live alone. They could go unconscious. They could die. This happens. This is recorded as happening. A lot of people live in fear of that.

A study by the British Diabetes Association found that 47 percent of its members experienced some different problems when they were transferred from bovine insulin to the biosynthetic human insulins during the mid to late '90s.

I have chosen to use beef insulin despite these unproven possibilities of BSE, TSE, CJD. Here's my story. I was diagnosed with type 1 diabetes or what I have renamed as pancreas failure -- that's the new "in" word ■ -- when I was a young child and I spent 35 years on bovine insulin without any complications at all. After I was switched to the biosynthetics I began to experience really wild blood swings from blood sugars up to 600 down to 40, up and down.

Any of you who are doctors who

deal with people who have diabetes know what I'm talking about. Almost immediately I began to experience memory loss, confusion, and circulatory problems and muscular problems like severe cramping.

Within four years I was diagnosed with kidney failure. I already mentioned that I had a transplant. Now I had to live with the side effects of imminosuppressants which is like another disease of its own which makes diabetes quite simple in comparison.

These wild swings of high and low blood sugar, especially when you go low after having been very high, and this happens up and down constantly, are implicated in the damage to the small blood vessels of the retina and the kidneys. I believe that my kidney failure was because of or caused by bio-synthetic human insulins, which is all that is available commercially in this country any more.

I had no idea that insulin itself could be a problem until I had a chance posting on the Diabetes Forum web site and I began to do some research of my own and also to come in contact mostly through the Internet with other people with diabetes who were complaining about some of the same stuff that I was.

This was pretty new to me and they weren't making it up. I wasn't making it up. Hey, something is going on here. Anyway, six months ago I resumed beef insulin imported from the United Kingdom. I figured I've got nothing to lose. I spent 35 years on this stuff. It's not going to hurt me.

The first thing I noticed was a much more leveling out of my blood sugars and a return of my memory and it's nice. What was it one of your politicians said, something about losing your mind? Dan Quale, you know the one.

Other problems like my circulatory system maybe is improving. Certainly my muscle cramps and things have improved completely. I know that I'm doing a lot better on the bovine insulin than I was on the bio-synthetic. You can't really do much worse than lose your kidneys.

From my contacts I know that there are more people than these 50 who are importing from Britain who would benefit but many people are scared off by the BSE warnings on the FDA's web site and others are skeptical because it appears that the FDA is only very grudgingly supporting it or, sorry, not supporting it at all but is only grudgingly approving it.

I hope that this advisory committee will recommend to the FDA that they remove the restrictions on a medication that is essential to those of us who depend on it. I will just close by saying that one size does not fit all and one insulin does

not fit all.

Thank you.

DR. FREAS: Thank you, Moira, and we appreciate your coming this long distance to make this presentation before the committee. Thank you very much.

Our next speaker in the open public hearing is David Korroch. He is Executive Director of the Norfolk Eye Bank.

MR. KORROCH: Thank you for the opportunity to speak today. I would like to compliment the committee on your efforts towards diligently ensuring the safety of tissue in the United States.

My name is Dave Korroch. I am Executive Director of the Lion's Medical Eye Bank and Research Center of Eastern Virginia located in Norfolk, Virginia. The Lion's Medical Eye Bank recovers and provides for transplant over 500 corneas per year, restoring sight to citizens of Virginia, the United States, and other countries.

My comments today are to call to your attention the potential effects of the implementation of the draft guidance for industry to screen out potential tissue donors who may pose a risk of transmitting variant CJD or any other form of CJD. Specifically I would like to address Section 4, Parts 4, 5, 6 and 8.

Section 4, part 4 will rule out for corneal donation those who have traveled to the UK and have spent months or more cumulatively in the UK from 1980 through '96. Part 5 will rule out current or former US military members, civilian military employees, or other dependents who reside at US military bases in northern Europe for six months or more from 1980 through 1990 or else were in Europe for six months or more from 1980 to '96. And part 6, as you are aware, excludes those who lived cumulatively for five years or more in Europe from 1980 until the present.

While the intention of these guidelines is to only remove from the donor pool those who fall into these categories they effective exclude all military and their dependents. It will not be feasible for the transplant agencies to access military travel records in a timely manner to determine whether the potential donor's travel history falls within these guidelines.

Specifically the sensitive nature of corneal tissue requires that it be transplanted as soon as possible after recovery to retain the viability of the corneal endothelium. Every eye bank in the United States that is accredited by the Eye Bank Association of America asks families consenting to donation questions about their potential donor's behavior and medical history that are designed to reveal any potential presence of CJD.

The Lion's Medical Eye Bank

averages between 20 and 30 cornea donors or 10 percent of our donor base from military personnel and their dependents based at Oceana Naval Air Station in Virginia Beach, Langley Air Force Base, and the Norfolk Navy Base.

This is a loss of at least sixty corneas that could have restored sight to people suffering from corneal trauma, degenerative disease, congenital malformation, or infection. On its face that number doesn't seem like much but when you add our eye bank's numbers to the numbers of other eye banks serving military areas the potential loss of corneal tissue could be significant to the corneal blind in the United States.

Section 4, part 8 excludes from donation those potential donors that have used certain bovine-derived insulin to control their diabetes. Again, while the intention may be to rule out those specific

donors who have used such products the effect is to exclude all insulin-dependent diabetics as potential cornea donors.

There is no reliable way for transplant agencies to confirm that patients with IDDM are not using certain types of insulin. Since 1999 the Lion's Medical Eye Bank has had 165 donors with a history of IDDM representing over 300 pieces of potentially sight-saving tissue. That represents a little over 11 percent of our donor base. Between those two categories we are talking about 20 to 25 percent of our cornea donor base being excluded.

In closing I would like to remind you all that corneal transplants are among the most successful of all tissue and organ transplants and that 46,000 patients a year rely on the steady supply of corneas to help them regain their sight. Also as a note an upper age limit of 61 would exclude 27 percent of eye donors or 10,000

transplantable corneas in the United States. The proposed guidelines could put in jeopardy the hopes of thousands who may need their sight restored through corneal transplantation.

Thank you for your time.

DR. FREAS: Thank you, David, for your informative presentation.

Is there anyone else in the audience who at this time would like to address the committee on topics relating to this meeting?

Seeing none, I will now close the open public having and turn the microphone over to the chairman.

DR. BOLTON: Very good. Thank you, Bill, and thanks to those three speakers from the public that contributed to our discussion today. What you said is not always easy for us to hear but it's important that we hear it and it's important that the FDA hear it as well.

At this time I would like to open up to committee discussion in general before we have the questions presented to us. We shouldn't spend too much time in general discussion because I think our directed discussion after the questions are presented will be more productive.

So if anyone had anything they would like to say now, questions, comments regarding the presentations that we have had this morning.

Steve?

DR. DeARMOND: This morning or could we say something about later?

DR. BOLTON: Oh, this morning and this afternoon, whenever.

DR. DeARMOND: The question I have is what were the reasons for the bovine insulin ban? I don't remember reading it in all the tome of things we received. Could that be concisely presented? Is it just because they came from cows in Great

Britain?

DR. BOLTON: Would somebody from FDA like to present that information? The question is what is the basis of the banning of bovine insulin.

DR. DeARMOND: Well, that might be the wrong term. The inability for it to be marketed over here in large quantities. Maybe that's better.

MS. CHU: Bovine insulin was available in this country in the past. We had two manufacturers, Nova ---- and Eli Lilly. A few years ago Nova ---- decided not to market bovine insulin and then in 1999 Lilly also withdrew marketing of bovine insulin. So therefore the two approved bovine insulin now became not available in this country. We can only approve a product when a manufacturer submitted an NDA to us and then we evaluate the data and find the quality and the safety and the efficacy information adequate. Then we will approve

the product.

DR. DeARMOND: Well, did they stop manufacturing it because of the FDA --

MS. CHU: No, it has nothing to do with FDA. It is completely due to the manufacturers' own strategy, i.e., marketing products. They decided not to do that because it is much easier for them to have limited product lines. When firms market multiple products it became very complicated, manufacturing, distribution.

DR. DeARMOND: Well, how do we respond to these comments? It doesn't seem to make sense. There's a market for this. I can't understand. Is it just too expensive to manufacture from US cattle pancreases? If there is a market for it and these people are paying premium price for it it seems like the companies would want to do that. And if it is a better product than synthetic human I'm lost in all of this.

MS. CHU: We would not know the

strategy of the firms; however, I do know that bovine insulin was sold much cheaper than human synthetic insulin.

DR. BOLTON: I don't want to pursue this too much longer because it is really off the subject of our meeting today. Perhaps we can take this up with FDA and have a presentation on it another time. My interpretation is that it is basically market forces that caused cessation of production of bovine insulin in the US and if market forces dictated it could be reinstituted but it doesn't seem like there's call for that right now.

It may be that the patient population that desires bovine insulin is too small to make it cost effective. I don't know.

MS. KNOWLES: I don't know if this is a correct interpretation but I think that what these two women were trying to share with us was that the decision we make today

and tomorrow may impact them further. That is how I interpreted their comments.

DR. BOLTON: No, I don't think so. I don't think our deliberations today have anything to do with insulin.

DR. GAMBETTI: As a point of clarification my understanding is that really FDA bans only bovine insulin imported from the UK. That is the only FDA limitation. Am I right?

MS. CHU: No, that's not true. Our policy is we will not import drugs derived from bovine manufacturer in Europe as long as the source material is not from BSE country. So we do have bovine drugs on the market in this country that are manufactured in Europe but bovine material will come from non-BSE countries.

So therefore our policy is that we ban bovine material derived from bovine countries not the manufacturing site, from BSE countries.

DR. BOLTON: There are questions regarding the tissues and the tissue-based products aspect of our discussions. Lisa?

DR. FERGUSON: I have a real basic question. Could the FDA clarify exactly what list of tissues would be affected? I have heard semen and oocytes. Are those included? Is there something else beyond that that we are not thinking of that would also be included in the guidelines?

DR. SOLOMON: Ruth Solomon, FDA. The proposed rules when finalized would include the tissues that we currently regulate, that is, musculoskeletal tissue, ocular tissue, and skin.

It would also include reproductive cells and tissues, hematopoietic stem cells, and dura mater and heart valves would become tissues instead of devices. It would also include cell therapies.

DR. PETTEWAY: Just a point of clarification, from what we have seen the

processing of different tissue types is really different and probably carries different risk based on how it's processed so the response to these questions is not meant to be generic, is it? Or should the committee advise based on one tissue class versus another?

DR. BOLTON: You are referring probably to part B and I have a clarification for that when we get there, but it has more to do with recommending whether FDA should recommend or require specific types of things rather than us recommending specific methodologies and what have you. We will get into that discussion at the time.

I sense that there are not very any overwhelming general questions or discussions. Maybe we should move right to the questions at hand and then we can discuss them in a more relevant way.

Ruth, are you going to present the

questions for us? Very good. It takes the job away from me. It's nice to see that technology has not taken over everywhere. We're going to have overheads.

The questions, I'll just tell you up front, A and B, we are asked to vote on. The voting for A is going to be relatively straightforward. The voting for B is what becomes a little bit more complicated because we are going to vote on a somewhat more abstract issue than what it appears there.

Ruth, you have the floor.

DR. SOLOMON: The first question is, "Which of the following measures and controls is (are) appropriate to prevent TSE agent transmission to recipients of human cells and tissues"?

1A says recommend additional donor screening and testing measures such as upper age limit, a head trauma exclusion, or a negative brain autopsy or biopsy.

DR. BOLTON: Actually, I'd just like to stop right there at 1A and have discussion on that and vote before we come to 1B because it is otherwise going to get too complicated. The question is we are going to be asked to vote whether we believe that FDA should recommend additional donor criteria and those are criteria in addition to a negative history for CJD or familial CJD, the variant CJD risk factors that have already been suggested to be incorporated into the preliminary draft of the guidance, is that right?

DR. SOLOMON: Draft, the draft guidance.

DR. BOLTON: And these additional criteria are being considered are, first of all, an upper age limit, not specified but the concept, head trauma exclusion, or a negative brain autopsy or biopsy, which implies then that we would require that brain autopsies or biopsies be done. So I

will open this up for discussion now. Ermias?

DR. BELAY: I have a question. I think I understand the rationale for upper age but I'm struggling with the rationale for head trauma exclusion. What's the rationale behind that?

DR. BOLTON: Well, I had that same question in the conference call before this meeting. The rationale is that with head trauma if the person were incubating CJD it might release brain tissue into the circulatory system and contaminate other tissues.

I'll give you my personal feeling on this. I think the likelihood of the coincidence of major head trauma in an incubating CJD case is pretty rare and I don't know that we can use that as a means to exclude tissue donations. So in my opinion I think that's not a good additional criterion to recommend but I think you have

to each form your own opinions.

Steve?

DR. DeARMOND: Yes, I would agree. What if it's a 35-year old who runs his motorcycle into a tree? You wouldn't expect him to have CJD so it doesn't really make much sense. What if they had the head trauma 20 years before they die? If they had CJD at some point it should have already presented itself. So it doesn't make sense.

DR. BOLTON: Well, I think the head trauma is coincident with death so it has to do with that and it's a major feature of the deceased.

Yes, Pierluigi.

DR. GAMBETTI: A more basic question, it looks like we are talking about A; 1 and 2 are debatable, as we can see. The only one it would really be very helpful to be, number 3, but we heard that there are problems of feasibility.

So what prompts these additional

exclusion criteria? Is there really any factual event that prompts us now to discuss additional criteria, because that's my understanding, to those that already exist? In other words something bad happened that we have to add criteria to whatever was available before?

DR. BOLTON: Ruth, would you like to address that?

DR. SOLOMON: No, nothing bad happened. These were suggestions that we have received from others and we are not saying that we support these. We just wanted to put them on the table.

DR. BOLTON: My sense is that it's an attempt to be all-encompassing. If we're considering these issues let's consider all of the things they could come up with that might have some benefit. Again, I think you are right. The first two are very questionable. The third one is concrete but may not be implementable.

Again, we also heard discussions from different tissue processors saying that they do not process central nervous system tissue and then during the collection process we may be proposing to open the cranium and take out the brain and I assume that maybe would happen after the other tissues are taken but who knows and now we have a potential for contaminating the very tissue that we are trying not to contaminate in the process of determining whether it is safe by doing a brain biopsy or an autopsy.

Pedro?

DR. PICCARDO: I agree with what Pierluigi Gambetti said. I think the question is restricted to a negative brain autopsy or biopsy. Now, the issue is about percentage of certainty. So if the question to the committee or the question generally is we want 100 percent certainty I don't think we can get away from the autopsy if a label or whatever you consider is

appropriate and then there is the risk-benefit factor included, et cetera, et cetera. Then because of what we heard today, then the autopsy could be waived.

But I think the issue is I cannot separate the "c" part from the percentage of certain things which we are asked to talk about.

DR. BOLTON: Dr. Doppelt.

DR. DOPPELT: I just have a question regarding that. Someone, I think it may have been you, pointed out that in terms of brain biopsy there are results and the confidence you have in the results varies from one site to another. So a single biopsy isn't going to give you what you are looking, 100 percent certainty, so it doesn't sound like it is achievable, number one, and, number two, getting biopsies on all these people just isn't going to happen. I mean, it's not workable.

DR. PICCARDO: Yes, I think I made

a comment on that, but I think Pierluigi Gambetti also brings forth the same concept. Now, there is some work that we are doing right now as we speak and this is not related to CJD. This work has not been presented yet. It will be presented soon. But I think it is pertinent to this discussion. I am going to enforce this not related to CJD, but it is related to a genetic form of prion disorders in which we could analyze by autopsy three patients that we knew had the mutation because we sequenced the PLV gene.

At the same time these three people died of accidental cardiac arrest in their 40s, three of them, and it's interesting to see. So we had their full brain, which we analyzed, we had the genotype, and we had a lot of tissue ---- chemistry. In two of those cases, after extensive pathologic analysis of the whole brain, meaning cerebral and cerebellum, in

two of those cases there was one area of the cerebellum that had an equivocal PLP deposition and plaques and all the rest was all negative.

So to give an idea of the complexity of the issue that's why I started saying I think from that lesson and from the lessons that we heard before, I mean, if you don't have the full brain for 100 percent certainty I don't think you can say that.

DR. BOLTON: Yes, that's what I was going to say. I think, summarizing what Pierluigi and Steve had said earlier, is that it doesn't seem to make sense to talk about doing a biopsy when in fact it may be cheaper and faster and safer to take out the entire brain.

So then I think you are really considering whether we want to suggest that FDA recommend that that be done on each patient for donation, again recognizing the possibility, although rare, that if an

individual did have incubating CJD that you are now opening the cranium and taking out the brain, which may be infectious, and at the same time or at some point with the same individual that is going to be possibly donating the tissue.

Yes, Beth?

DR. WILLIAMS: I was just going to say I think there are some differences in risk here. Obviously dura mater material is going to carry much greater risk and that might be a tissue where you might want to require brain examination as compared to bone or the ligaments. But there are some differences there.

DR. DeARMOND: Yes, for the cornea. This was related more to the cornea, which has a high possibility in a CJD patient of being contaminated, but from the reluctance of pathologists who will take out, what did we see, 45,000 corneas are removed? If they had to do a brain biopsy

at this stage I think that number of corneas would drop dramatically because they are reluctant to do this until we work out a high throughput system of some sort that's easy to do.

So I think these questions should be put to the future. We don't have a high throughput system. Systems are being developed but they are not necessarily easy to do at this stage, but it's possible to have a very simple system in the next couple of years, maybe in the next six months.

DR. BOLTON: Lisa?

DR. FERGUSON: Well, is it also possible for things like dura mater or cornea that are a risk to maybe combine some of these and not necessarily say you have to do a brain biopsy on each and every one? If you have a 20-year old is that useful? But if you have a 55-year old perhaps it might be. Can you combine it and say well, okay, if you are less than this age, no, but if

you are over this age, perhaps?

DR. BOLTON: With two comments, I'll punt that to the FDA, but I think that they would prefer to harmonize the guideline so that it is more uniform and in fact you may have a single donor that is donating various tissues which then, of course, you have to go to the most restrictive set of conditions and that may be difficult to implement. So what's your feeling on that?

DR. SOLOMON: Yes, that's correct. The tissue approach is trying to create a minimum floor of donor screening, testing, and GTPs for all cell and tissue donors. We brought the question of which tissues should we apply these things to TSEAC in January of 2001.

We didn't really get a definitive answer. Basically you just said that dura mater and cornea are the most risky, but we didn't get any other feedback. So we would prefer to even though it may not be

scientifically valid to try to harmonize, as you said, the requirements or recommendations, certain basic requirements for all tissue donors and then other requirements for other tissues.

DR. BOLTON: So you would prefer that in A here we talk about the general case, the floor, if you will, for donors, not to say that in the case of corneas and dura mater, although there is a question but it seems like dura mater is becoming increasingly unpopular in terms of being produced, but those might have additional recommendations.

DR. SOLOMON: Yes, possibly.

DR. BOLTON: Is there additional discussion?

DR. DeARMOND: There might be and I would guess there is data that's already available if the tissue banks or the eye banks are able to plow through it. The analogy here would be to cord blood banking.

This has been done probably because cord blood banking is newer than these other things but it is possible to go through and look at the point at the donation and collection process where the donor gets excluded. Is it because of transmissible disease testing? Is it because of the medical history that was obtained from the chart? Was it because of an interview with a family member? That data would all be there if someone could dissect it and that would really form a solid base of information to decide which of these steps really gives the key information that causes donor deferral.

You could presume that this would apply to CJD or the kind of issue we are talking about here. This is pretty well known for cord blood and I would guess that the eye banks and the tissue banks could look at their donor information and pretty easily figure out what steps cause them to

identify and defer potentially infectious donors and that would really form a basis for information to make these decisions.

DR. BOLTON: Are there additional questions or discussion?

MS. HECK: I'm speaking to that issue that the gentleman just raised. Ellen Heck from UT Southwestern, EBAA. I think by far the largest percentage of our donors are deferred pre-retrieval and that is in the questioning and medical history portion of our deferment.

A range of between eight and eleven percent are deferred because of serological testing but by far the largest number of deferrals comes in the front end of the process. Of course, there are other tests that come in in the physical condition of the tissue, but if you are looking for exclusionary criteria for risk factors they are primarily going to be at the front end.

DR. BOLTON: But I'm looking for

more detail on the front end. For instance, with the analogy with cord blood banking you take a history from the mother, you look at the baby's chart, and you can also talk to the father.

Which of those three steps really gives the key information on which the decision is based? I would guess at least with tissues there is a medical record and there is some sort of interview with the next of kin. There might be other people or other sources of information and you can tell from that where you learn what you need to know in order to make a decision about that donor.

MS. HECK: That's not different for our tissues. It's the same place, the medical chart and the interview.

DR. BOLTON: What I'm saying is the data are there if you want to look and see which of those is the thing that really tells you what you want to know.

DR. DeARMOND: This is very complicated. I can see all the risk-benefit issues coming up here. Certainly there's going to be a big loss of tissues if we are too stringent on it.

The big problem comes after the age of 50. The problem, I shouldn't say "big." The problem begins there. Looking at those curves this morning, the donation of curves go up to about 60, I think, and then they stopped. The tissues are not taken very much after the age of 60, just as the CJD curve.

DR. BOLTON: Is that not true? What did the curves --

DR. DeARMOND: It depends on the tissue.

DR. BOLTON: To what age, 61 to 80?

MR. KORROCH: Anywhere from 25 percent to 33 percent of corneas transplanted in the United States are taken

from age 61 to 80.

DR. DeARMOND: So right in the CJD area.

DR. BOLTON: Yes, I think you have to weigh the prevalence in its many forms of sporadic CJD versus losing 25 to 30 percent of corneal transplants, which I think would be devastating.

Is there other questions or discussion? What I would like to do is to go through and vote on A, those three criteria, with respect to the floor level of all tissue donors. Then we can come back and revote on them with respect to neurological tissues or high-risk tissues like corneas and dura mater. Does that make sense? We'll make it two votes. It will be easier to make the decision that way.

DR. DOPPELT: I just wanted to ask one quick question about the brain biopsies. You mentioned if you take out the entire brain you run the risk of contaminating the

tissue that you are trying to protect but what about contaminating the environment, also? Two weeks later or three weeks later you find out that the brain was positive. What happens to all those instruments in the room and the equipment that came in contact with the tissue?

DR. BOLTON: Well, presumably all of that is going to be decontaminated every time it's used anyway but it's a risk if in fact the decontamination procedures are not successful. Of course, I realized as I was saying that that if you take the brain out and it is positive you should find it and those tissues would not be used anyway. But it is a risk for those who are doing the procedure, I suppose, taking out the brain.

DR. GAMBETTI: That's why I was saying that probably an operation like that has to end up being done in specialized institutions, not just in any possible institution, exactly for that reason that

you mentioned.

DR. BOLTON: And that then means really regionalizing the tissue collection centers because you are not going to ship the body to collect a cornea, I don't think.

DR. EPSTEIN: Yes, I just wanted to add a third stage of voting. I think if a committee member has a proposition to put on the table for use of a combined criterion such as the brain autopsy only for donors with age over X it would be very useful to vote on that as well. Now, if there is no such proposition, well, okay.

DR. BOLTON: We'll take that as stage 3.

MR. RUSSO: Richard Russo, Osteotech. I thought I'd give you one specific fact that I managed to collect prior to coming to the meeting. I called two OPOs and asked them about the percentage of donors that they recovered that would be above 60 years of age.

One OPO located here on the east coast in the Maryland area said that they get 50 percent of their donors above the age of 70. One that was located in the State of Indiana said 50 percent above the age of 60. Now, these were tissue donors as a whole.

I would like to give you then one other perspective in addition to that fact is that, of course, with the informed consent products people are going to have to explain to the donor's family that they are going to have a total removal of the brain in order to do an autopsy.

Most of these donors at the moment have families that prefer to do an open casket funeral and the bodies are reconstructed to allow for that. In certain parts of the country getting the donors to approve the collection of tissue from the upper extremities is difficult because in the warm weather in the South, for example, people are set out in half-sleeve shirts and

things like this.

I think that might have a dramatic effect on donation if you said you were going to have to open the skull. I think that needs to be considered. I don't have any information for you but I just wanted to present that as something to consider.

DR. BOLTON: Maybe our neuropathologist can comment.

My experience, which is extremely limited, is that you can actually remove the brain and reconstruct the face without any obvious sign.

DR. GAMBETTI: I personally think that there is more risk to disfigure involved in biopsy, trans---- biopsy, than by removal of the brain with a regular craniotomy. That does not disfigure at all. Everybody who does autopsy has a tremendous experience with that whereas with the other system you may create in fact a much more visible scar.

DR. BOLTON: Yes, a comment from the floor. Introduce yourself, please.

MR. PARDO: P.J. Pardo, Tutogen Medical. The guidance document by CDRH for the processing of dura addresses already the brain autopsy and biopsy as well as some of the other issues that the committee has brought. Currently dura is regulated as a medical device, so therefore it falls under the CDRH purview at this time. Thank you.

DR. FERGUSON: I just want to make sure I understand the question and exactly what we are voting on. I'm sorry. I'm a bureaucrat. I should be able to do this. But if we vote yes on this baseline thing essentially we would be saying that we believe that extra criteria are necessary for all of this list of tissues given earlier. Is that correct?

DR. BOLTON: Yes, the first vote and we will take them one by one. The first vote will be do we recommend that FDA add

this criterion as an additional donor eligibility criterion for all tissue donations. That will be the first vote. So if there are not any other questions I think we can take that and I believe we'll take a voice vote for this.

So the first part of the question A will be do you believe that the committee should recommend an upper age limit as an additional donor eligibility criterion for all tissue donors?

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: No.

DR. FREAS: Dr. Bailar?

DR. BAILAR: No.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: No.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: No.

DR. FREAS: Dr. Doppelt?

DR. DOPPELT: No.

DR. FREAS: Dr. Bolton?

DR. BOLTON: No.

DR. FREAS: Ms. Knowles?

MS. KNOWLES: No.

DR. FREAS: Dr. Belay?

DR. BELAY: No.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. McCullough?

DR. McCULLOUGH: No.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: No.

DR. FREAS: Dr. Linden?

DR. LINDEN: No.

DR. BOLTON: We would like to get the industry's perspective.

DR. PETTEWAY: No.

DR. BOLTON: That was pretty clear.

Now, the next one, do you believe that the committee should recommend a head trauma exclusion donor eligibility criterion for all tissue donors?

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: No.

DR. FREAS: Dr. Bailar?

DR. BAILAR: No.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: No.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: No.

DR. FREAS: Dr. Doppelt?

DR. DOPPELT: No.

DR. FREAS: Dr. Bolton?

DR. BOLTON: No.

DR. FREAS: Ms. Knowles?

MS. KNOWLES: No.

DR. FREAS: Dr. Belay?

DR. BELAY: No.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. McCullough?

DR. McCULLOUGH: No.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: No.

DR. FREAS: Dr. Linden?

DR. LINDEN: No.

DR. FREAS: The industry's opinion?

DR. PETTEWAY: No.

DR. BOLTON: Moving right along now, do you believe that the committee should recommend a negative brain autopsy or biopsy as an additional donor eligibility criterion for all tissue donors?

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: No.

DR. FREAS: Dr. Bailar?

DR. BAILAR: No.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: No.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: No.

DR. FREAS: Dr. Doppelt?

DR. DOPPELT: No.

DR. FREAS: Dr. Bolton?

DR. BOLTON: No.

DR. FREAS: Ms. Knowles?

MS. KNOWLES: No.

DR. FREAS: Dr. Belay?

DR. BELAY: No, but I would like to make the dura mater as an exception.

DR. BOLTON: We'll come to that next.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. McCullough?

DR. McCULLOUGH: No.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: No.

DR. FREAS: Dr. Linden?

DR. LINDEN: No.

DR. FREAS: The industry's opinion?

DR. PETTEWAY: No.

DR. BOLTON: Question 1, Part 2A, do you believe that the committee should recommend an upper age limit as an additional donor eligibility criterion for special cases, high-risk tissue such as cornea or dura mater?

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: I need some more information here. If I'm correct concerning numbers, if I understand correctly, if we require an autopsy or a biopsy we are dealing with a number of 20,000 cases of cornea transplant a year?

DR. BOLTON: Forty-five thousand,

but first we are just talking about an upper age limit. You have two more to go before you get to the autopsies.

DR. GAMBETTI: Oh, I'm sorry. No.

DR. BOLTON: Should I repeat the question? Do you believe that the committee should recommend to the FDA that an upper age limit be used as an additional donor eligibility criterion for high-risk tissues?

DR. FERGUSON: Now, is this separate from what we might be voting on as combining some of these things, perhaps?

DR. BOLTON: Yes, we'll ask for combinations later.

DR. FERGUSON: Okay, no.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: No.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: No.

DR. FREAS: Dr. Doppelt?

DR. DOPPELT: No.

DR. FREAS: Dr. Bolton?

DR. BOLTON: No.

DR. FREAS: Ms. Knowles?

MS. KNOWLES: No.

DR. FREAS: Dr. Belay?

DR. BELAY: No.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. McCullough?

DR. McCULLOUGH: No.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: No.

DR. FREAS: Dr. Linden?

DR. LINDEN: No.

DR. FREAS: The industry rep?

DR. PETTEWAY: No.

DR. BOLTON: Next, do you believe that the committee should recommend head trauma exclusion as an additional donor eligibility criterion for high-risk tissues?

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: No.

DR. FREAS: Dr. Bailar?

DR. BAILAR: No.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: No.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: No.

DR. FREAS: Dr. Doppelt?

DR. DOPPELT: No.

DR. FREAS: Dr. Bolton?

DR. BOLTON: No.

DR. FREAS: Ms. Knowles?

MS. KNOWLES: No.

DR. FREAS: Dr. Belay?

DR. BELAY: No.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. McCullough?

DR. McCULLOUGH: No.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: No.

DR. FREAS: Dr. Linden?

DR. LINDEN: No.

DR. FREAS: The industry opinion?

DR. PETTEWAY: No.

DR. BOLTON: Now it gets complicated. Do you believe that the committee should recommend to the FDA a negative brain autopsy or biopsy as an additional donor eligibility criterion for high-risk tissues?

DR. DeARMOND: If we say that by "recommend" you mean it's not being forced, this is not law, this is a recommendation?

DR. BOLTON: Good question. We would be recommending that they recommend. I suppose that would be in guidance rather than in regulation. So it is not being proposed as the force of law, I suppose. It would be the recommended procedure.

Jay, do you want to comment on that? Am I getting this right?

DR. EPSTEIN: I don't think we have completely decided that because we have yet to publish a final rule and then there will also be a guidance and where we draw the line between what's in the rule and what's in the guidance may not be clear at this point in time. But I think our general intent, whether it ends up recommendation or guidance, is if the committee feels it is an important additional donor eligibility or exclusion criterion we would seek to make that an enforceable standard by whatever mechanism.

DR. BOLTON: Dr. Linden?

MR. LINDEN: Jay or somebody else from FDA, can you please clarify the existing rules or recommendations for dura? My understanding is the same as the gentleman from Tutogen, that it is already there for dura.

DR. EPSTEIN: That's correct. The current regulatory status of dura mater is

that it is a device. We do have guidance in place which is the basis for device approvals for dura. That includes a criterion for examination of the brain. Now, as Dr. Solomon said earlier, under the proposed rulemaking dura mater and also heart valves would have their status removed from device approval as pre-market approval into regulation under the provisions for control of communicable disease as a cell or tissue or cell- or tissue-derived product.

So therefore they would then be captured under the more general scheme. Now, this does not mean that we might not repromulgate a specific guidance for a specific tissue. I think it would be our expectation that in whatever final guidance we do for cellular and tissue products we would indicate that the existing guidance for dura should still be practiced but it would no longer be a pre-market approval process. It would be subject to

verification on inspection, basically.

DR. BOLTON: Ruth, do you want to add to that?

DR. SOLOMON: The current CDRH guidance into any draft guidance that we would issue under the tissue scheme.

DR. BOLTON: In any case I guess our recommendation would be useful in guiding the FDA however this ends up being placed in whatever guidance and/or regulation so we will vote on it with that assumption.

DR. DOPPELT: I just want to make one point. In terms of whether it is binding by law it's a recommendation, it's nice. In the real world if the FDA says I think this is nice everybody says we have to do it. That's the way the world works.

DR. WILLIAMS: I guess I had a question about high risk. Are we talking about both cornea and dura, both of them together, or are we going to split it?

DR. BOLTON: It is up to us. We are freewheeling at this point so what is your pleasure?

DR. WILLIAMS: I think they should be different. I think one carries a much higher risk than the other.

DR. BOLTON: Ermias?

DR. BELAY: I agree with Beth. I think they should be different. I would also like to point out that the recommendation to do an autopsy for dura mater donors was actually recommended by this committee.

DR. GAMBETTI: Can I know the number that we are talking about? We said 45,000 for cornea. How about dura? How many cases are we talking about?

DR. BOLTON: Dr. Wolfe, would you like to comment on that?

DR. WOLFE: I think it's down to several thousand a year at the most. It's continuing to drop as people wise up.

MR. PARDO: As a former producer of dura I do not know of anyone in the industry that is processing dura under a 510(k) today. They might be doing it under the prior to 1976 guidelines but I do not know of anyone producing dura.

So again the suggestion that you made that the two tissues should be separated is probably a very wise suggestion since the regulations for dura are already in place as recommended by this committee several years ago.

DR. WOLFE: Isn't that Miami organization doing dura processing still? Do you think they are doing it under the old regulation? Is that it?

MR. PARDO: I'm not sure. There was only two 510(K) approveds. We had one and I don't know who had the other one and we are no longer producing dura, either.

DR. WOLFE: When did you stop producing dura?

MR. PARDO: In 1999, when the new regulations came into effect. Basically it makes it almost impossible to produce dura under those regulations.

DR. BOLTON: Dr. Bailar?

DR. BAILAR: If I understand the harvesting process you are not going to get dura without opening up the head anyway.

DR. BOLTON: That certainly would be the easiest way to get it.

DR. GAMBETTI: That was exactly the point I was going to make. Dura mater is different from corneas in this regard because you have to do a corneatomy anyway. And the committee when they made the recommendation actually made the point that since you are already opening the brain why don't you take the brain tissue as a sample.

The other relevant issue is dura mater is a little bit different from corneas because for dura mater there are the alternatives, fascia and also animal

products, whereas for cornea you have to use human corneas.

DR. BOLTON: It's a sure sign that we have sat through too many presentations when we miss something like that but that is a good point.

Should we then vote on these individually and take them now so that the question would be, taking dura mater first, do you believe that the committee should recommend to the FDA that a negative brain autopsy or biopsy be an additional donor eligibility criterion for dura mater donors?

DR. GAMBETTI: Start with the dura mater. Yes.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: Yes.

DR. DeARMOND: Yes.

DR. BAILAR: Yes.

DR. PICCARDO: Yes.

DR. DOPPELT: Yes.

DR. BOLTON: Yes.

We'll keep voting yes until somebody says no.

MS. KNOWLES: Yes.

DR. BELAY: Yes.

DR. PRIOLA: Yes.

DR. McCULLOUGH: Yes.

DR. WOLFE: Yes, until they are banned and then it won't be necessary.

DR. LINDEN: Yes.

DR. PETTEWAY: Yes.

DR. FREAS: And the industry opinion is yes so it is 14 yes votes, unanimous.

DR. BOLTON: So in the final part of something Part of 1A it will be do you believe that the committee should recommend to the FDA that a negative brain autopsy or biopsy be an additional donor eligibility criterion for corneal donors?

DR. GAMBETTI: No.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: I think I have to say no, also, until it's specified better.

DR. FREAS: Dr. Bailar?

DR. BAILAR: No.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: No, but I think the label should be something to the effect of the risk-benefit. Something should be on the label.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: No.

DR. FREAS: Dr. Doppelt?

DR. DOPPELT: No.

DR. FREAS: Dr. Bolton?

DR. BOLTON: No.

DR. FREAS: Ms. Knowles.

MS. KNOWLES: No.

DR. FREAS: Dr. Belay?

DR. BELAY: No.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. McCullough?

DR. McCULLOUGH: No.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: No.

DR. FREAS: Dr. Linden?

DR. LINDEN: No.

DR. FREAS: Industry opinion?

DR. PETTEWAY: No.

DR. BOLTON: Now, I would like to entertain suggestions for combinations of upper age limit, head trauma, and/or negative brain autopsy or biopsy for either all donors or for selected higher risk donors. Is there any such combination that someone would like to suggest? I see none.

DR. DeARMOND: Would you please state that over again?

DR. BOLTON: Would you like to suggest a combination of the three criteria? In other words let's say a negative brain autopsy or biopsy for corneal donors over age 70, for example, some combination like

that, over age 70 with head trauma?

The one that I can think of logically is an elderly donor that's donating high-risk tissue like a cornea or dura mater. Well, dura mater we're already recommending a negative brain autopsy or biopsy result so that is a mute point.

But in the case of corneal donors you might suggest that. Now, I just put that out there, hearing that maybe 50 percent of the donors are over age 60 or over age 70, again, you are talking about maybe 20-some thousand autopsies a year. Oh, that's right, it wasn't corneas; it was all donors. So even 20 percent would still be a significant number of autopsies or brain biopsies.

Is there any inclination towards voting on that?

DR. DeARMOND: My dementia must be kicking in but didn't we just vote that for cornea and dura, the age limit, and said

there was no restriction?

DR. BOLTON: Well, for both we did individually. Whether you would want to put them in combination. Jay was asking that we ask for that. I'm not sure if it makes any sense, either, at this point in the day.

DR. FERGUSON: Well, I can see the logic for it but I don't feel like I have enough information at this point to make a good recommendation as far as the combination of age and everything else and to do the risk-benefit ratio there.

DR. BOLTON: That's our usual state of affairs here. I don't sense that there is any particular interest into going into that so I think we should then move on to Part B of this question which now Ruth can present to us.

DR. SOLOMON: 1B says specified methods of recovery and/or processing to prevent contamination and cross-contamination by TSE agents and the first

bullet is decontamination of instruments and surfaces.

I'll read the introductory part of Question 1. "Which of the following measures and controls is (are) appropriate to prevent TSE agent transmission to recipients of human cells and tissues?" And 1B has to do with recovery and processing methods and the first bullet would be decontamination of instruments and surfaces and we would be interested in a discussion of how that would be accomplished.

DR. BOLTON: Now this is where to me it got very confusing but I think after talking with Dr. Asher and Dr. Epstein that what they would like us to do is to basically answer the question should the FDA either require or recommend and, as we just heard, recommending is almost the same as requiring, specific decontamination procedures, specific methods of decontaminating instruments and surfaces

used for the recovery and processing of tissues.

Now, we are not necessarily at this point in time suggesting which one should be recommended but the concept is should they identify specific types of treatment, normal sodium hydroxide for an hour, autoclaving at 135 for an hour, whatever, much like I think Dr. Rohwer presented in his slide that represented the WHO recommendations. Should the FDA recommend specific procedures? In other words if they don't recommend specific procedures it will be left more general. I think we can have some discussion on that.

The same thing for methods of removal or inactivation of TSE agents, should they recommend specific methods? Is there enough known about specific methods and the last question is more straightforward, should single donor processing be mandated or should pooling

ever be allowed?

So let's take all of those in terms of opening for discussion.

Sue?

DR. PRIOLA: With the second one, methods for removal and/or inactivation from accidentally contaminated, we don't have a way to tell if something's been accidentally contaminated much less a means of sucking it out if we know what's in there, so that seems to me that's not even viable to consider, that second one.

DR. BOLTON: Yes, Jay?

DR. EPSTEIN: Perhaps I could help explain how we are hoping the committee would deal with this set of questions. It's at two stages. On the one hand we are asking should we incorporate into a regulation or guidance a statement such as there shall be validated procedures for decontamination of instruments and surfaces. That's yes or no and we are hoping you will

vote; however, at that point, assuming there is a vote yes, we then seek a discussion well, what kinds of things might we recommend in guidance. In other words, where is the science?

So, for instance, you could say well, FDA really ought to recommend that people adhere to WHO guidance in this area or you could say well, we think nothing short of the following procedures should be a bare minimum. So there is partly a vote needed and then there's partly an essay question.

I think that the issue with accidentally contaminated we don't really mean an accident. What we mean is that it is unintentional. It may be there, it may not be there, but it's inadvertent. It's something that may happen.

What we are really saying is that the second stage is validated procedures for clearance of TSE agents. In other words

should we promulgate a requirement that in effect obligates the industry to do validation studies on TSE clearance from tissues? Once again, if the answer is yes then a regulation might say you shall have validated procedures demonstrating clearance of TSEs from tissues and then the guidance would then need to say what exactly do we think is a sufficient demonstration.

So I hope that helps.

DR. BOLTON: Sue?

DR. PRIOLA: So then I want to backtrack. I don't know the WHO regulations. What do they apply to, just in general decontamination for TSE or are they specifically for organ collection? What are those guidelines aimed at?

DR. SOLOMON: They are aimed at all of the tissue and cells that I mentioned before. Organs are not on the table.

DR. PRIOLA: So they recommend that upon any tissue collection you

decontaminate with one mol of sodium hydroxide for --

DR. BOLTON: It's for the instruments and the surfaces.

DR. PRIOLA: That's what I want to know.

DR. BOLTON: It is decontamination of the environment and any instruments used.

DR. PRIOLA: For any tissue collection?

DR. BOLTON: I think that's right. And if you recall it's a sixth or seventh step in descending order of desirability. If you can do the first one, do the first one. If you can't do that, do the second one. If you can't do that, then do the third one, and they descend, I think at least presumably, in descending order of effectiveness as well.

David?

MR. ASHER: Yes, we should be clear that the WHO guidelines originally

were mainly intended to address safety in surgery; however, they are clearly relevant to the issue being discussed here. They would be a framework to consider decontamination procedures in such a setting and in general. They do list six measures in descending order of confidence.

DR. BOLTON: Pierluigi?

DR. GAMBETTI: Yes, just to see if I understand it, could the first question in the "B" part of the question, the contamination, be rephrased as follows, that we recommend that all tissue banks, whatever, all institutional organizations collecting tissue should decontaminate the instruments against the TSE agent?

I assume they all sterilize their instruments when they have finished using them. Are we asking here to add to their protocol sodium hydroxide, autoclaving at 154, to include also decontamination against TSE? Is that rephrasing it?

DR. BOLTON: If I understood Jay correctly what he would like is a two-part question. The first part is do we think that they should recommend or require validated decontamination procedures and, as he said, that's a simple yes or no.

If we answer yes then what sorts of guidelines or what framework of guidelines might be used?

DR. GAMBETTI: I thought that was automatic that they decontaminated the instruments every time, that they used sterile instruments every time.

DR. BOLTON: But not validated for TSE inactivation.

DR. SOLOMON: You are correct. This is specific additional decontamination just focused on TSE.

DR. DOPPELT: If you are going to ask that question it seems to me like in the previous question you have to separate high-risk tissue from the regular tissues,

could vote to recommend a particular method to the FDA at this point. So it seems to me this discussion might not be so difficult.

How would we know what to recommend? We didn't have a crisp presentation of here are seven options; do you want to recommend one of these? Then I could vote on it. I can't now because I don't know what they are.

DR. BOLTON: What we might do is recommend that we look at this again at our next meeting, at specific decontamination and sterilization procedures. Now, I'm still somewhat focused on instruments and environment. When we get to actual validation of processing steps for tissue as far as I'm concerned we are so far away from that that I don't even know where to start.

Every single tissue and product is almost going to be different and I'm not sure exactly where we start with that discussion so aside from suggesting that the

FDA should look into it I don't know what else we can do with that.

Ermias?

DR. BELAY: I was just going to comment on the Canadian situation to just set the record straight. We had been consulting with the Canadians at the time they had that problem and by no means would that hospital situation be representative.

It was a very unique situation. It was a panic kind of situation. They rounded up practically every surgical instrument in the hospital, which was up to 5- to 6,000 instruments, and they were trying to autoclave all those instruments within one day. The volume of sodium hydroxide they used was basically gallons and gallons. In that kind of situation there are always opportunities for error and accidents and that is exactly what happened.

DR. BOLTON: Dr. Wolfe?

DR. WOLFE: The suggestion I want

to make is both for 1B and 1C when we get to it. I think it is an extension of what you were just saying, which is I think that people here are probably going to vote yes to let's do something and in both the case of B and C, which is the processing, we would like them to come to us next time with the details because we could stay here all night and say well, this part of what this company presented looked good but it's proprietary; we can't find out what it is.

So I think not just for the sake of getting out of here but for the sake of having a more enlightened discussion next time we should just vote on the first part of this one and when we get the C the same thing and then the next time we will have a bunch of specific suggestions as to how to implement those.

DR. SOLOMON: The proprietary materials were procedures for decontaminating the tissue. This question

is asking about decontamination of the instruments and surfaces, just to clarify that.

DR. WOLFE: I understand that but still we don't have enough details. You were asking us to recommend which ones to do. I'm just saying it would be much simpler to come to us next time or in the intervening times with some of your suggestions since we will likely vote yes, show us something.

DR. EPSTEIN: Again, I think we have not put specific procedures in front of the committee to vote on. The question we are asking you to vote on is whether we should promulgate requirements or recommendations in these three areas, decontamination of instruments and surfaces, clearance from tissue per se and I think it would be helpful just to strike the word "accidentally" when you vote it, and single-donor processing.

So those are yes/no votes. Anything beyond that today, I think, is whatever comment you wish to make about specifics and if there are no comments that's fine, too.

DR. DeARMOND: Well, Mr. Chairman, will you rewrite the questions so we can actually --

DR. BOLTON: I will try and I am going to hold any comments from the audience at this point because I want to get on with it while we have this thought clearly in mind about what this question is.

(Discussion off the record)

DR. BOLTON: I have problems with this because we are really talking about should the FDA recommend specific validated methods for decontamination of instruments and surfaces used for recovery and processing. Jay, is that correct?

DR. EPSTEIN: Yes, again, our current guidance does not specify methods

for TSE decontamination. We have recommendations that there be validated procedures in place for control of contamination and cross-contamination. We have interpreted that to include TSE validation but there are no standardized methods at this point in time.

We are asking should the FDA create recommendations for the use of specified methods specific for decontamination of TSE agents (a) from surfaces (b) to clear from tissue, and then in addition should there or should there not be single donor processing?

I think we are getting caught up in the length of the sentence, which is really recommend specific methods for decontamination of instruments, recommend specific methods for removal and inactivation, recommend single-donor aseptic processing. That's what we are asking.

DR. DOPPELT: This would be

recommending decontamination of the instruments for TSE agents used on high-risk tissue. Is that right or wrong?

DR. BOLTON: We hadn't split that yet. We were going to vote on them separately, as we did before, but, I'll tell you, I think where I'm getting caught up on this is that it's difficult for me to vote to recommend methods when I don't know what methods we are talking about.

So I think I would prefer to say that the committee recommends that the FDA pursue specific methods for decontamination of instruments, pursue their own recommendations for specific validated methods for decontamination of instruments and surfaces, et cetera, because I don't know how we can recommend that they require these things if we don't know what they are going to be. We just don't have enough information to deal with that at this point.

Yes, Dr. Bailar.

DR. BAILAR: I agree with Dr. Wolfe, Dr. Bolton, that we don't know enough about the specifics here to vote on whether to adopt specifics and we have heard from FDA about that.

I am concerned a little bit, too, and I mean a little bit, that we not go too far. At some point we should begin to rely on the educated professional judgment of the people who are doing these things.

I would like to at least consider whether we can give them some flexibility in how they meet the basic requirement that these things be decontaminated.

DR. BOLTON: Well, I think that would be the area where the requirement would be to use a procedure that is validated to inactivate these agents and the choice of which procedure would be up to the local facilities.

The problem is there are essentially none of these that are

validated. I'm not sure what you would call a validated procedure for inactivating prions on stainless steel scissors and I'm not even sure how you would go about validating that.

What we want to recommend to the FDA is that they begin to move in that direction, to move towards a requirement, really. It is an issuance of guidance that these procedures be defined, at least a list or a set of procedures that can be used, and that at some point it be required that one or more of those procedures be used.

But we don't know what those procedures are at this point. I think it would be impossible for us even if we stayed here until midnight to define what those procedures are this time.

Steve.

DR. DeARMOND: Yes, the problem is the lead-in sentence, "Recommend specific methods," that should be struck. It's just,

"Recommend for HCT/P recovery and processing: decontamination of instruments," and I would say that that would be reasonable and I guess that's what they're actually getting at.

It is not, as was suggested, that we are getting construed by the language. The language is horrible in these sentences and have too much stated in them. We have to get to clearer language in these questions to answer them yes or no.

DR. BOLTON: Yes, Dr. Bailar.

DR. BAILAR: After this much discussion I think the message to FDA should be pretty clear and I'm not sure we need to vote on these things.

MS. KNOWLES: And there has been more than one time when other committees have rewritten the questions.

DR. BOLTON: Oh, we do this regularly. It's a common occurrence. We also have very often not voted on something

like this because we couldn't really decide. I agree with you, Dr. Bailar, that I think that our message to the FDA is relatively clear. If there was a way that we could state that and vote on it it would be helpful. So I would propose that we are recommending that the FDA pursue specific validated inactivation procedures or begin to define specific inactivation procedures for the decontamination of instruments and surfaces used for recovery and processing, that they begin to define validated methods for removal and/or inactivation of TSE agents from HCTPs, those two questions and nothing further.

We are just recommending that they move in that direction and that we should consider specific methods and processes at a later meeting. Is that satisfactory?

DR. DOPPELT: I second the motion.

DR. GAMBETTI: And also should consider separating high-risk from low-risk

tissues.

DR. BOLTON: And in those considerations should differentiate between high-risk tissue collection and low-risk tissue collection.

Does the committee sense that they understand the question? Are you shaking your head no, Steve? You are not allowed to do that, now.

DR. DeARMOND: No, go ahead and state it again clearly because you threw "specific" back in again. I don't see how the FDA has defined find specific methods. Those are still evolving and there are methods out there that already exist.

I thought the question was to recommend that the people involved in this decontaminate their surfaces and do these other issues. The problem with the lead-in sentence, it says that they should use specific methods and we don't know what those are so we have to eliminate that and

we are not going to know what they are for another couple of years, probably.

DR. BOLTON: I guess that's the difference in philosophy. Your suggestion is to require the tissue processors to decontaminate things now.

My suggestion is to recommend to the FDA they begin to define the processes that they should use and not worry about requiring them to do anything yet. So my suggestion is that we are telling them to begin to define the specific processes that would be used and to differentiate those with respect to high risk and low risk tissues.

We are not going to say anything about what we are requiring anybody to do yet because we don't know what we should do.

DR. DeARMOND: So that's why I say state the question again because the statement now puts the pressure on the FDA.

DR. BAILAR: But you are putting

the pressure on the FDA, not on the industry now.

DR. BOLTON: Yes, that's right. I'm putting the pressure on the FDA because I want them to come back to us with a defined set of methods that we could then discuss and decide upon as recommended validated methods. Or maybe they're not validated. Recommended methods that would be used.

DR. DeARMOND: Well, maybe one more time. State your question as you phrased it.

DR. BOLTON: Could I have the transcription read back to me?

DR. LINDEN: To me it sounds like in the first part it is decontamination of instruments. All of this discussion stems from the assumption that people are going to vote yes, at least for high-risk tissues on this first issue.

That issue, we can still vote on

that first thing because what you are asking FDA to do then is to say okay, come back to us and give us some more information on what techniques are available and then we can make a recommendation on what should be done if we vote yes on this first issue.

Is that right? It seems to me that it all stems from the yes-no vote on that first part. If you vote yes you want FDA to come back. I'm lost.

DR. BOLTON: I think we are all getting lost. That is an issue that I really don't want to go in and take a vote on something that we are really not sure about what we are voting on.

It's not going to do us any good and I don't think we have enough information to vote on anything that has any specifics to it in terms of methodology or anything so I think that what we can do is to convey to the FDA that we need more information, that we need them to develop their proposed

methodologies that they would like us to consider, and then come back and discuss that at another time.

We could, I suppose, vote to say we are interested in having these but we don't know what those things are specifically. Yes, we would like to have decontamination procedures for instruments and surfaces but we don't know exactly what they are.

DR. GAMBETTI: We would like to consider the possibility.

DR. BOLTON: Dr. Bailar.

DR. BAILAR: I still don't see the necessity to vote on anything here. I'm sure that FDA understands our concerns. I would like to leave it to FDA whether and when to come back to us with something that we can vote on here. I don't even want to pressure them into doing that.

MS. KNOWLES: But I think we have to say that and then vote on it.

DR. GAMBETTI: Yes, I think the message should not be that we are rejecting. We are willing to discuss this if it is presented in a better way, a more understandable way.

If we don't vote it may look like we are rejecting the whole issue.

DR. BOLTON: That is exactly right. The committee recommends that the FDA define specific decontamination procedures for instruments and surfaces used for recovery and processing and define or propose methods for removal and/or inactivation of TSE agents from HCT/Ps for future consideration by this committee as either regulation or recommendations.

DR. FERGUSON: With a distinction between low- and high-risk tissues.

DR. BOLTON: With a distinction between low- and high-risk tissues. Could we take a vote on that?

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?

DR. BAILAR: 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?

because we don't seem to have much of a problem. Theoretically there could be but we have not seen a problem for bone ligament and blah, blah, blah, so you have to separate it, I think.

DR. BOLTON: Good point. Other discussion? Questions?

DR. BELAY: I think FDA is concerned that whatever kind of donor default criteria you use it is possible that some infected donors could slip through and could we recommend to prevent that from contaminating other grafts by recommending additional sterilization methods.

DR. BOLTON: Yes, that's another issue. You might have an individual incubating sporadic CJD slip-through but if you are only taking low-risk tissues would you recommend these specific decontamination procedures or would you only recommend them if they were taking both low-risk and high-risk tissues? The problem here is really a

logistical one for the collection agency because they are then going to have to separate their surgical instruments between low risk and high risk.

It may very we well be worth doing that. On the other hand if you get a mix-up and you don't have proper decontamination-sterilization features, then you have defeated the purpose of segregating those two sets of instruments and possibly sites. I don't know if site would be different.

So additional discussion with that thought in mind?

DR. DOPPELT: I don't think the issue of separating instruments is that big of a deal. If you take dura there are only a few places that are doing it and probably pretty soon nobody is going to be doing it. That is the reality.

Corneas versus the other tissues, they are in point of fact using different types of instruments. If you want to

separate them that's not an issue.

DR. DeARMOND: I presume and, again, you couldn't write a test this way. The medical students would lynch you. I guess the idea is that we would like for all of these tissues in addition to disinfecting or sterilization of bacteria fungi and viruses we would like to add the TSE component to it.

DR. BOLTON: That's correct.

DR. DeARMOND: That doesn't seem to come out in here very well because what they ask is specific methods and those are evolving and there's a series already out there that seem to be fairly effective.

DR. BOLTON: Right, and I believe that in the highly likely event that we would vote yes on the first question there that we could simply recommend that specific procedures like those recommended by the WHO should be considered.

I'm sure that they will come back

to us at some point and ask us again to talk about this. I think that that would get across the appropriate thinking of the committee.

Ermias.

DR. BELAY: It might be appropriate, as you propose, to look at the issue by high-risk tissues and the other tissues.

DR. BOLTON: It's easy enough to do that and it's actually easier to make the vote that way so why don't we do that again? Is there additional discussion at this point?

DR. DeARMOND: Just one other point. It turns out a lot of the decontamination methods that are even used for bacteria and fungi work to some degree with prions, also, and the same thing could be true with sodium hydroxide and high temperature, probably destroy an awful lot of the other material. So ultimately one

method may be useful in the future but we don't know that yet.

DR. BOLTON: Lisa?

DR. FERGUSON: Just one question on the last point about the pooled processing. Are there any of these tissues that are actually being processed as a pool? I mean, all the presentations talked about single-donor processing. Is there something that we're missing that would be in a pool?

DR. BOLTON: Jay, would you like to address that?

DR. EPSTEIN: At the present time we believe that there are no pool-processed tissues although historically there were and the question is whether we should put in the final rule what we put in the proposed rule, which is a prohibition against commingling in processing.

Just to be sure there's clarity, the proposed rule offered the possibility of request for waiver against that prohibition.

DR. DeARMOND: So is that true even now for plasma products?

DR. EPSTEIN: No, no, I'm just talking about tissue. Plasma products, plasma derivatives are pooled products of necessity.

DR. DeARMOND: I see.

DR. BOLTON: It's understandable that this committee immediately reverts to blood and blood products because we have talked about it for so long.

DR. DeARMOND: They are a tissue, also.

DR. BOLTON: Yes, but not being considered here. I would just like to say I think it's wise to always keep that option open for a company to apply under special conditions, to produce a product from pooled tissue, although it might not be desirable now but we might not foresee some point at which case that would be appropriate. So I think that's a good idea to keep that open.

DR. DOPPELT: I just want to add one point about pooling. It was just said, and I think that's correct, that right as of now there isn't anybody, any tissue banks, that are pooling.

But there had been a few up until recently that were and they changed their practice but if you don't have a restriction against pooling there very well might be some banks that would revert to pool processing simply because it's more economical to do so and, as has been pointed out by many members, they may actually have a little bit more confidence in their procedures than perhaps there should be for the TSEs.

DR. BOLTON: Lisa?

DR. FERGUSON: Well, can I ask FDA a question? And this might get into compromises with your rulemaking. If we're voting on this process and we make a recommendation for a single-donor processing

is that based solely on TSE concerns or are you guys going to go ahead and do that anyway based on other concerns? Am I making sense?

DR. EPSTEIN: I think the proposal for single-donor processing was in fact based on TSE concerns primarily. That's not to say that there are not risks from other agents that we don't have methods to control but the lead concern in the proposed rule really was TSE.

DR. BOLTON: Additional discussion, questions?

First Dr. Linden.

MR. LINDEN: Well, I just want to agree with you that I would hate to see the pool issue be closed because there may be very valid reasons to do so, as in plasma derivatives, which are in fact safer than FFP. So if it's linked with some sort of inactivation process that can only be done in a pooled fashion you could actually be

safer than if you are not. So I wouldn't want to close that option out.

DR. BOLTON: Yes.

MR. RUSSO: Richard Russo, OsteoTech. I just wanted to support Dr. Linden's comment. I do think that there will be additional technologies in the future. If the FDA were to adopt a rule that would give a blanket prohibition against anything without any opportunity to make a variance submission you would have to move heaven and earth to change that particular rule. I just think it forecloses progress in the future.

It should be right now that there shouldn't be any multiple donor processing without an explicit approval from FDA.

DR. BOLTON: Thank you.

Yes, Dr. Doppelt?

DR. DOPPELT: I would just like to ask if anybody has had any experience sterilizing equipment using the World Health

Organization criteria because the one example that we heard one hospital presumably did what they were supposed to do and somehow ruined all of their equipment.

I'm not sure how that happened but if that is a common event hospitals can't afford $10 million on every case.

DR. BOLTON: My laboratory routinely does the following, which is a variation on the WHO. Everything, surgical instruments and what have you, immediately go into one normal sodium hydroxide at room temperature. They soak usually overnight but at least for one hour.

Then to that is added sodium dodecyl sulphate, SDS, to a one percent concentration. That then is usually diluted five to ten-fold and autoclaved. Then the instruments are taken from that and washed and rinsed and then set up and sterilized by conventional autoclaving.

I think, as Dr. Rohwer said, many

stainless steel instruments hold up to this beautifully well. We do have some very nice German stainless steel instruments that have gone through this many, many times.

And then occasionally you will get a set of instruments that just falls apart on you and I don't know what the difference is. They are all supposed to be stainless steel. It just seems to be somewhat unpredictable. I assume it has to do with the quality of the steel but I don't know exactly why.

Clearly, instruments that are not stainless steel will suffer terribly. You do get an electrolytic reaction going on in one normal sodium hydroxide and you can get all kinds of interesting things happening.

Steve?

DR. DeARMOND: And we don't know what went on at that hospital, whether they got the instruments from one surgical suite and then mixed them all together so they had

to decontaminate everything because that seems excessive and whether they decontaminated materials that really weren't in contact with tissues and destroyed those in the process.

There is a hierarchy of decontamination that you go through beginning with the disposable for the highest infectivity probability, including very good surgical scissors because it's cheaper to replace a $500 or $1,000 pair of scissors than to have a problem with the patient.

DR. BOLTON: And there is another level of concern here and that is that you need to decontaminate the instruments before anybody touches them to try to scrub them and clean them. That is our primary concern is that I don't want anybody trying to scrub an instrument, especially a sharp pair of scissors, unless they have already been what we consider terminally sterilized so that's

a major concern.

DR. DOPPELT: So one message here is if you buy cheap instruments, crummy instruments, and they fall apart you shouldn't have bought them in the first place. Is that right?

DR. BOLTON: Yes, Dr. McCullough first.

DR. McCULLOUGH: I think while it's relatively straightforward to vote on the first part of whether the FDA should require demonstration of effective decontamination process I don't feel comfortable voting on some particular process. I mean, we had a nice show and tell from several different groups or manufacturers and at least a couple of those processors were proprietary so we don't know details.

As far as I know the committee has never really seen exactly what the WHO recommendations are. I don't see how I