at

the same thing.

DR. NELSON: I think the third issue here, which I think is under c), No. ii), is I think it says "potentially reduces bacterial contamination" which I think is cleverly worded. I think that is an issue. Certainly, the amount of bacterial contamination is reduced with sequential samples, but I am not sure how much the unit is reduced, and we may need more data on that.

But, to say "potentially," I think it means that this new system is not necessarily--I mean, it is not necessarily harmful and it may be beneficial and do we require a phase III trial in the U.S. or something like this to do it, which would be--or is this something which can be done without this kind of an efficacy trial.

DR. SIMON: Again, with the lateness of the hour, I am just trying to make sure the understanding is correct that, from what the experts have said, it appears that the primary benefit would be reducing the staff infections in the platelet concentrates.

Of course, that means there would be little benefit in the units from which on platelets are going to be made. Is that still correct?

DR. VOSTAL: You mean, in the whole-blood collections?

DR. SIMON: Right. And then you have the

at

apheresis collections, of course, where you would get the benefit to the platelets, and that the more serious, fatal reactions would likely to be less effective than the less serious febrile-type reactions. Is that a reasonable summary?

DR. VOSTAL: I think it is, but I also think that we really don't know. These are data from small studies. We really don't have an idea what the actual true contamination rate across the country is and it is going to be difficult to see if this--I think we have to make a decision on this limited set of data or we are never going to know if it is really going to provide benefit or not.

DR. KLEINMAN: Also, in terms of efficacy, Toby, it seems to me we haven't seen whether this reduction in the first tube, if you let that platelet sit for four or five days actually takes it to zero where, if it just reduces the number of colony-forming units, these culture studies were generally performed within the first 24 hours.

So, I would say, in addition to small numbers, we really don't know about efficacy because the right clinically significant studies or blood-storage studies haven't been presented either.

DR. VOSTAL: So I guess one of our questions, one of the last questions, is--

DR. NELSON: I guess, instead of studying for

at

fatality as an endpoint, one could study colony-forming units after a certain period of time in the platelets or the bag or whatever. At the rates that have been reported, that could be done with a smaller number, I suspect. That is question No. 3.

Do you want us to vote on question No. 1, Jay? Okay. Can we stay with question No. 1, then, and say are the criteria that the FDA has proposed, which doesn't say that it will definitely--but it says closed system, at a diverted volume, unidirectional flow and the volume is sufficient for testing and possibly to reduce bacterial contamination.

DR. FITZPATRICK: On the volume, besides being adequate, is there--can it be put in there that it is a volume that will be limited so that the--I mean, we don't want to force blood centers into having to weigh that pouch and make sure there is only so much blood in it, that it needs to not be able to be overfilled because then you get into the problem of drawing too much blood from the donor.

DR. EPSTEIN: We say both necessary and sufficient.

DR. BIANCO: You would want to leave some blood for the patient. [Laughter.]

DR. SIMON: The only other group that we didn't hear from are the testing labs and I presume there is no

problem with this blood being used for testing. There are no negative factors that any of you see in it. We don't know?

DR. NELSON: If there is hepatitis in the skin plug.

DR. STRAMER: We are assuming the collection tubes would fulfill the same requirements as in the inserts for testing that we have now.

DR. SIMON: There is no reason to think they wouldn't.

DR. STRAMER: No. We routinely test serum from most serology tests and plasma for NAT. But, anticoagulants are qualified for serological testing as well. But serum is still the preferred sample. But I don't see why there should be any issues that we have heard that would prevent successful testing.

DR. NELSON: That would be one of the criteria. Do you want to vote on this? All in favor of these three criteria, yes?

[Show of hands.]

DR. NELSON: Opposed?

[No response.]

DR. NELSON: Abstentions.

[No response.]

DR. NELSON: Industry?

DR. SIMON: Yes.

DR. NELSON: Consumer?

MS. KNOWLES: Yes.

DR. SMALLWOOD: The results of voting on question 1; 14 yes votes, no no votes, no abstentions. Both the consumer and industry representatives agreed with the yes vote.

DR. NELSON: The second question is up there; for products that meet FDA's approval criteria, which we just voted on, do the available European studies provide sufficient data to support the claim that diversion of an initial 30 ccs of blood significantly reduces the bacterial contamination of the final product.

DR. MITCHELL: I don't think, first of all, that we have been able to show that. First of all, there is limited data. It sounds like a lot of the things that they are seeing are seeing contaminants, that those are not the things that cause the disease and, even with the diversion, there still remain substantial amounts of bacteria in the blood, apparently.

I don't think that it should be recommended at this point. I don't think we have good enough information to recommend it, particularly if there are other factors involved like cost. If it is a tradeoff, and it would be the same--just a better way of collecting the samples that

need to be collected, then, perhaps, it should be considered for that purpose.

But, for decontamination, I don't think that we have been shown that there is a significant difference.

DR. STRONCEK: I guess I interpret this question as saying that we are not recommending it but we would allow manufacturers to make the claim, or advertise that this pouch would reduce--it is not deaths. It says bacterial contamination. I think the data suggest that there is less bacterial contamination. Whether or not it prevents any deaths is another question.

But, still, getting septic from a platelet transfusion is not a good outcome, either.

DR. NELSON: This question doesn't say deaths. It says, "reduce bacterial contamination." So I think what they are questioning is if you implement this and then you culture, or measure, the blood--or the platelets or the blood in the bag, is it lower because of this initial 30 ccs.

There was a small amount of data, but I don't think a whole lot, unless I missed something, on this question.

DR. CHAMBERLAND: I just had a question, a clarification. The way question 2 is worded, at least it suggests to me--and this is what is confusing me--as

at

manufacturers approach FDA with their product, wouldn't they have to present their own data that they have derived to show that their bag, in in vitro conditions, inoculating, sort of repeating these experiments that were done, would show a reduction in bacterial contamination?

Wouldn't they have to provide their product-specific data as opposed to relying on published data?

DR. VOSTAL: Yes. Ideally, yes. We would require them to provide in vitro testing and a clinical trial. However, to run a clinical trial to prove that you are actually decreasing the contamination rate would require a very large clinical trial.

So we actually think that it is probably a good idea to have these types of systems on the market, but the question we have is if somebody comes to us with this type of system, can we allow them a claim of bacterial contamination reduction just based on the data that is already published, and not make them go through that whole trial.

DR. CHAMBERLAND: So there are two parts to this. One is the in vitro piece where you inoculate and then look for, hopefully, reductions in bacterial contamination. And then, in the final blood product which I believe you said was not done in one of the studies, that's correct. And then I understand what you are saying, the clinical trial is

another issue.

So this question is really applicable to the clinical trial.

DR. VOSTAL: To the clinical trial because even if the company did an in vitro study, I think at least the study that was published by Dr. Wagner, it is an artificial system. You start off with a very high contamination on that port and you can show that you decreased the bacteria in sequential collections.

But it really don't represent what happens when you puncture a skin. So, in order to understand what is really going on, we would have to have a large clinical trial. On the one hand, we understand this would be the ideal way to do it but, on the other hand, we understand that companies may not be lining up to do those clinical studies.

So we think if we want to see this reach the market, maybe we should consider allowing a claim based on what is already published. I think that is the question we are trying to ask.

DR. KOERPER: It seems to me that the company at least has to show that its system is equivalent to the European system, for instance. They have got to do something to show that their system is effective, safe and effective. I don't think they can say, "Oh; here, we came

up this system, so approve it because a European study with a different system showed reduction."

The companies have got to do some studies.

DR. NELSON: Couldn't a company use the same language that the FDA used in question 1, that it potentially reduces bacterial contamination without saying that it does?

DR. VOSTAL: I think that is the question we are asking the committee. To get back to your question, what we are saying is their system matches the criteria that we presented in the first question, is that sufficient? Does the criteria that we presented represent what was published in the European study? So, if they meet the criteria, can we give them the label?

DR. KOERPER: But it seems like they have to do some cultures of some blood collected through their own system. I just have difficulty with simply because they added and extra bag--I think you need to show that their system of clamping it off after collecting the first sample, then clamping it off and then collecting the rest to go ultimately to be transfused, that you don't get bacteria, somehow by that extra manipulation of that extra set of tubes.

DR. VOSTAL: I think that is a very good point and that is what we are discussing.

DR. KOERPER: I don't know that it needs to be 8,000 donations. I don't know what the right number is, but it seems like they should have to do some collections.

DR. VOSTAL: That is really question No. 3.

DR. McCURDY: One of the suggested benefits of this collection of the specimen is to avoid loss of units for having insufficient amount of blood to do the testing. I have been unable, in my own mind--and I haven't heard anything presented here, as to what the order of magnitude is of that. It wouldn't take a lot of units saved to pay for the bag and, perhaps, a possible reduction or something like that would be sufficient for the bags to achieve a fair amount of use.

DR. NELSON: I think they could make that claim without a clinical trial. But the real issue is what claim can be made about the safety and bacterial contamination.

DR. McCURDY: The safety of the bags, I wouldn't think, would be at issue--

DR. NELSON: No; safety of the blood.

DR. McCURDY: Whether it would increase the safety of the blood, my question, I guess, is do we need to have such a claim in order to make a certain amount--a change in the way things are done.

DR. NELSON: I don't think we do. One could answer no to this question and still have the bags have a

benefit in terms of what you pointed out.

DR. McCURDY: Precisely.

DR. STUVER: Can I just be clear because it sounded like they were saying that this question could imply that it just potentially reduces, but it specifically says "significantly reduces." I am assuming we are using significantly in a statistical manner. It is very specific in the question in that way, that that would be the kind of claim that could be made, not "potentially reduces."

DR. VOSTAL: I think the word "significant" is in there because if we were going to require a clinical trial, we would look for a statistically significant difference, to give them that claim.

DR. STUVER: That is a major claim, then, to give them.

DR. FITZPATRICK: I just have a couple of things. I will be brief. They could just market this as an alternate collection system without making any claims for safety or bacterial contamination, and that would solve that whole problem. The other is, on the BaCon study, of those twenty-six apheresis platelet units that were contaminated, do we know how many were collected with diversion pouches?

We heard from Haemonetics and Kobe that they have been doing that for several years now. So that would be a piece of information that would help. The other is that, in

at

the past couple of months, we have seen in the literature recommendations that we change the skin prep and that that would have a dramatic effect on bacterial contamination.

So there is more than just one thing going on to change that. The third is, we need to focus, I think, on the fact that we probably are not going to affect fatalities by doing this. So I think it is an alternate method of sample collection that may have benefit, but we don't know what that benefit is.

DR. KAGAN: I have one comment. Wouldn't the requirement for the manufacturer be to validate that it meets the criteria in 1. a), b) and c) and not necessarily the bacterial contamination. They have to prove that their product does what it says in a), b) and the subsets, not necessarily the other items.

DR. NELSON: I don't know. If they were to claim that this product definitely or significantly reduces bacterial contamination in the unit, as opposed to potentially reduces bacterial contamination, they might have to show that, I guess. Isn't that right?

DR. EPSTEIN: You see, the issue here is that the legal standard is adequate scientific data. We don't have to hold the companies accountable for clinical trials. The question is--and Jaro, I think, stated it precisely--if they satisfy the design criteria as put forth by FDA, should we

permit a superiority claim for safety compared to other available collection systems.

I think we have heard some arguments that maybe that is not so wise, which could be the conclusion of the voting. But that is the question. That is the very question.

DR. BOYLE: I am concerned just as little bit in terms of not actually the wording but the interpretation of the wording because the interpretation of a claim that it significantly reduces bacterial contamination is going to be that it significantly reduces morbidity or mortality, which is something that has not been demonstrated here.

So my concern is not just simply the terms but how those are going to be interpreted and how it is going to marketed. So that would be my concern.

DR. NELSON: A brief comment?

DR. BINION: Steve Binion, Baxter Healthcare. I just wanted to clarify and go back to the Advamed meeting last November in which manufacturers were invited to participate. This was one of the points that came up. There seems to me, at least among some of the committee members, to be a presumption that blood-pack-unit or device manufacturers are interested in this claim.

I think it is worth noting that one of the first issues industry put on the table at that meeting was that

the requirement for significant additional development expenses associated with clinical trials because, if it were a necessity of offering this technology to have it tied to this type of claim is, frankly, a large disincentive for at least some manufacturers.

The purpose for participating here today was at the request following up on inquiries from customers in the U.S. as well as discussions with CBER to speak to the feasibility aspects of making this type of collection system which is already in use outside of the U.S. available in the U.S.

So, at least I would ask you to consider the fact that some manufacturers may not have even entertained some sort of additional safety claim on this basis. Certainly, there does seem to be, and that was really the point to my question, for CBER seeking clarification of the regulatory process. If this technology is desired for implementation in the U.S., then there should be technical and manufacturing standards that could be put in place that would allow it.

DR. EPSTEIN: I would flip that around. The issue is really the converse. If we think that there is a valid labeling claim for improved safety, that we would permit, without demanding clinical trials--we are, in fact, creating an incentive for the bag manufacturers to go ahead and do this because they can make that claim.

I understand the point that Steve made, but FDA was looking at it the other way around.

DR. KLEINMAN: I think if there were sufficient European studies that nailed this down, they maybe you could extend the claim to anybody who could take off 30 ccs. There is only one study published. So what you are saying, is there one study published, which didn't do any direct measurement, which is sufficient to support the claim.

I don't think that study is sufficient to support the claim for that particular bag. So maybe the question should be, if there were to be more studies from Europe and, apparently, there are some under way, that then would provided a critical mass of data, maybe it wouldn't be necessary to duplicate those studies in clinical trials in the U.S.

But I think, as of today, where is the data? There is no data there.

DR. NELSON: The question uses the word "available European studies." Let's vote on this. How many believe that--how many want to vote yes to this?

DR. STRONCEK: Before we vote--I am going to vote yes for this, but there is a reason. I agree with everyone who says the data is not good and there is not much data. But, the fact of the matter is, if you wanted to do this study in the U.S. and you are a small center, there are no

bags available. You can't just go buy a bag that would be used in Europe and collect blood here for transfusion.

So, a vote against this is really a huge disincentive for the availability of this product in the U.S. I think a vote for it would encourage manufacturers to do it. It is unfortunate that is the way the system works, but if we vote no, this bag just--I don't suspect this bag will become available.

DR. NELSON: Sue Stramer?

DR. STRAMER: My comment has nothing to do with this question so perhaps you should vote first. I want to recall a previous comment I made regarding question No.1. So I can wait after at vote for question No. 2. I am patient.

DR. DODD: Roger Dodd, American Red Cross. It seems we have heard a lot of interest from the potential users of this product and it might be possible that they are the ones that should want to make the claim.

What the committee needs to do is to make sure that the product is available so that that claim can be made by those who really have most interest in making the claim that they are improving the safety of blood supply.

DR. NELSON: So how does that mean we should vote on this?

DR. DODD: You should vote to--I don't know how

you vote on that question in that context.

DR. NELSON: Let's vote in any case. I don't think this vote should be interpreted to mean that we don't like the idea or that we don't like the bags, but we are voting on what the FDA asked us to vote on, I guess. How many would vote yes, that the available European studies provide sufficient data to support the claim that diversion of 33 ccs significant reduces the bacterial contamination of the final blood product.

[One hand raised.]

DR. NELSON: How many would vote no?

[Show of hands.]

DR. NELSON: Industry?

DR. SIMON: No.

MS. KNOWLES: No.

DR. SMALLWOOD: The results of voting on question No. 2; there was one yes vote, thirteen no votes, no abstentions. Both the consumer and industry representative agreed with the no vote.

DR. NELSON: Maybe we could ask the question, "We wish that the available data would support the use of this good idea," or whatever.

So, then, finally; if the studies are not adequate, what kinds of studies performed in the U.S. would be needed for such a claim?

Here, we get into the conundrum, if there are no bags, then there won't be a study. But it would seem to me that we wouldn't need to demonstrate a mortality endpoint but that if we could show, in whatever number it took, that there was a reduced bacterial contamination, even if they were Propioni bacteria or whatever, this would be enough to make the claim.

But I don't know how many bags would need to be--I think it would be feasible to do this if the bags were there. With Paul's concern, maybe the incentive of having an adequate volume and not having to get rid of units and other things would make this feasible or attractive.

I don't think the cost--it doesn't sound like the cost would be major to switch to this, but I don't know.

DR. CHAMBERLAND: Just following up on Steve Kleinman's comment, question 3, or whatever, suggests that the studies would have to be performed in the United States. I am not sure that the studies would have to be performed in the United States. If good data could be obtained in Europe or other sites where these bags are being use, and that could be examined, I agree with Steve that there is an overall paucity of data, at least that have been presented.

So if there are more data available, I am not necessarily thinking it has to be derived in the U.S.

DR. NELSON: I would agree. I think maybe this is

the first time today that we are going to change the FDA's question. We used to do that all the time. Today, we didn't do it.

But I would say if the studies are not adequate, what kind of studies performed anywhere, or what kind of studies would be needed for such a claim. They could be performed wherever. If the data showed it, it didn't have to be in the U.S.

Do people agree with that change?

DR. SCHMIDT: I think I hear you talking clinical studies, the effects on people, rather than just in vitro studies.

DR. NELSON: In the bag. That is what I--I would not require clinical studies.

DR. SCHMIDT: Would you accept artificially in the bag?

DR. NELSON: Possibly. Yes; that might work.

DR. DODD: Ken, the committee has been supportive of the notion, it has been supportive of the criteria that the FDA have laid out, and it would appear to me that this might offer the option of the FDA approving bags that meet their design criteria for sale and then encourage the development of what are now phase IV clinical trials which is, basically, the mechanism for inactivated products.

Thus, data would emerge from usage of the product

which could then subsequently be used to provide a safety or labeling claim. I think there is enough interest among the users to take a product that is approved by whatever mechanism the FDA chooses.

DR. NELSON: Yes; I agree. We don't need to vote on this, do we? This is an essay question. [Laughter.] Let me just turn it into a multiple choice, or a yes-or-no, and say, does the committee agree that, if further studies are done, that manufacturers could make this claim and that we would encourage studies to be done on this issue.

After all, bacterial infections are quite important. They are, as pointed out, more common now than viral infections in transfused patients.

DR. MITCHELL: I am still concerned that I think that there should be something to demonstrate some kind of clinical benefit in addition to in vitro. And I don't know exactly what that should be and I don't necessarily think that you need to follow 3 million patients and see what kind of infections they get.

But I think I would want something showing that there is some kind of clinical significance to in vitro testing.

DR. VOSTAL: I wonder if I can get a clarification on the studies that we were talking about. There could be two different kinds of in vivo studies. One would be where

you use donors and collect a blood product and test that for bacteria. The next step would be looking at the transfused product and the outcome in the transfused patients.

Which study would be--would the first study be sufficient, or would we need to go all the way to transfusing patients and following morality?

DR. NELSON: I think you could infer that if pathogenic bacteria were in a unit that was to be transfused, whether it be platelets or whatever, that that probably isn't good. But the numbers to show morbidity, mortality, et cetera, would probably be prohibitive in order to get the product out.

DR. KOERPER: I think the first step is just to show that when the blood is collected that there is a reduction or, hopefully, zero bacterial contamination in the final bag that might ultimately be transfused into someone. Then, if the Red Cross and AABB, as they are collecting data on these reported cases of sepsis and/or death, if one of the questions they could ask is was there a pre-donation collection port, or not, however many million collections there are a year.

You need that denominator because the number of fatal ones is so few per year. So, if that extra one piece of information could be collected on each fatal or serious septic episode, in terms of whether there was a pre-

collection blood--I think that is the only way we can answer the risk of fatality and serious sepsis.

DR. NELSON: As I remember the data, though, on platelets, it was one in 3,000 that had bacterial contamination?

DR. KOERPER: Right; which is different than sepsis and death.

DR. NELSON: So a study of 20,000 or 30,000 would be able to answer the question, probably--I am not a statistician but that is my guess--about the bacterial contamination question. Once that was answered, then the manufacturer could say, we have shown that it reduces bacterial contamination. That would probably be enough for it to be widely used, I think. So I don't think that is a prohibitive kind of study.

DR. BINION: Steve Binion, again, from Baxter. I just wanted to, I guess, further clarify Baxter's willingness to collaborate in the potential availability of this sampling technology for blood-pack units in the U.S. is not predicated upon any blood-pack unit product-superiority claim.

In fact, what I was trying to point out earlier is that if that type of data became the barrier for introduction of this technology in the U.S. that, yes, that would, at least from one manufacturer's perspective, present

at

a significant disincentive to making this technology, which is already available elsewhere, available for use in the U.S.

Thanks.

DR. HALEY: Rebecca Haley with the American Red Cross. We will not stop collecting the data that we have in the American Red Cross. Again with approximately one in 60,000 septic episodes for platelet transfusion and one in 250,000 fatalities, it will take a little while.

I don't think anybody in their right mind would set up a randomized study where you left the bacteria in this one and took them out of that one. We are interested in getting a safe product a whole lot more than we are interested in getting some kind of claim.

What I tried to show is that there are a great many things that are ripe for the taking out. If we could start with that and then do the next step when it comes up, we will continue to collect our information and continue to report it whenever we have an opportunity.

I am sorry I was out of the room because we were talking about the BaCon study which, by the way, has lost its funding in the CDC because nobody was interested enough to continue that. That was another way to keep up with that information.

DR. NELSON: But I don't think the Red Cross's

studies of septic episodes--without a trial, nobody--I think the only feasible way that I see of doing this is just measuring how much bacteria there is in the bag and a certain number with this collection system and without it.

I think that kind of study is quite feasible. I think a mortality or a morbidity study randomized trial, I don't see that that is particularly feasible.

DR. HALEY: I agree.

DR. CHAMBERLAND: Perhaps Matt or others would like to speak to this a little bit more but, while it is true that national surveillance, vis a vis the BaCon project, is, at this point, no longer an option, for something like this, that may actually not be the best way to try and evaluate the impact of an intervention because, even BaCon, we acknowledge that there clearly was underreporting, underrecognition.

So other approaches might include really developing much more intensive surveillance in a sample of hospitals or other settings and comparing pre- and post-intervention and looking to see if you see any reduction in events. I don't know, Matt, if you wanted to comment on that.

Dr. KUEHNERT: I think you said it very well. I think that BaCon, one of its chief limitations is that it does not gather information at the hospital level to the

point where I think it would be adequate to evaluate an intervention like this.

I think you really have to have a person or group of people who do active surveillance at the hospital level rather than passive reporting. But that is not to say it needs to be a randomized blinded trial, but that it needs to be active surveillance at the hospital level to really be effective.

DR. NELSON: Jay, have we sufficiently addressed this?

DR. STRAMER: Just one last thing. This was for Toby, now that he just walked out. Anyway, on his question regarding qualification of assays, I was reminded, and this was before my time at Red Cross, that the Red Cross had looked at an in-line pouch previously for a different purpose. But when we looked at the rates of some of our viral-marker tests, it did show significant increases.

So I think we would want to validate any changes in the tubes and the processes that we use before we just--

DR. NELSON: With NAT testing?

DR. STRAMER: No; this happened to be with syphilis, but we wouldn't want to lose that many more donors because of syphilis false-positivity. I just remind us that we would want to do validations.

DR. NELSON: Tomorrow, we will start at 8:30 and,

at

theoretically, done by noon. So that probably means later.

[Whereupon, at 6:55 p.m., the meeting was recessed, to be resumed on February 16, 2000, at 8:30 a.m.]

- - -

# *CERTIFICATE*

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO