fact rewriting the criteria that we are asked to give. The question was whether or not we thought that they were appropriate and adequate and it seems to me that we have decided that they are not appropriate and adequate and we are not rewriting them. Which would you prefer? Do you want us to rewrite them or do you want us to just tell you what we thought about the original ones?

DR. VOSTAL: I think we already know what you thought about the original ones. I think any comments are very helpful and if you care to rewrite them for us that would be helpful in itself.

DR. BROWN: We are not doing a whole lot of rewriting. We changed a word and eliminated a parenthesis. That is not bad and if you want to eliminate necessity to perform the study at two different sites it seems to me there is a kind of a sense around the table that that would be okay as well but since we are talking about minimums it could also be left in.

DR. VOSTAL: The concern we have is that if we get data from a manufacturer who has had 5 years of perfecting their procedure we are always wondering whether that will work in somebody else's hands and I think that is what Dr. Leitman was trying to point out.

DR. PRIOLA: And that is a very valid point because we have had that experience in the research field

where you can't replicate what somebody does.

Yes, Dr. Turner?

DR. TURNER: That is exactly the concern we had in the UK which is exactly the reason we are going down the road of commissioning our own independent validation studies.

DR. ALLEN: The third bullet point that requires TSE infectivity from BSE or vCJD, I assume that would be spiked experiment?

DR. PRIOLA: That would presumably be along the lines of what Dr. Brown said which is 301V. It is the rodent version of BSE, yes, and that could be spiking.

DR. BROWN: And the study performed at two separate sites, what you might want to do is just add since apparently the real reason is indicate that this is a test which is doable in more than one place which is neither an issue of cross contamination or maybe even differences but we might want to reword differences in laboratory practice and just indicate reproducibility in different labs.

DR. COKER: I just have one comment on that. If the manufacturer decides to use to do the tests well then will they be required to use another contract lab because most of the manufacturers or some of them do not do the studies in house? They actually contract it out. So, if you are requesting two sites that means they will have to

have two contractors doing the tests.

DR. PRIOLA: So,with the modifications that have been made to these bullet points does the Committee feel comfortable on voting?

DR. GESCHWIND: There is only one thing. The infusion aspect doesn't seem to be put in there that there has to be a model.

DR. PRIOLA: You mean the transfusion?

DR. GESCHWIND: The transfusion or is that No. 2 where there has to be a model in which you are infusing a unit.

DR. PRIOLA: I think that is why sheep was originally up there.

DR. GESCHWIND: Right, but I thought we had taken that out.

DR. PRIOLA: Okay, rodent, sheep or other model.

DR. BRACEY: I thought we changed it to say that the key point was demonstrating lack of infectivity.

DR. PRIOLA: Yes, elimination.

DR. BRACEY: Elimination of infectivity so that we weren't really, we were requiring the process of an entire unit but not infusion of an entire unit.

DR. PRIOLA: Any other comments?

Shall we vote?

Oh, sorry, Bob.

DR. ROHWER: I have a question for Paul. Paul, I am not clear on what you mean by demonstrating that there is sterility in a unit because right now we don't have, endogenous sterility in a unit because right now we don't have as far as I know the capability of doing that unless we do a transfusion in sheep in which case we could but it would take years to know whether the sheep is actually transmitted or not especially if we are looking at very low individual titers and so, I see a practical issue here that needs to be considered.

DR. BROWN: You used a full unit in the hamster.

DR. ROHWER: Yes, but we only measured 5 mls of blood for that unit.

DR. BROWN: But that represented a unit for a hamster, more than a unit.

DR. ROHWER: Oh, that is more than a unit for a hamster. Is that what you mean? That is what I want to get at. Is that what you mean?

DR. BROWN: Yes, right.

DR. PRIOLA: Dr. Epstein?

DR.EPSTEIN: This is the very issue I was trying to raise before in other words if a whole unit in a human might contain 5000 infectious units and if the processed leukoreduced unit still might contain 2 or 3 thousand infectious units and then you only do an assay on a few

milliliters then you do not have the ability to assure that you have sterilized the unit. If the residual infectivity were for argument's sake 20 or 30 infectious units then at any feasible volume studied in a rodent model you could not exclude a residual infectivity of a whole unit and in fact that is --

DR. BROWN: Of a whole human unit, but that is what we are saying.

DR. EPSTEIN: But how else will you model filtration of a volume which may contain endogenous infectivity of 5000 or 3000 IU? This is precisely the dilemma and that is why we have stratified two potential labels. One potential label says that the filter has been shown to reduce the infectivity. The other label essentially says that it has been shown to remove the infectivity of the transfused unit and we understand fully that you can't get to that second endpoint without either waiting a long time or some advancement in the experimental models but we are not really comforted that showing logs reduction in a scaled down model shows that you have eliminated endogenous infectivity and that is precisely the point.

DR. BROWN: I couldn't agree more with you, Jay but we can't figure out how to do the experiment or we would do it.

DR. BOLTON: You know how to do it, 10,000 hamsters.

DR. ROHWER: I agree that I do know how to do the experiment but I despair of talking anybody into doing it.

DR. EPSTEIN: But the endpoint may be that we get to labeling A and not labeling B because the end point isn't that we can't review claims for filters. The issue then becomes what exactly is the claim that has been supported by that experiment.

DR. BOLTON: You could achieve the first bench mark by a spiking and clearance study or the hamster endogenous study maybe, but the second bench mark you would have to meet by say for example doing a sheep transfusion study or

a 10,000 hamster study or something that would end up being equivalent to examining an entire unit of blood.

DR. TELLING: But even in the sheep transfusion study a negative result wouldn't necessarily give you the confidence that there was no infectivity in that blood.

DR.BOLTON: There would have to be more than one sheep. What would be the statistical number? I don't know that anybody is going to do that study to get that second label.

DR. PRIOLA: Because you have to determine the level of sensitivity in sheep.

DR. BROWN: Of course, you could also use a filter with a T-median level column, I mean do a real scale down which is actually a serious problem in terms of people being comfortable with X degree of scale down or Y degree of scale down as opposed to the real thing and you can never do the real thing. You can't do an experiment on 10,000 pints of plasma. So, it is a question of degree and I have to say that personally I am comfortable in seeing a reduction of a concentration of whatever is in endogenous infected blood whether it be 10 or 30 or 50 infectious doses per ml eliminated in a reasonable number of mls to say that I have sterilized, I mean just as a practical matter as we have just been talking about.

DR. PRIOLA: Any other comments?

Okay, let us move to the vote, keeping in mind what has just been said and we have proposed slight modifications to those bullet points.

Let us vote yes or no to are the FDA's proposed minimum criteria for validation of TSE infectivity reduction by filtration adequate and appropriate.

MR. BIAS: I think we can just state what has been modified.

DR. PRIOLA: Okay, good point. So, the modifications as I remember them were to demonstrate elimination and to take out rodent and sheep. Do we still

agree for that first bullet point? Do we still agree with that?

MR. BIAS: Are there two animal models that are okay if we are taking out rodent and sheep?

DR. PRIOLA: I think we just leave it to the FDA. I mean we can leave that open. You don't have to constrain the animal models. I think that was the idea.

DR. BOLTON: I think Paul's suggestion was two different species, two different strains.

DR. PRIOLA: Yes, but that is getting, I mean stili that is two animal models or more than one animal model. So, I don't think we have to get that specific.

DR.BOLTON: Would you accept mouse scrapie and hamster scrapie? I am trying to figure out are you going to select --

MR. BIAS: I am sure they will but are we sure they are going to select an animal model that applies?

DR. BROWN: I think it is probably important to specify two strains, two hosts rather than two animals because you could. You know, you could study two different strains of scrapie and you could study two different strains of scrapie in mice and that wouldn't be adequate in my opinion.

DR. PRIOLA: So, two strains, two hosts in those parentheses instead of sheep and rodents, two strains, two

hosts.

Okay, was there another? Now, I can't remember if there was another modification. The two sites? Do we still want the two separate sites? Oh, to minimize issues of cross contamination and reproducibility, so to take out differences in laboratory practice.

DR. BROWN: You could even depending on how the Committee felt include the word "preferably" after the word "study."

DR. PRIOLA: Preferably performed to give them some leeway.

DR. TELLING: So, a clarification, implicit in what one of those combinations of animal, host and strain will be is bullet point No. 3, question mark. So, one of them should be BSE or vCJD.

DR. PRIOLA: Right.

DR. BROWN; The other point here is that I see nothing on this slide about a spike experiment.

DR. PRIOLA: There is a recommendation, that is right, for the first one. So, you had recommended demonstrate elimination of endogenous infectivity and reduction of spiked infectivity going back to the two approaches by 3 logs.

DR. TELLING: Again, that is implicit in bullet point No. 4 because the only way you would be able to

detect the scrapie is by spiking, right?

DR. PRIOLA: Right.

Lynn, did you have something you wanted to add?

DR. CREEKMORE: Just that with the point that Glenn was making about the TSE infectivity from BSE or vCJD strain it doesn't say endogenous versus spiked. So, it doesn't connect back to that demonstrate reduction of endogenous because they could choose to do a spiked experiment for that.

DR. BROWN: Susan, I think you have to have a bullet in here. Either put it in as a first sentence on bullet point 4 or add another bullet but you have to mention explicitly a spike experiment. You can't just leave it implicit in the PrP bullet.

DR. PRIOLA: We can add it to the first one, reduction in spiked infectivity and that will take care of that.

So, it is starting to get a little bit confusing. So, I just want to make sure. You know, I don't want to get stuck on this for the next 20 minutes. So, the modification of the first one is elimination of endogenous TSE infectivity or reduction of spiked infectivity, and, excuse me, and reduction of spiked infectivity by 3 logs in animal models, two strains, two hosts. We can't give this detail. The 301B is implied. It is definitely implied in

TSE infectivity from BSE or vCJD strain, I am sure. So, I think that is okay. Then the other change was bullet point 5 and that is cross contamination and reproducibility. Is that correct?

Okay, so, let us go ahead and vote on this issue.

DR. FREAS: We will go around the table.

Dr. Bolton?

DR. BOLTON: Yes.

DR. FREAS: Dr. Johnson?

DR. JOHNSON: Yes.

DR. FREAS: Dr. Telling?

DR.TELLING: Yes.

DR. FREAS: Dr. Creekmore?

DR. CREEKMORE: Yes, amended.

DR. FREAS: Dr. Hogan?

DR.HOGAN: Yes, as amended.

DR. FREAS: Mr. Bias?

MR. BIAS: Yes, as amended.

DR. FREAS: Dr. Allen?

DR. ALLEN: Yes.

DR. FREAS: Dr.Priola?

DR. PRIOLA: Yes.

DR. FREAS: Dr. Geschwind?

DR. GESCHWIND: Yes.

DR. FREAS: Dr. Brown?

DR. BROWN: Yes,with the modifications.

DR. FREAS: That is unanimous, yes, with modifications.

DR. PRIOLA: All right, the final thing that we have been asked to address is -- is this a voting question as well? I am sorry I don't know. Is question 2 on top of 2 a voting question? It seems like it is. It is, okay.

So, does the FDA's proposed labeling for a filter meet the appropriate criteria for a claim of reduction of TSE infectivity in blood or blood components and we have already gone through all this I think with the first question.

So, this filter has been shown to reduce TSE infectivity in blood from an infected animal model plus C, right?

DR. FREAS: Right, that is the disclaimer that goes along with it.

DR. PRIOLA: And that disclaimer goes with both or if you get a transfusion model the label would be B.

DR. JOHNSON: Shouldn't it say it has been shown to eliminate? We already said that in the other.

DR.BOLTON: No, because the spiking experiment won't necessarily --

DR.JOHNSON; Or reduce by 3 logs.

DR. BOLTON: That is going to be too confusing.

DR. PRIOLA: I think maybe David is right that since we have reduced for the spiked reduced would be better there. Does anybody have any major objections to the way these labels are phrased?

DR. BOLTON: No major objections. I just would point out that phrases like infected animal model I am not sure what that means tot he general public. So, some thought maybe could be given to what phrases of those type mean the most to people.

DR.JOHNSON: The general public won't be buying filters.

DR. PRIOLA: Let us go ahead and I don't sense any major problems with this. So, let us go ahead and vote on this final question.

DR. FREAS: Dr.Bolton?

DR. BOLTON: Yes.

DR. FREAS: Dr. Johnson?

DR.JOHNSON: Yes.

DR. FREAS: Dr. Telling?

DR. TELLING: Yes.

DR. FREAS: Dr. Creekmore?

DR. CREEKMORE: Yes.

DR. FREAS: Mr. Bias?

DR. BIAS: Yes.

DR. FREAS: Dr. Allen?

DR. ALLEN: Yes.

DR. FREAS: Dr. Priola?

DR. PRIOLA: Yes.

DR. FREAS: Dr. Geschwind?

DR.GESCHWIND: Yes.

DR. FREAS: Dr.Brown?

DR. BROWN: Yes.

DR. FREAS: Again, a unanimous yes with nine people voting, I believe.

DR. PRIOLA: Okay, that I think, thank you all very much for your patience. I know it has been a very intense day and this meeting is adjourned.

DR. BROWN: Sue, congratulations. In 5 years as Chairman I never had a clean slate of unanimous votes at a single meeting.

DR. PRIOLA: That is because of the participants.

DR. FREAS: I do have one more announcement regarding Dr. Alan Jenny. I received this message. The services will be held Tuesday, November 1, at 1:30 p.m., at the Starkwellin Funeral Home, 609 7th Street, Boone, Iowa, and memorial contributions will be accepted in Dr. Jenny's name for the local Ike's(?) Club for Conservation, and if you need more information, please see me.

(Thereupon, at 5:50 p.m., the meeting was adjourned.)