEIN: No. I mean, Topic #2 is the draft guidance that we published which contains the travel exclusion recommendations so we're about to discuss that.

DR. BOLTON: After the break. So let's meet back here in 15 minutes. That's at 10 after 6:00.

(Recess)

DR. BOLTON: We will now begin Topic #2, which is the FDA Draft Guidance on Preventative Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and variant Creutzfeldt-Jakob Disease by human cells, tissues, and cellular- and tissue-based products.

And after having said all that I'll just remind you that this is in fact a draft guidance. And so the first presentation will be by Dr. Melissa Greenwald, and she will present the Draft Guidance. And then after that Dr. Allen

Williams will present the Possible Effects on Tissue Supply. Dr. Greenwald?

DR. GREENWALD: Thank you. To update the committee and in order to do this I'm going to be presenting background information about how the draft guidance came about and point out the main differences between the tissue draft guidance and the blood final guidance which has been published and present the specific recommendations that are made in the draft guidance.

The need for guidelines to prevent the transmission of CJD and vCJD was discussed at a January 2001 TSC Advisory Committee meeting. The committee did vote unanimously that there is a significant risk of transmission of vCJD from HCT/Ps as compared to the risk of vCJD from blood transfusions.

The committee agreed that the tissues for the greatest risk for

transmission are dura mater and cornea and the committee also stated that there is no reason to believe that the risk for transmission of vCJD in tissues is less than that for sporadic CJD.

There was a majority agreement that the FDA should recommend donor deferral criteria for possible exposure to the BSE agent. It was also noted that there needs to be a way to make allowances for HLA-matched hemopoietic stem cells.

There was no advice from the committee regarding specific deferral criteria, including such information as what countries to include, time periods of potential exposure, or duration of exposure. There was no vote regarding whether a donor history interview should be required for all HCT/P donors.

Because of CBER's concern for the potential public health risk associated with vCJD in tissue and based upon the

recommendations of the committee a tissue draft guidance was written and was published this month. The guidance was modeled after the blood guidance that was published as final guidance in January 2002, using the same donor deferral criteria. So we used the same criteria. At this time there is no information available about risk reduction versus supply reduction for tissues like that that is available for blood.

There are three main differences between the tissue and blood guidances. Since a tissue guidance will not be implemented until after the donor eligibility rule is finalized we're not going to do a two-phase implementation of this. Also, the tissue guidance has wording that may sound confusing but we will not disallow the collection and use of HLA-matched hematopoietic stem cells in cases of urgent medical need when there's matching issue.

Also, because little is known about the impact of this guidance that it would have on the tissue supply there is a request for firms to submit data either known or generated assessing the impact of these recommendations on the tissue supply.

Moving on to the content of the guidance itself, I'm only going to go into detail about the specific recommendations and just give you an overview of the rest of the document. The background section establishes the regulatory authority for creating this guidance, states the public health concern regarding CJD and vCJD, and also explains the TSE Advisory Committee recommendations that we just discussed. There is also discussion about CJD and vCJD as disease entities giving information about clinical presentation, diagnosis, and epidemiology.

There is discussion about the basis for making a CJD recommendation,

including previous recommendations made in guidance as well as a discussion of known cases of CJD transmission by tissues. The tissues known to have transmitted CJD include dura mater and cornea.

Next there was a discussion about the basis for making the vCJD recommendations. There's a listing of the five currently recognized risks of exposure to BSE agent, and includes supporting information about the exposure risks.

And finally the recommendations themselves. It is recommended that firms determine ineligible any donor who has any of the following risk criteria.

Number one is any donor who has been diagnosed with vCJD or any other form of CJD.

A donor who has been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system or any other neurological disease of

unknown etiology. However, a tissue from a donor with dementia may be acceptable based upon an evaluation by the medical director if it is confirmed by gross and microscopic examination that the dementia is caused by cerebrovascular accident, a brain tumor, head trauma, or toxic/metabolic causes and is confirmed not to be caused by a TSE.

Donors who have an increased risk of classic CJD, those being recipients of dura mater transplants, recipients of human derived growth hormone, or persons with relatives who have CJD.

Donors who have spent three months or more cumulatively in the UK from 1980 through the end of 1996.

Donors who are current or former United States military members, civilian military employees, or dependents of military or civilian employees who resided at US military bases in Northern Europe for six months or more from 1980 through 1990 or

elsewhere in Europe for six months or more from 1980 through 1996. And yes, these geographical locations are defined in the document.

Donors who have lived cumulatively for five years or more in Europe from 1980 until the present. And this time in Europe will include time spent in the UK from 1980 through 1996, which is one of the other deferral criteria.

Also donors who have received any transfusion of blood or blood components in the UK between 1980 and the present.

And the last one is for donors who have injected bovine insulin since 1980 unless it can be confirmed that the insulin was not manufactured from cattle in the UK.

Some important additional information that is contained in this draft guidance. As I said, all geographical references in the deferral recommendations are defined. Recognition is given to

HLA-matching issues with hematopoietic stem cells. If hematopoietic stem cell donor would otherwise be determined ineligible by recommendations 3 through 8 the risks of using the cells may be outweighed by the benefits and in that case HSCs may be collected and stored and their use may be considered an urgent medical need.

It's also recommended that the CJD/vCJD screening questions be included in the donor's medical history. Unfamiliarity with the term "CJD" may be taken as a negative response. Donors who have CJD in blood relatives are excluded unless the diagnosis of CJD was subsequently found to be inaccurate, the CJD was iatrogenic, or lab testing shows that the donor is without the mutation associated with familial CJD. Obviously this is going to be more important for reproductive donations.

There is provision to allow HCT/Ps from donors considered ineligible to be

retained for nonclinical scientific or educational uses with proper labeling and storage and industries affected by this draft guidance are encouraged to submit any data that they have now or could obtain through studies concerning the effect of implementation of these recommendations on the tissue supply.

And this is currently draft guidance and is not necessary to be implemented at this time. When final guidance is issued there will not be a two-step phase in period.

So our charge to TSEAC today is not a vote. We would just like for you to comment on the recommendations made in this draft guidance. You directed us to make recommendations for donor deferral and these are recommendations. We would also like you to please consider how information may be obtained about the effect of implementing these tissue donor deferral criteria on the

tissue supply in the United States and the next speaker, Dr. Williams, will be speaking more directly to that issue.

DR. BOLTON: Thank you, Dr. Greenwald. Are there questions now for Dr. Greenwald or would you like to hold them until after our next presentation? So Dr. Williams will now present on the possible effects on the tissue supply of the draft guidance.

DR. WILLIAMS: Thank you. As most of you are painfully aware, the discussions related to the travel deferrals to protect against the theoretical risk of variant CJD exposure was a carefully constructed balance between this theoretical risk and the estimated loss of blood donors which in itself would have a negative impact if that would exceed certain levels.

So what I'm going to discuss today is very briefly some of the considerations that went into arriving at the data which

allowed those discussions and then some of the implications for the tissue donor pool which for the most part is far less well-defined than the blood donor pool in general. And I'll end with a few comments as a segue into tomorrow morning's discussion on some of the impact in the blood donor pool of the latest guidance related to variant CJD.

Very briefly, in early 1999 surveys of donor travel were conducted. This was a cooperative venture between a number of blood centers and the survey was conducted actually at the request of this committee to provide travel data related to travel in the United Kingdom and we also included Europe in that survey measurement.

These surveys were done among geographically and demographically representative blood donor populations and ultimately they supported estimates of the national impact of a travel deferral on a

donor population with many assumptions inherent, one of the major ones being that in the face of the very limited information a linear response existed between travel in a country that had potential BSE contamination of its meat supply could be equated to potential to transmit variant CJD through a blood donation.

The estimates that arose from that study ultimately include the level of donor loss that would occur at different time exposure levels, and secondly the estimation of the overall risk burden, again related to time, and a portion of the risk removed by different policy options.

Going back to June 1999, this was the initial graph shown to this committee, which basically used that time travel information to compute the overall burden of risk and the percentage of donors that would be deferred in any given time period used as a deferral criteria and, as you know,

ultimately in that initial policy decision we ended up with a deferral for six months travel in the United Kingdom at an estimated loss of 2.2 percent of the donor supply and a removal of about 86 percent of the theoretical risk based on that risk burden estimate.

The methods used in that estimate were a random sample of donors at 12 blood center sites in really a very short time period, a two-month time period. We mailed out 19,000 anonymous scannable surveys in a single mailing with a cover letter, got about half of those surveys back, and the survey asked questions about travel, basic demographics, sex and age, first time or repeat donation status, and educational level.

Now, there has been a history of conducting surveys within the National Heart, Lung and Blood's REDS study and this really served as the basis for attempting to

collect the data by this mechanism.

Some known advantages from this in prior surveys is that in the setting of a well-defined sampling frame and experienced field sites, surveys are well-established, reproducible data collection tool for the blood donor population and there are now quite a list of published studies from REDS and others showing that this data are reproducible.

In addition blood donors being a special population they generally provide a favorable response rate. If you get down under 50 percent you start to wonder about the validity of the survey rate's internal validity and we generally enjoy a 50 to 70 percent response rates depending on the length of the survey.

Also, the anonymity factor is important, particularly when you're measuring something like donor risk, because if you have information in a linked manner

it implies some sort of operational consideration for blood that may have been donated previously. Also, surveys allow a wide scope of information and simultaneous collection of demographics so it applies real-time data collected that can be stratified against different variables, including demographics, and really very easy to conduct analysis.

However, surveys do have limitations. The findings tend to be reproducible but difficult to validate against truth by another mechanism. Some important sample subsets may be underrepresented in the response. For instance, we tried to get data about military populations and the extent that they traveled in the UK and Europe. We got something like a 10 percent response rate. So obviously the data there weren't terribly reliable and in fact that has turned out to be a very important variable in a blood

donor setting.

The Office of Management and Budget under the Paperwork Reduction Act requires review and approval of data collection using federal funding. Under survey mechanisms this generally takes from six to twelve months to get that approval. So any sort of rapid response capability that is a hurdle.

And finally in conducting information like we would need to make these sorts of estimates you have to deal with a matrix of multiple countries visited times in multiple travel time frames and that makes a lot of complexity in the survey document.

For instance, this is one question out of the 1999 survey, did you live in the UK, and then lists all the countries included in the UK or the Republic of Ireland between '80 and '89 or 1990 to 1996 and then provides a total of nine different

categories of time periods. So it's complex for the donors to answer this as a survey.

Now, in thinking about how to assess impact on the tissue donor pool the media thinking is well, we'll do a survey and see what the responses are likely to be. The problem is it's a little different population, a little different setting, and even in a donor screening situation it's going to have some different characteristics and I just wanted to point out some of these difficulties and make some suggestions as to how facilities might approach collecting data and then as requested submit this to FDA to document what the impact might be.

First of all, the tissue donor pool has epidemiologic characteristics but they're really not well-defined compared to the blood donor population. Even blood donors in the typical blood center of the demographics beyond age, sex, and ZIP code are not too well known and really through

the REDS study have we been able to collect extended demographics like educational level and travel by specific survey mechanisms. So in general tissue donors are not well characterized so the sampling frame is a little difficult to establish.

Sites generally are not experienced in research data collection. Those of you who have conducted surveys know that if you put a stack of forms on the table and ask someone to fill them out you won't get a very well-controlled data collection and subsequently the data may not be that reliable. So trained staff is very important in doing something like this.

In the face of unknown demographics perhaps one way is to assume general population demographics for the tissue donor pool. That will certainly vary where demographics are known. In the case of semen or oocyte donors there are age restrictions and those can be factored in.

Motor vehicle data on organ donation perhaps might be relevant to tissue. I don't have those data available but perhaps that might get a sense as to what the demographic shifts are in terms of willingness for an individual to identify themselves as organ and tissue donors.

The tissue donor populations have been described. This is information provided by Dr. Solomon from musculoskeletal and skin. We're talking approximately 20,000 donors or 750,000 tissues, ocular tissues, mainly corneas, about 47,000, including 5,000 non-US tissues.

And in the future potential regulatory oversight of cord and peripheral stem cells, dura mater, semen, oocytes, where again even the donor pool size is as well as the demographics are unknown at this point except for the known age restrictions.

In the blood donor setting, as presented before, there are several stages

of donation and in the blood donor setting I think it's pretty clear that most of the self-deferral done by donors occurs before they ever appear at a blood center to donate the blood.

That's through information provided through the media, letters transmitted by the blood center, telephone conversations with the blood center at the time they make an appointment, and so forth. There's also some self-deferral at the actual blood collection site. Then there's the interview-based deferral data from this you'll be seeing tomorrow from a number of blood organizations. And the final category, those who fail to appropriately defer. And this has implications because, one, it's a false negative response, which obviously we try to avoid, and secondarily there are some implications of having post-donation information available on a product that's been previously collected.

This is a shift that I would predict would occur for tissue donors. Clearly self-deferral before collection might be applicable in some cases but certainly for cadaveric donors that's not a consideration and probably the primary way of collecting data is going to be by secondary interview of family members or others who know the donor well.

This raises a new issue. Whereas an individual may know their travel history, complex as the question may be, relatives may have a much more difficult time answering that question and we'll probably have to address the don't-know factor. I know this individual was in the UK for a period of time. It might have been two months, it might have been two months. I just really don't know. I suspect that's going to be larger in the tissue population.

Again, there's going to be a failure in some cases to identify a

disqualifying factor resulting in false negative responses. It may result in an ineligible donor or post-donation information and there needs to be considerations as to how to handle that information when that occurs.

The data from the blood donor surveys were looked at intensely demographically and the age and education variable clearly was the most associated with travel, as one might expect. There's an age-increasing prevalence of travel to the United Kingdom and this was confounded with the education variable.

The data shown here are for travel ever to the United Kingdom. This is not the six-month deferral. It's travel ever. And the overall figure for the surveyed population was 22.8 percent. And you can see the marked increase from those who have less than a high school education less than 1 percent travelled, some college 20

percent, those with post-graduate degrees 36 percent for an overall of 22.8 percent, quite a difference between the range.

Age also showed a big correlation, and in fact confounded the educational variable. Educational variable, while useful if the data were available, these are not generally available on most blood donor populations because the centers really have no reason to collect that information. So to try to stratify that would be difficult. Age, however, is available and you see a similar breakdown from the younger donors, 16.4 percent up to the older plus-65 donors approximately 31 percent.

Also, first-time repeat status, you see in general for UK travel by sex gender is not that much different, a little higher in males overall but you find if you look for the older population the women tend to travel as they get older and females exceed males in the older population but in

general it's an even comparison.

And then first-time versus repeat. A pretty clear distinction, first-time donors closer to about a 14 percent travel prevalence versus repeat donors, which comprise 80 percent of the donor population, much closer to the mean overall.

Now, how to assess the travel deferral impact among tissue and cell donors? Based on the factors that I've outlined, probably the major one being lack of an adequate sampling frame, the survey mechanism to assess tissue donor loss may not be viable. It may be possible on a local setting and if any sites wish to use the same or similar survey that was used in the blood donor survey we'd be happy to share that and you're welcome to try to collection the information but I think trying to define a well-constructed survey in the absence of a good sampling frame is going to be quite difficult.

One potential way to approach it is to consider travel deferrals for first-time blood donors at the local blood center in a geographic area where the tissue donors are being collected, particularly if one can do some age adjustment against the two donor populations.

This may reasonably predict donor travel characteristics of local tissue and cell donors. Admittedly some donors will have originated from other areas of the country but so do blood donors. It would be, I think, quite difficult to pinpoint differences in the two populations from that aspect.

Alternately for centers that implemented the deferral the initial impact of the variant CJD deferral for all donors at the local blood center might be usable. After about the first two months or so of implementation there's a culling effect of repeat donors so after that point one needs

to consider first-time donors only.

So that's one potential way to look at it and if sites could compute that figure and determine how that would impact the necessary tissues that they distribute that would be useful information.

Finally one might consider a well-designed pilot implementation program. I think this would get not only at the potential impact of donor loss but also could be used to identify operational difficulties, another area where I think FDA would be very interested in having information to produce the final guidance.

A second consideration here is that, as hopefully you'll hear tomorrow, there are some innovative programs being developed in the blood donor setting, ways to recognize donors who are lost by the deferral and actually provide incentives for them to identify donors to replace themselves. And as this continues a

deferred donor identifies additional donors that continue to be recognized by the blood center for their important contribution to the blood collection process.

So that's another area that can be used to help offset donor loss and a program started by Stanford is starting to pick up steam in some other blood centers now.

Finally I want to comment on the ability of our country to assess rapid data related to blood donor loss and tissue donor loss. The REDS study has been mentioned many times here and it's been an absolutely critical mechanism for data collection over the past 12 or 13 years. As it undergoes its renewal I'd like to suggest some things for the committee to consider and potentially recommend.

One is that the REDS collection sites be expanded from their current 6 up to 10 or 12 to provide better representation of the country, including some of the coastal

areas not currently represented. The site already has capable donor and donation data systems. Perhaps this could be expanded to cover areas like blood collection data, inventory, and distribution so that we better understand the dynamics of how blood is collected and used, which is also relevant to the overall supply.

NHLBI generally has been very responsive to HHS data needs. There are some things which would facilitate this further in a new study such as a rapid survey capability, provisions for providing OMB exemptions for critically needed data, having established IRBs which are educated to recognize blood donor-related issues, having experienced staffing on board to address the rapid response need, and then finally where the bureaucratic hurdles can't be surmounted potentially have some of the sites participate in private sector cost sharing to facilitate data collection.

In the 1999 survey actually the blood centers supported the data collection effort and it wasn't until the data was in hand and in a database that federal funds were then used to analyze it. So that's one potential way to proceed.

These are just some thoughts about the tissue donor pool and potential ways to get at the information survey mechanism. Again, we would be happy to share the instrument and the procedures, but it will be a little tougher task in this donor population. Thank you.

DR. BOLTON: Thank you, Dr. Williams. Now what we should do is take any questions or have any discussion regarding both of these presentations, which really again focus on the draft guidance to reduce the risk of transmission of CJD and vCJD in the human cell tissues and cellular-based tissue products.

Comments, questions? Dr. Wolfe.

DR. WOLFE: Perhaps this could have been said earlier, but then we would be later here. I really feel obligated to spend a minute or two on the whole issue of dura mater again. Dr. Gambetti and colleagues in a paper wrote I guess last year in Neurology, "Even the most stringent donor screening and dura mater processing practices may not totally eliminate the potential for an infectious graft. Because of this inherent albeit small risk of CJD transmission by dura mater grafts surgeons may want to consider the alternative use of autologous fascia lata, temporalis fascia, or synthetic substitutes, and there's also US-based bovine pericardium as well."

And I think that what Dr. Gambetti and his colleagues are saying is unlike the issue of the cornea, where there isn't any alternative, I mean, a lot of what we've been talking about today and I think that although a little prolonged it's been a

useful conversation, there are tissues that either are not a very high risk or are irreplaceable. You can't do synthetic cornea or retina or whatever else.

And the thing that distinguishes dura mater is (a) it is very high risk. It's two-plus, not four-plus, as brain but it's up there next to brain and there is a growing number of substitutes. When I raised this issue in the first incarnation of this advisory committee five years ago there was a vote essentially saying there was no circumstance anyone could think of where you couldn't use something other than dura mater.

There was a surgeon then, a neurosurgeon from the UK, who told us about the fact that at that time there had been a ban for I think eight years. It's now thirteen years it's been banned in the UK, five years it's been banned in Japan, and just last month after a poll of

neurosurgeons in Canada it was banned in Canada.

So we have three countries doing something that's much more intelligent than what has gone on here and I just want to raise this because under this topic of measures to reduce possible risk of transmission of CJD or Creutzfeldt as we were taught in the earlier days this has got to be seriously considered.

I mean, if it is necessary, which maybe it is, to poll neurosurgeons that should be done. I did a very informal poll based on neurosurgeons who had been residents when I was 35 or 40 years ago and two neurosurgeons to whom I had referred patients. One was at UCLA, one was at Hopkins, one was at the University of Virginia, and one was at Medical College of Virginia, and none of them were using dura mater, none of them said their departments had been using it for several years, and one

of them, John Jane, who is the editor of the Journal of Neurosurgery, signed the petition that we filed last August to the Device Division. Tell me why this is regulated as a medical device and I'll be informed.

So I just want to put this on the table because rather than seeing in Dr. Williams' last slide the future of an expanding number of people using cadaveric dura mater it's going out of style. You heard from several companies they don't do dura mater any more, to use modern vernacular, and this is an example of where the so-called invisible hand of the market place, the Adam Smith notion, should not be allowed to operate. This will die of its own accord. But we would all feel terrible if between now and the time it dies of its own accord without a ban by FDA there is another case in the United States. It would be a tragedy.

None of us who had an automobile

accident who would wind up unconscious in the emergency room and would need dura, would need some sort of repair to broken or destroyed dura, would like to have dura mater put on our brains. And if we don't and we don't want it for our families I don't think we would like anyone else. The minority of neurosurgeons really needs to be taken out of the loop on this. Enough of that topic.

DR. BOLTON: Additional discussion. Lisa?

DR. FERGUSON: I had a question for Dr. Williams. I mean, your slides on the number of corneal donors? There was a number on there, 5,000 non-US. Does that mean that they were non-US citizens but the corneas were harvested in the US or does that mean that those were obtained outside the US and brought in?

DR. SOLOMON: EBAA could probably answer this better but no, those are corneas

that were obtained in the US from US donors that were exported outside of this country.

DR. BOLTON: So they're exports.

Dr. Bailar?

DR. BAILAR: I'd like to follow up on Sid Wolfe's comment. I don't feel like I'm well enough educated about this to come to any decision today. Is it fair for us to ask FDA to come back at our next meeting with some specific analysis and perhaps a proposal? I'd like to hear directly from people who still use dura mater to find out why they do so.

DR. BOLTON: We're actually not considering anything to do with dura mater at this time. That's just basically a statement by Dr. --

DR. WOLFE: The topic is mentioned in the guidance. That's all. I mean, it's one of the topics there. That's all.

DR. BOLTON: Ermias?

DR. BELAY: I beg to disagree with

the assessment that the gentleman made. And the reason is I'm not aware of any CJD case that resulted from a dura mater that's processed under the current FDA recommendations.

In other words I'm not aware of any CJD case that's resulted from a dura mater that's processed under the current approved FDA recommendations. All the dura mater CJD cases that we've been referring to, almost all of them, the vast majority of the cases received a single brand of dura and that dura was produced before June 1987.

And that company was a single company producing a single brand of dura, which is Lyodura, so I think we need to make that distinction very, very clear.

DR. WOLFE: Most of the cases were, but the last case, and you're technically right, was a process using 10th normal, not 1 normal, sodium hydroxide. But the literature is replete with both scrapie

and other transmissible spongiform encephalopathy causing organisms being resistant to even 1 normal.

So I think that it's a little bit iffy. I agree with what Dr. Gambetti has written. Dr. Brown has said the same thing, that we just aren't sure, even with the modern methods, that we're going to be able to pick this up.

And if you combine that with the donor selection problem, and we've heard over and over again today that it is entirely possible that there is infective brain tissue in someone that has no pathological or clinical evidence of the disease, so if you combine the defect there with I believe still a residual defect in the processing and the presence of enormous alternatives I just don't see any need for it.

DR. BOLTON: I don't want to beat this to death. If we have discussion on

other aspects of the draft guidance other than dura mater? Yes?

DR. DOPPELT: I'd like to turn to the issue of the history of travel in England and Europe and the question is for blood donors, I mean, they're alive and you can ask them their own history. For tissue donors in general they're not alive and so what kind of accurate information are you going to get from the next of kin in terms of how long somebody was traveling, where they were, the specifics? I mean, they're probably not going to have that information. It's not retrievable.

DR. BOLTON: I agree. I think this is one of the key issues in terms of our input into the draft guidance in the previous meeting where we made some of these recommendations and now where we're being asked to comment on the draft guidance.

It's how do we deal with these don't-know questions that Dr. Williams

discussed and what impact these may have and how to ascertain what the impact will be in fact on actual tissue donations.

Because again we're faced with the same problem we had in the blood and blood products area is that we have to weigh the hoped-for increase in safety versus the ultimate loss of some tissue that's going to be donated and the impact on the supply.

And so I think that's an area that I would like to focus discussion on now, and get any questions out or thoughts about that. In other words how are we going to or how will the collection sites accurately assess the travel history and how will they handle the uncertainty? What does an "I don't know" mean? Did your loved one reside in England for three months or more from 1980 to 1996? And how is that going to be handled? Is there discussion?

DR. WOLFE: Just a suggestion on that. I mean, it is possible, obviously,

with the consent of relatives, near friends, to check passports. I mean, it's not quite the same but one can at least get some kind of crude information that has to do with foreign travel and where it is.

I mean, it's complicated but so is being in the dark and not having a clue because of exactly what was just mentioned about foreign travel, the person's dead. Passports are alive.

DR. DOPPELT: I'm on my second passport. I don't know how long they're good for but usually you pitch them and so that information may not be available. Second of all, if I croaked I don't think anybody would be able to find where I stuck my passport. I may even have trouble finding it.

DR. BOLTON: Lisa?

DR. FERGUSON: I have a comment and a question again getting back to how many cells and tissues are covered under

this and my focus is on the reproductive tissues, I suppose.

I'm very familiar with what's been done in the animal world in regards to the lack of transmissibility, especially of BSE, in semen, embryos, and oocytes. I wonder has similar work even been started or attempted in the human arena? Is there anything to draw from there?

And if there is, I mean, do we need to lump those into this type of guidance? Does that even make sense?

DR. BOLTON: I'm not aware of any information that would bear directly on infectivity in those tissues in humans. Steve, do you have? And Paul Brown is not here. Bob Rohwer, do you have any?

I don't know that any information exists in that area and extrapolating from hamsters and mice could be very risky in that sense.

DR. FERGUSON: Or even from cattle

and sheep would also be risky.

DR. BOLTON: Cattle and sheep, exactly.

DR. PRIOLA: This is Paul Brown's paper that was actually in our packet, thank God, and they had at least one instance where one patient tested semen and two patients vaginal secretion and neither transmitted. It's a very, very limited data but negative, which probably doesn't really mean much.

DR. BOLTON: Very good, Sue. You get an A-plus. Sue gets an A-plus for doing her homework. Dr. Bailar?

DR. BAILAR: I have two questions. Maybe we should take them separately. The first is what is the chance that somebody would still be an unrecognized carrier as a result of exposure, say, 25 years ago? Would most of them have come to the surface now with some kinds of symptoms?

DR. BOLTON: For variant CJD?

DR. BAILAR: Yes.

DR. BOLTON: We don't know that. I mean, we are in a probably early but impossible to tell apart of the epidemic curve for variant CJD in those individuals who have resided in the UK for their entire lives. Obviously someone traveling through and living there for three months or six months or a year, has received, if any exposure, a lower exposure and their incubation time clearly could be several decades or longer.

So I don't think that we can expect that a majority of variant CJD cases have appeared as yet, especially for those who have limited travel and limited exposure to the BSE-contaminated beef or beef products.

DR. BAILAR: The other question is why should it make a difference whether somebody was wearing a uniform? If some constraint is good for people who were in

the military while they were there why shouldn't it apply to everybody else and vice versa?

DR. BOLTON: You mean in terms of the exact wording of that restriction?

DR. BAILAR: The wording of the guidance here.

DR. BOLTON: I think it has to do with whether those individuals were eating on base or food supplied on base or whether they would have access to that food. Now, if you were a civilian living there but not associated with the military, not living on base, you would have had a different food supply. It has to do with the source of beef either in the northern European theater or the southern European theater. Much of that was sourced from the UK during the high-risk period and that's why there are the differences in the years that are described but that's basically what the difference is.

Other questions or discussion? Yes, Dr. Linden.

DR. LINDEN: Well, I really just wanted to second Dr. Bailar's comment. I think the feeling in the industry is that there's a concern about donor loss but in most cases people are not going to know and if the answer is unless you know definitively that's okay that might be okay. If the answer is well, you need to find out or defer then we basically have no tissue, I think. That would really be a problem. But perhaps there could be some sort of pilot study to really look at how this would apply in the donor tissue.

DR. BOLTON: This is my concern is that when you actually get to the mechanics of implementing this what's going to be the procedure when the answer is I don't know, and what's the time delay and just the basic fact of the close relative not having the information at hand, not perhaps being

motivated sufficiently to go out and find that information within a prescribed period of time, is that immediately going to lose us many, many donors for tissue? And I don't know that there's any way to answer that here except to ask for pilot implementation and to see the effects in those sites.

Now, the question is then who is selected to be the pilot site and who's going to volunteer to do that if that were the case. I'm not exactly sure how that would go. Perhaps, Dr. Doppelt, you could comment on that.

DR. DOPPELT: Well, I don't think anybody's going to be very enthusiastic about taking that project on. I mean, I think it comes down to what Jeanne said. You go through this donor screening form, which is fairly detailed, and it is up to the medical director to decide what's a plus/minus answer and which way do you

interpret it but with this situation you may wind up with yes, they were in England but I don't know when and I don't know how long.

And so then what do you do with that? You know that there could potentially be a problem. And so many people may just say well, pitch it, forget it, but that's going to have a negative impact on supply and perhaps unnecessarily so. So I don't think you're going to get many volunteers.

DR. BOLTON: Dr. Bailar?

DR. BAILAR: This might be a good topic for a little survey. You could ask people coming through for, say, blood donation was your spouse in England during this time period and if so for how long and see how many of them say gee, I don't know.

DR. BOLTON: I'm trying to think how you would validate the answers. I mean, you would get responses back and one way to view that would be what percentage of I don't know answers there were.

But in terms of the affirmative answers or the negative answers you wouldn't have any way of validating whether those affirmative or negative answers were in fact correct.

DR. BAILAR: I don't think you could directly validate them but I think there would be a fairly high level of accuracy if somebody says yes, he was stationed in England and I was with him for eight months or no, he was never gone from home as long as three months. That's pretty specific.

DR. BOLTON: I think it's worth considering having something like that done.

DR. DeARMOND: So what I'm understanding is we have no data on this at all yet or it's very speculative and so an experiment has to be run. And the experiment that's being proposed is that we use the same deferrals for blood and blood products and apply it to tissues and if we

implement that over the next six months to a year we'll see what the effect is on tissue donation. Is that one way to think of it?

DR. BOLTON: Well, I think we're a step back from that. This is a draft guidance which is now open for public discussion and the question I think immediately to us is what's our first feedback on this and obviously the comments from the public and the input from the public are being solicited before it goes then to guidance.

So I think basically what we did previously was we suggested that there was risk for variant CJD in these tissues and that something should be done. We in fact did not specify countries or times and what the FDA has done is to incorporate the guidance for blood donations.

DR. DeARMOND: And do we have any new data on that from the United Kingdom about the true infectivity of each of these

possible donated organs? Do we know more about the cornea?

DR. BOLTON: I think we know nothing more than we knew then.

DR. DeARMOND: So it's a reasonable concept that the cornea is going to be infected based on CJD itself, on sporadic CJD, but we don't know and we don't know about any of the organs. The viscera are involved in variant CJD but are any of the other --

DR. BOLTON: I note Nick Hogan standing up, probably to remind us that the article from Collin's group he discussed earlier --

DR. HOGAN: Nick Hogan. The infectivity of any of the partitions in sporadic CJD is less than .0025 percent that in brain, a variant CJD. In variant CJD retina it's 2.5 percent that of brain and in optic nerve 25 percent of brain. Those are the only good studies. The stuff that Paul

did was a gemisch of stuff that was thrown into chimpanzees and you really can't use that data qualitatively.

DR. BOLTON: So in that sense those data provide substantial justification for being concerned about corneal transplants from anyone who has been exposed to variant CJD and that's about the limit of what we have in terms of new information.

DR. DeARMOND: So we're to evaluate whether this guidance is a reasonable approach to it or unreasonable. Is that the bottom line?

DR. BOLTON: I guess so, yes, and probably variations in between.

DR. DeARMOND: Right.

DR. BOLTON: Parts of it may be reasonable but parts of it may be --

DR. DeARMOND: Once again we have no concept of the impact at this stage or very little concept. Like with blood, we have fairly good data on the impact of the

deferrals.

DR. BOLTON: Well, I suppose we had better estimates of the impact because we had more of the survey information that was done on that actual population because you have repeat donors and it was well known that, for example, there were coastal differences in foreign travel versus the central part of the country.

So we could recognize that there were regional differences and we had some way to calculate what the impact would be. Unfortunately, with the tissue donors there doesn't seem to be a ready way to get that sort of information.

I don't know if there's any sort of database on people who have pulled out tissue donor or organ donor cards, for example, and to try to assess that. I mean, the way that it's been done so far is to try to look at, again, blood donors and see how they fall into this.

But I don't know that you could make the leap from a blood donor to a tissue donor. So I don't know exactly how we would get this information except to try maybe to survey existing donors through surveys of their relatives at the time of donation before these are implemented to try to see what percentage of their existing population would be deferred under these guidelines.

DR. DeARMOND: So it gets down to an experiment?

DR. BOLTON: Essentially, yes.

DR. GAMBETTI: Is there a way in which one could get some information concerning foreign travel by tissue donors as compared to the blood donors by comparing the demographics of the two populations?

For example, if the AIDS subdivision and education and all the other parameters are similar I think what one could assume then the pattern of foreign travel might be comparable. So that would

be just a short cut but I don't know whether it's possible.

DR. DOPPELT: Well, if you wanted to do a survey of potential donors, I mean, it may be that we could persuade some of the tissue banks to do that. But in point of fact the tissue donors are the low risk. It's a low-risk tissue. The higher risk are the corneas and it may make more sense to do that.

On the other hand we also heard that 20 percent of the donors it's legislative consent so there's 20 percent right off the top that they're not going to have a clue. So you're dealing with 80 percent of the 45,000 donors so that may be a place to start but I don't think turning to the standard tissue donors is really the best way to go because that's really a low-risk tissue.

DR. DeARMOND: So that's a good suggestion, maybe focus. If that's for the

first one how you implement this is focus on the corneal donors and what information can be gained from them before we go to any other recommendation, before we implement the whole thing. They might be asked all these questions, if possible could be asked of their loved ones, and see if any responses of any importance to us can be derived. That would be a good idea, keep it to one tissue, a high-risk tissue.

DR. BOLTON: You mean keep the deferrals to high-risk --

DR. WOLFE: The experiment to one tissue, the survey or experiment, whatever.

DR. BOLTON: That sounds like a reasonable suggestion. I see a pained look from Ruth there.

DR. SOLOMON: I just wanted to comment on what Dr. Doppelt brought up about the I don't know. The same situation exists when we ask the next of kin these very detailed questions about the sexual habits

of the deceased in terms of MSM in the last five years or for a female donor have you ever had sex with someone in the high-risk group in the past 1twelve months.

Those are also difficult questions to answer and I'm wondering what does the industry do now when they get a I don't know on one of those.

DR. DOPPELT: Right. Actually, I think that's a little bit easier because when you get an I don't know there's no other source of information so probably unless there's something else to indicate in terms of the physical exam that might indicate that there was some high-risk behavior they would probably accept the donor.

On the other hand for travel in Europe, I mean, it's more likely that somebody will know yes, they did travel but then the details I don't know. So that actually puts you further out on a limb.

DR. BOLTON: Well, the real question is when the answer is I don't know is that interpreted as yes or no because you have to go one way or the other and, I mean, given the fact that these are rare and the risk is very low I suppose you could assume that accepting the donor could be the default but then basically what you'd be saying then is unless you tell me for certain that this individual falls in one of these categories we're going to assume that he or she does not.

What does the committee feel about that interpretation?

MS. KNOWLES: If someone says I don't know I think it's really better to err on the side of caution and you have to also remember in terms of high-risk behaviors that there are still a lot of people in this country who are men having sex with men, do not self-identify, will never tell anyone in their family, and I just think we have to

remember the literal translation of the word "assume" and just not assume.

DR. BOLTON: Dr. Bailar?

DR. BAILAR: I think again it would help to know whether the I don't knows are common or uncommon. If they're pretty uncommon it isn't going to matter much and I would throw them out. If it makes up a large part of that 20 percent I'd have to think again.

DR. WOLFE: It would seem that with 45,000, if that's the estimate of eye donors, corneal transplant donors, a year that with a survey instrument that was modified somewhat from the one used in the blood area and administered proactively to people as they are signing up or as their families are signing up for donors we could in a very short period of time get answers to the question Dr. Bailar raised, well, what percentage is I don't know, and actually start getting some demographics and

in probably six months accumulate enough date to have a much better idea of what we are dealing with with this highest of risks, putting aside dura mater for the moment. Because whatever recommendations there are to be made for the lower risk tissues they're going to be less stringent than this and this is doable, I think.

DR. BAILAR: Yes, the people you ask in this survey do not need to be next of kin of potential donors.

DR. WOLFE: That's right.

DR. BAILAR: They could be any kind of sample from that part of the population, like blood donors. I'm just trying to think of an easy way to get to enough of them.

DR. BOLTON: But I would suggest that with 45,000 corneal donations a year and I'm not sure if that means 45,000 corneas or 22-, but whatever it is you're still talking about in a half a year getting

5- to 10,000, perhaps, responses on a survey that could be fairly easily designed.

DR. WOLFE: Then the Eye Bank should be very interested in cooperating with us for reasons we've heard today.

DR. BOLTON: Right, so I think that that would be a reasonable recommendation for us to give to the FDA in terms of how to collect information on that. And that will tell us a lot about what impact this may have on donations if one were to implement this for all donations or only for corneas.

So I think we can assume that we've effectively communicated that to the FDA. And is there any other discussion with respect to the guideline? Hearing none, then I will adjourn the meeting. Move to adjourn the meeting for this evening, and we will resume in the morning. Do I hear a second?

DR. WOLFE: Second.

DR. BOLTON: All in favor? Take a formal vote. Very good. We stand adjourned until tomorrow morning at 8:30. But if you want to come here early you can have coffee.

(Whereupon, at 7:10 p.m., the PROCEEDINGS were continued.)

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