BSE epidemic relative to that in the U.K. as we've already seen.

In addition, the magnitude of risk reduction achieved by fractionation, in general, is likely to be greater than that achievable by donor deferral. And finally, there were concerns that if there was a deferral for travelers to Europe or if they were prevented from donating plasma, that there could be effects on nationwide and worldwide plasma supplies. This is obviously uncertain, but there was a potential.

For the implementation of geographic donor deferrals, those who were on the Committee probably remember that it really had to be thought out over several different meetings. The concerns about blood and plasma supply were addressed through conducting surveys and estimates of the risk benefit prior to making these recommendations. Certainly, they came before the Committee as well for advice. Phased implementation of donor deferrals which is important for blood especially because some centers have been relying in part on blood from Europe. Blood supply monitoring occurred both by blood supplier organizations and by HHS after the deferrals were implemented and in some cases that still continues.

And we also made a recommendation to perform pilot studies if a blood bank or blood organization wanted to implement more stringent deferrals than those that we recommended.

Finally, product disposition. This is an additional safeguard. This is post-donation discovery of a risk factor or disease. For BCJD diagnosis, all products including plasma derivatives are withdrawn. Of course, this hasn't happened yet. For CJD diagnosis, all components in unpooled units of plasma are withdrawn. But if the plasma is already pooled, it moves forward into fractionation. And for risk factors, likewise, all components in unpooled plasma are withdrawn is a post-donation discovery of a risk factor occurs.

So that is the review of the current donor deferrals and the disposition of components and then I'll leave it to Dr. Williams to go into greater depth about the effects of these donor deferrals.

DR. WILLIAMS: Thank you. What I'm going to do is give a little bit of a retrospective of the policy development process since around 1999, primarily for the benefit for some of the new members of the Committee who weren't part of this process all along. And show some of the data that helped underlie

some of the decisions that were made and I hope leave you with the thought that as a Committee, you should feel free to consider where new data may be needed to make decisions into the future and feel free to speak up and when those data are needed as the Committee in 1998, in fact, did under the chairmanship of Paul Brown.

So as I mentioned the talk is entitled "Development of FDA Recommendations for Deferral of Donors Based on Risk of BSE Exposure."

Next slide.

The goals overall, and I think these have held true throughout the response to this epidemic is that an effective response is needed to the spread of variant CJD in Europe and the potential threat that it holds to the blood supply, that there needs to be an optimal balance between variant CJD risk reduction, interventions and blood supply, certain preservation as you've heard several times already. There needs to be an implementation plan that's sensitive to the dynamics of the donor recruitment process and the realities of sharing blood around the country. You can't necessarily assume because you lose proportion of donors in part of the country that that immediately fills up by supplies from elsewhere although certainly

the ability to identify needs and share blood supplies has improved quite a bit in the past several years. And there's a need for both a coherent, scientifically explainable and uniform national policy.

Now ideally, one would be able to have a risk model based on data, but to do that in this situation would require data that we largely don't have. That would be the likelihood of dietary exposure within a country with endemic BSE, knowledge about the length of the incubation period, both the mean and the range; the prevalence of an asymptomatic carrier state. This is an updated slide from some time ago. Presence of a variant CJD agent, whether it occurs in blood during the incubation period or carrier state. Of course, now we know that and hopefully, rarely that is the case, but we know that's no longer theoretical; and the susceptibility of the recipient population, whether based on genetic make up or other factor.

Because of the very limited data, database model, empirical model isn't possible and the prior comment, notwithstanding, we did base most of the analysis on a linear risk model under several assumptions and this is at the risk of exposure to BSE for variant CJD is linear and related to the duration

and the likelihood of a dietary exposure. This is a concept that this Committee has discussed previously numerous times and has several assumptions that underlie the use of survey data to support policy making. These are that the data regarding travel and residence in a BSE endemic country as a valid surrogate for dietary exposure to BSE and the subsequent potential to transmit variant CJD via blood.

The major data collection activity that served to support policy making was a blood donor travel survey actually commissioned by a prior TSE Advisory Committee to measure travel and duration of travel within not only the U.K. but countries in Europe which were known to have endemic BSE at that time. This was based on a probability sample of accepted donors at 12 blood centers in late 1998, early 1999 and involved 19,000 mail surveys meant to be simple, a single page mailing, together with a cover letter. We had a 50 percent response rate to that mailing and the survey collected travel and residence data from the U.K., limited European data and some basic demographics on the respondent population.

The data was requested by the Committee

and has been presented extensively at previous meetings. And throughout this talk what I'm going to do is just mention some of the high points from some of these discussions.

Overall, what's the prevalence of any U.K. travel or residence between 1980 and 1996? That figure is 22.8 percent overall for the donor population to defer. Any donor who has ever been in the U.K. is 22 plus percent of the donor population. Similarly, for any European country, recognized as having endemic BSE in 1999, that about be about 35.5 percent.

Now in some of the calculations, we needed both a numerator and a denominator, so what we had available was duration of time spent in a BSE endemic country and we converted that to person days exposure. That's derived from the total estimated cumulative times spent by donors in a defined geographic area. And then from the other side we knew what the prevalence was of donor travel to that area and we could establish a cutoff value, for instance, three months, six months, one year, five years and define and estimated proportion of donors who spent time in the area and if they were deferred what the donor loss would be.

Some of the characteristics of the blood supply which had to come under consideration is, for instance, 80 percent of the blood supply in the U.S. comes from donors who have donated before, so any deferral that either targets the older donor population or for some reason targets donors who have donated before, that's a costly deferral because these are largely individuals who donate several times a year and you lose subsequent donations from deferred individuals.

The blood supply itself is stressed. It's an aging donor base and just simply through economics there are fewer large work site collections than there used to be. So recruiting donors and actually collecting blood is a more dispersed operation and generally more difficult than it was 10 or 15 years ago.

From the other side, we know that the blood supply is at least somewhat elastic. There have been losses due to previous events such as implementation of antihepatitis B core testing and change of hemoglobin determinations from ear stick to finger stick that deferred somewhere in the range of 3 percent of donors, so we know that we recovered from those changes in operations and predicted that we

would at least have that much elasticity.

However, we know that periodically in the summer and in the holiday periods there are spot shortages and even regional shortages of the blood supply.

Also, a concern, we know the public response to crises, we know the public response to appeals, but we don't know what the long term impact is of deferrals as far as those donors who responded to the appeals or other associations with the deferral process.

And as mentioned earlier, there needs to be a capability of monitoring supply impact. That's been the basis of several discussions of this Committee to be able to assess what the downstream impact is of an intervention.

So an example of some of the calculations that were done in the first consideration was for the six month deferral for travel residents in the U.K. There were a total of 252,804 person days of exposure in the survey population. If there was a cut point at six months, we removed 217,000 of those person days, resulting in an 86 percent theoretical risk reduction based on that linear model.

We knew that the donor loss related to

that was 2.2 percent and just an arbitrary index based on the ratio of percent person days removed to percent donor loss, this had an index of 39.

Looking at the next possibility and in fact, the U.K. deferral currently in place, the denominators are same, the numerators are somewhat higher. A little higher proportion of risk removed specific to the U.K., a little higher donor loss, 3.4 percent. As you can see, a little lower index of efficiency.

Going down to one month, again, 97 percent of U.K. risk removed. Considerably higher donor loss, 6.4 percent and the index reflects that as 15.

And then just one example of a combination, were the current deferral to go from its current three month in the U.K. to one month, the additional risk, theoretical risk or risk removed based on the total U.K. risk model would be an additional four percent removal. This would have an additional three percent donor loss with a very low relative efficiency factor. So some gain in risk reduction, but at very high cost in terms of donor base.

And this is simply a graphical representation of some of the data I just showed and

you can see as time spent decreases the slope of the curve reflects the fact that your risk reduction is much lower for each increment of donor base lost.

As a result of the extensive discussion on these data in June of 1999, the Committee made its recommendations and subsequently the FDA issued guidance in November of 1999, recognizing that there would be an estimated 2 percent donor loss with respect to a six-month U.K. deferral and made that recommendation for exposure between 1980 and 1996, recognizing that the U.K. had put in very strong food supply safeguards and the Committee was comfortable with the 1996 cutoff; also receipt of bovine insulin in the U.K. And it's not mentioned, product retrieval recommended if the donor was later discovered to have variant CJD.

Now subsequent to that guidance, there was evidence of the epidemic expanding in Western Europe, as well as new data became known with respect to supplies of U.K. beef to DOD European bases. There was recognition in concert with the expanding BSE epidemic that part of the country's blood supply was sourced in Western Europe, the so-called Euroblood imported by the New York Blood Center. And there was some residual risk from the U.K. as was potential

European exposure.

The analysis then took a slightly more sophisticated tack in large part due to assistance from Larry Schonberger and colleagues at CDC who went to a weighted risk model and assigned the U.K. a value of one, given that that was the BSE epidemic focus. Based on U.K. imports and observations of BSE in France and several, I think two variant CJD cases in France, France was assigned five percent relative risk weighting. And other parts of Europe for various factors were assigned a .015 percent risk factor.

In considering France in relation to the U.K. throughout these calculations, we did not specifically assess travel residents in France, but did the relationship that any travel to U.K., compared to any travel to France had a relationship of 12.7, so we used that as an adjustment factor.

Specific to the DOD bases overseas, we knew that U.S. bases were supplied with about 30 percent of their beef supply came from the U.K., so we assigned that a 35 percent factor compared to 1 for U.K. itself.

Again, based on subsequent discussions, FDA issued revised guidance in January of 2002 and I'm not going to walk through these because Dot showed

these to you in the prior talk.

And this was the impact on that theoretical pie chart representing the risk. The DOD risk was entirely removed, based on the interventions put into place. The -- I'm sorry, not entirely. There's a small residual left there.

The U.K. deferral was reduced, not quite half. You can see there's still a residual U.K. risk exposure there. And similarly, the European deferral was reduced, but not entirely removed.

Euroblood was just eliminated, so that risk was entirely removed.

The incremental risk reduction based on this later guidance was 72 percent so that the total risk removed with the two recommendations considered in concert was estimated to be 91 percent of the total geographic dietary risk exposure.

Some advantages and disadvantages regarding the FDA recommendations. The deferrals were tied to BSE observational data and there was a ratio in the deferral of 3 months for U.K. exposure to 60 months or 5 years in Europe. This represents a worst case situation for all of Europe except for France. Remember that proportion was .015. So a conservative relationship, but still we maintain that 3 month to 60

month ratio.

We knew that the impact in the New York area with a loss of Euroblood was going to be severe, but collectors were encouraged to take aggressive donor deferral measures. Many did and in fact, the New York area blood supply actually did pretty well with an aggressive recruitment campaign by the New York Blood Center, some assistance from other centers, but the impact was dealt with.

As Dot mentioned, there was a pilot provision, allowing flexibility for sites to put their pilot programs into place and assess the donor impact. And the provision for deferring donors who had been transfused in the U.K. provided some protection for the potential for human to human passage of variant CJD and some, at least embryonic evidence that there might be some adaptation of strains in passage between species or within species. And the deferral continued to recognize food chain protections.

At the time the transfusion transmission of variant CJD remained theoretical. Of course, that has changed now. A big disadvantage is the complexity of this deferral itself. Any time you're trying to get survey response answers or get individuals to give a medical history, you need to keep your questions

simple and to the point and this is a complex screening paradigm and we recognize this.

The estimated four to six percent loss exceeded experience of the past. And it was hoped that the ability of the rest of the U.S. could compensate for the severe impact of donor loss in the New York area and in other coastal areas.

There were considerable discussions of the impact of this deferral. As I mentioned, the projected loss was about five percent nationwide. Importantly, the actual loss was not directly measurable. We just don't have a means to do that. While donors certainly are deferred on site and with respect to a direct question about their travel and geographic exposure, in fact, many donors self-defer long before ever coming to the Blood Center and Blood Centers frequently and talking on the phone to donors, encourage them to self-defer if they have a particular exposure.

So you'll see data reflecting deferrals, but most of that is on-site deferral data and really doesn't capture the full picture.

There were known to be some disproportional impacts of travel deferrals; coastal cities thought to have about 150 percent effective

loss and rural U.S., about 50 percent of the total loss. New York Euroblood area was not only impacted by the loss of the blood from Europe, but also by the travel deferral which particularly hit the coastal and financial centers of the coastal areas.

TSEAC recognizes these potential impacts and requested supply monitoring and assessment and I think to the extent that those systems could be brought to bear, we did get a reasonable assessment of how this deferral impacted the blood supply and now with the development of the HHS BASIS model for monitoring, I think those capabilities have improved.

That said, seasonal and regional blood shortages still persist and I think anyone in the blood collection community will still tell you things are tough out there in terms of bringing donors in and retaining them, maintaining supply.

What are some of the future potential challenges? Well, obviously, the recent documentation of transfusion transmission during variant CJD. Asymptomatic incubation period is very worrisome. The deferral for U.K. transfusion in 2001 was precautionary. It begs the question as to whether additional deferrals of individuals with previous transfusion in France or Europe or elsewhere may be

indicated.

We tried to squeeze the survey data for one more piece of analysis to see if we could address that and this is combined with the data shown here, different data from the NLRBI-sponsored REDS program which assessed the percentage of donations given by transfused allogeneic donors within a nine-year period. And you can see this changes, reduces a little bit over time, but overall, there's about a 5 percent basic prevalence of prior transfusion anywhere within the U.S. donor base.

A quick age-specific breakdown, as you might expect. This is higher and older donors ranging from 10 to 11 percent and much lower in the young donor population in the U.S. donors.

Now using some of these data with a number of assumptions, combined with the survey data, we tried to extrapolate some potential impacts for transfusion in other parts of Europe. And I think it's important to state some of the assumptions that were made. There was an observation of 5 percent prevalence of transfusion history. U.S. donors, overall, we extrapolated that to be the same for donors who had extended period of travel or residence in Europe.

The only way we could get at that was from the survey data, those donors who had at least a five-year or travel residence history. Now that's a conservative estimate of what would be a lifetime transfusion exposure. Conservative, but it's the only data we have available.

Also assuming that the rate of transfusion among residents and travelers to Europe parallel the U.S. experience and again, the prevalence of travel to France was .7 in relation to travel to Europe.

So putting all of that together, the history of transfusion within the U.K. and this is a deferral that was already accomplished by the 2001 guidance, would result in deferral or did result in a deferral of approximately 2 donors per 10,000. Similar calculation for history of transfusion. Any part of Europe excluding the U.K., approximately 3 donors per 10,000 and then specific to France with that correction of 1.4 per 10,000. So many assumptions, many extrapolations, but it gives us a ballpark estimate of the types of deferrals that might be experienced.

This is, I believe, my final slide. As subsequent meetings are held, the Committee is going to be faced with, I'm sure, new challenges. One could

be the spread or in fact the recognition of BSE or variant CJD in geographic areas that hadn't been previously recognized. There are no donor exposure travel or residence data available for donors beyond the U.K. and European BSE countries. So just to make the Committee aware of that, should something break in Asia or elsewhere, there are no data to support those discussions.

Despite many of the limitations, many assumptions, I think it's fair to say that the survey data did provide a framework for risk to donor loss estimates. That supported policy making. And I know Dr. George Nemo is here from the National Heart, Lung and Blood Institute. Their REDS Program was just recently renewed. I anticipate that they may well have a survey component to that program and I think as a Committee, you may wish to consider relevant new data collection activities that would support future deliberations on the topic.

Thank you very much.

DR. PRIOLA: Dr. Allen.

DR. ALLEN: Thank you, Alan, for summarizing that. It was very helpful. You indicated and I will confirm from personal experience that it is cumbersome to go through the questioning in the donor

deferral or donor data collection room. Recalling exactly where you've been, when and trying to add it all up is -- takes time. It confuses the people collecting the histories and it certainly is cumbersome at best.

Is there -- do you have any data from other sources, from blood collection centers or others in terms of the impact on the blood donation process because of this? I mean we can talk about the number of donors deferred. You talked also about that some people just don't even bother coming in because they don't want to have to go through that, even though they may be eligible to donate.

Do you have any information on the impact overall of this?

DR. WILLIAMS: I think, obviously, probably the blood collection community is better positioned to comment on their experiences. I think one thing I can say with a comment is that as part of its biologic product deviation reporting requirement to the FDA, any -- what's known as post-donation information needs to be reported to the agency. And the travel deferrals, specifically the U.K., European travel deferral and the malaria travel deferrals are far away the leading cause of this post-donation

information.

That being a donor was accepted as a donor based on history given at the time of screening and in subsequent to the donation event, recalculated or was reminded by a spouse or in some other manner, transmitted information to the Blood Center that hey, wait a minute, I wasn't really eligible.

The travel deferrals are a leading cause of that information and I think reflect that. The comment that FDA has worked very proactively, I think, with blood collection community, particularly the American Association of Blood Banks, to try to streamline and improve the donor history process and we've had many discussions at the Blood Products Advisory Committee about progress in doing that.

The questionnaire that's in place in some centers now and soon to be rolled out at other centers, for the first time uses questions that have been cognitively evaluated either by focus groups or one interview by the National Center for Health Statistics or focus groups conducted by other sources. So I think we are taking steps to improve the questionnaire and streamline it and make the questions the best that they can be, but it still remains an imperfect process.

DR. PRIOLA: Dr. Nelson?

DR. NELSON: Yes, one deferral criteria that I really hadn't thought much about and I wonder its impact and you didn't really mention it and that is having received insulin from -- bovine insulin from the U.K. and I don't know the impact of that. I think maybe one percent or more of the population is diabetic and that's increasing and I wonder if people would know where the insulin that they got came from and is that -- how does that -- did you ask about the prevalence of diabetes in your -- among -- in your survey?

DR. WILLIAMS: No, we didn't collect that at all and I agree with the implication of your statement. Rather than those who actually received U.K. bovine insulin, it's probably those who weren't sure and answered conservatively probably had the bigger impact, but we don't have specific data on that.

DR. NELSON: And even -- I was in the hospital recently and post-operatively now there are many places in order to control post-operative hyperglycemia which is suppose to improve wound healing and all the rest, people get insulin post-operatively. They may be one or two units to control

and who knows where that comes from.

Are there data, of the insulin that's used in the U.S., how much of it comes from bovine, U.K. bovine sources. I mean I have no idea.

DR. SCOTT: You can be reassured that none of it comes from the U.K. now. What has happened is that there are some people with diabetes that feel that this kind of insulin is the best kind of insulin to regulate their disease and so they personally have imported it and continue to import it and it's really that group that we intend to capture.

DR. PRIOLA: Dr. Bracey.

DR. BRACEY: Yes, just a couple of comments. Being from the hospital side, clearly, the inventory or supply is fragile. We continue to experience shortfalls and then for us that do collect, as mentioned before, these travel questions are really, really difficult. I mean if you -- it is the number one reason for BPD. I mean it's not a week that goes by when I see some of these things coming across, so there are issues.

I was reading in the materials about the export of blood from Britain to other places and how much of that activity has taken place? Is that going to be a significant concern?

DR. WILLIAMS: I'll comment specific to the whole blood. That collection brought in by the New York Blood Center prior to the guidance was sourced, I believe, in Netherlands, Switzerland and either Austria or Germany. That was the whole importer of whole blood and specifically red cells, Group O red cells.

With respect to any other products, I'd leave it to Jay or someone else to address.

DR. EPSTEIN: There have been very small scale distributions of products under IND that were manufactured from non-U.S. blood, by aside from those which probably dozens to at most hundreds, there have not been any plasma-derived products made from non-U.S. plasma. The red cell products are only in exactly the ones that Alan has already outlined, the Euroblood products from Germany, Switzerland and the Netherlands.

DR. PRIOLA: Dr. DeArmond?

DR. DeARMOND: The Department of Defense personnel in Europe during the time that was dangerous, what's known about them because they accounted for 40 percent of the deferrals. As I recall, they had a disproportionate effect on blood donation since they tended to be high level donators.

Do we know anything about the deaths of those individuals? Has any follow-up of the military personnel or DOD personnel been made and is there any plan to do any such thing?

DR. WILLIAMS: I think as far as variant CJD exposure and morbidity or mortality related to that, I don't know specific studies, but I would have to assume that there haven't been any specific variant CJD events in that population.

With respect to the deferrals, that was one population that we didn't capture very well by survey. We attempted to, but in turns out military staff, despite all their great points, do not respond well to surveys. So we got about a 10 percent response rate in the military population and really had very little data to go on and in fact, those areas that depended greatly on military bases, particularly in the Carolinas and some areas like that, were hit very hard by the deferral, simply by the loss of those populations.

DR. DeARMOND: I guess that means we can't do autopsies on all those individuals.

DR. PRIOLA: Mr. Bias.

MR. BIAS: My question was, Dr. Scott had mentioned pilot programs for looking at the deferral

issue. Has any blood collector taken the FDA up on that offer? What are some of the obstacles related to that?

DR. WILLIAMS: That was an element of the guidance because there were numerous discussions about what risk reduction was appropriate and what level of deferral could be sustained, specifically, the American Red Cross had determined its own deferral policy. And in fact, had largely implemented it by that time. It was slightly different than the FDA recommendation and I think the Agency basically wanted to create an environment where if that had a severe, not sustainable impact on the blood supply that there would be room to revert to the recommended regulatory policy. And I'm only aware of that one organization that's used a different deferral policy.

To some extent some of the differences remain, although a large part of the policy now is harmonized. I see Dr. Page here. He may have a comment.

MR. BIAS: One more comment. One thing that has changed since we've implemented these policies is that we do track people's travel a little bit more significantly since 9/11 and I'm wondering if there's any way to correlate the information so that

we can take that out of the process, since we know where people are going and know where they've come from supposedly. I'm sure not all can support that data, but it is something to look toward in the future since we are now tracking that information.

DR. WILLIAMS: I agree. Any source of data can be valuable. We, in fact, tried to do some of that based on immigration figures and some travel data that were available. It remains to be seen how useful it might be in practice, but I think any aspect could be useful, yes.

DR. PRIOLA: Dr. Bracey?

DR. BRACEY: Yes. This is somewhat tangential, but one thing that I've noted that is happening a lot in the U.K. is a look at the other side and that's the demand side. We do know that if one looks at blood transfusion practice across the United States and in fact, across the globe, there's a lot of questionable transfusions.

And I'm not sure we're really putting enough effort into supporting studies to improve practices along those lines. And I would hope that one of the things that we can do as a Committee is to sort of stimulate some thought and discussion about recommendations along that line.

DR. PRIOLA: Any other comments or questions for any of the speakers?

Okay, so I guess we'll move on to the open public hearing portion of the afternoon.

DR. FREAS: To date, I have received four requests to speak in the afternoon open public hearing. The first request is from the American Red Cross, Dr. Peter Page, would you come to the podium?

Excuse me, we have to read one statement that I forgot about, each and every time we have an open public hearing.

Please pay attention to this statement.

DR. PRIOLA: Thank you, Bill. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by

the topic of this meeting. For example, the financial information may include the company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. FREAS: Thank you, Dr. Priola. Dr. Page?

DR. PAGE: I'm Dr. Peter Page, Senior Medical Officer at American Red Cross, headquarters here in Washington, D.C. I'm a full-time salaried employee and I have no expenses related to this meeting.

Dr. Roger Dodd is the investigator on this study and would ordinarily be presenting, but he's out of the country now, so I'm going to try and present the data on the Red Cross study which has been referred to earlier.

It was designed in 1994, actually with input from the FDA by the Red Cross and the Centers for Disease Control and was implemented in 1995. In

order to attempt to assess the risk of transmission of classic CJD by blood components from whole blood donations.

In 1997, the coordinating responsibility for the study transferred to the AABB and the now former NBDRC, National Blood Data Resource Center, which discontinued being in existence a year or so ago. So late in 2003, the study management returned to the American Red Cross and Dr. Roger Dodd, primarily.

In September of this year, a cooperative agreement on the study was reached with the CDC which provides funds to ensure that this study can continue and that agreement is for five years.

The way the study works is this. Upon a U.S. Blood Center learning that a blood donor has been diagnosed with CJD, and the source of this information is usually a concerned family member of the CJD patient, who knew that they were a blood donor an thought that the Blood Center might want to know and have a concern with regard to recipients, so when a Blood Center learns this, they can track the prior donations from the patient who develops CJD and determine what blood components were sent to which hospitals and so that they can -- the recipients can

be identified by the hospital transfusion service.

The recipients are not notified, however. This is consistent with FDA guidance and as you'll see in a minute, has been reviewed and considered by the Red Cross IRB and the CDC IRB.

So we then have the name of the recipients of prior donations from patients -- from donors who ultimately developed CJ.

Each year since 1995, the names of these patient recipients who got the components are checked against the national death index or NDI Plus from the National Center for Health Statistics for multiple causes of death to see if any of the transfusion recipients died with CJD.

This takes awhile. The data that we have here are up through deaths through the end of 2001. We have just submitted a request to them for a follow-up through the end of 2002 and I don't have that data here yet, but we should be getting it shortly.

So there is a delay in the data and the data I have is not going to show that much more since when it has been presented earlier.

As I mentioned, the Institutional Review Boards have reviewed and approved the study. Changes have been made to the protocol following the reporting

of the possible transmission of variant CJD through transfusion and FDA's new guidance.

No notification is necessary for the study. That is, no notification of recipients is required, but medically appropriate notification and counseling may be provided at the discretion of the health care providers. Initially, we were precluded from doing that.

Both the CDC and the Red Cross IRBs must be consulted when a case of variant CJD occurs in the United States or a test becomes available or if classic CJDs should be associated with blood transfusion. Those have not happened, but we will certainly do that.

Now the results, just to recap what has been provided before and the numbers are only a little bit larger. We've had two new patients enrolled in the last year, so we have 28 donors who became CJD patients who are enrolled in the study. Their prior donations blood components went to 368 different recipients of blood. As of February 2003, we learned that the end of 2001, 102 of those 363 recipients were still alive; 241 had died. Of the 241, none had a diagnosis of CJD. Two-hundred-forty have diagnoses that are not CJD and one is still being researched and

is pending, one of the deaths. And there are 25 other recipients that we are trying to identify and follow up on.

The overall follow up in person years is that of the alive recipients who are 966 person years of follow up without CJD. Of those recipients who have died of other causes, we have 430 person years of follow up, totalling almost 1400 person years.

The first line on the study is the total of what's below it, but it relates to the long-term survivors, surviving recipients of the transfusions, long term here being more than five years.

You can see on the first line in yellow that we have 116 recipients who have lived more than five years, of whom 84 are living and will hopefully continue to live so that we can increase that number of follow up for over five years. But you will see that since many of the donors who have developed CJ have been long-term donors who have donated a while ago, we are lucky in that respect to have at least a few recipients with longer-term follow up. There are 27 from 11 to 15 years; 13 from 16 to 20 years; and 4 with over 20 years of experience, 3 of whom are still alive. And we will continue to follow up.

So in summary, no cases of CJD, classic

CJD have occurred in 342 recipients of blood components from donors who subsequently developed CJD, representing almost 1400 person years of follow up. This long-term follow up of these survivors will allow for more accurate estimate of the risk, if any, of transmission of CJD by blood components.

The real reason we wanted to speak here was not so much to update the data, since it's not that much more from previous presentations, but to advertise the program and make physicians, Blood Centers and families of CJD patients aware that the study continues to exist and is looking for more recipients to enroll. It has involved Red Cross as well as non-Red Cross Blood Centers.

So when a CJD patient has been a volunteer blood donor, we would hope that family members or friends would contact the appropriate local blood collecting center to make them aware of it. Many volunteer blood donors are proud of their donation history and make it known to their family and friends.

Blood Centers learning of a blood donor having developed CJD are continuing to participate in the study by contacting the Holland lab and Roger Dodd's study. I believe that this information will be on the website. We have requested that, so you can

get the fax number for contact and Karen Fujii, Ed Notari and Shimian Zou -- and Shimian Zou is here today -- will be glad to talk to you about how to input.

I want to acknowledge that most of the work in this study was done by Marian Sullivan, who is no longer part of this project as she's got other employment and Dr. Larry Schonberger is the key co-investigator who provided funding and other support and we also appreciate the many Blood Centers, Red Cross and non-Red Cross, including the military blood program who have participated. The staff members are listed there and I'll just end by leaving the contract information up.

Thank you very much for your attention.

DR. FREAS: Thank you, Dr. Page. I think, as always, for the open public hearing, we're going to hold our questions until the end.

The second request I have to speak in the open public hearing is from the America's Blood Centers, Dr. Michael Fitzpatrick will be the presenter.

DR. FITZPATRICK: Good afternoon. I'm Mike Fitzpatrick and I am fully employed by America's Blood Centers on a full-time basis.

Just to -- before I preface and read the written statement which the Committee has and was available outside, a couple of comments. One in my former life as head of the Department of Defense program, I can respond to one of the questions. There's an active surveillance program that the military participates in, just as civilian physicians. Prior to my retirement a year ago, there had been two suspected cases of neurgenerative disease and deaths that were fully explored and were negative. One was classical CJD and the other was not variant CJD, so there's an active surveillance program for the active duty and retiree members.

Most of the folks that were in Europe during that time are retired, like I am now, and so are in the civilian health care sector or are on the retiree sector.

Moving on, as you read the statement you may consider that ABC is a salmon swimming upstream today. Our members and our organization take blood safety very seriously. We do not take variant CJD lightly or the deferrals that have been put in place. But we want to raise a point to the Committee and to the audience. The precautions that have been put in place were put in place a number of years ago based on

theory and probability and assumptions and on very little data because there was very little data available at that time.

There is more data available, but not as definitive of an amount of data that we would like at this point in time for you to look at. And there is the definite concern about a second theoretical wave of cases.

Our concern, my concern especially today is that I've heard lots of discussion about more stringent requirements to reduce the risk. However, I've seen no data to show that there is an increased risk over what was done several years ago. And in theory, the things that have been put in place appear to be working. Two transfusion-related cases have been reported in the U.K.. And there is a possibility of a carrier population, but that population is defined. There are stringent controls now over what enters the food chain and the exposure of people to the agent has been greatly reduced and we need to keep that in mind.

BSE cases in countries other than the United Kingdom have not materialized as we thought they would. We will have just France and Italy. So with that thought in mind, I'd like to move on to the

written statement.

We are, as you can see from the first paragraph, a network of 76 members, collect about half the blood in the country and we have one international member, Hema-Quebec in Canada is a member providing blood to a fourth of the Canadian hospitals.

It's been almost eight years since the implementation of the safeguards to protect the bovine and human ends of the food chain from BSE, and the human form of that disease variant CJD. The FDA announced donor deferral criteria in August of 1999, five years ago, based on the application precautionary principle and the hypothesis that the prion responsible for variant CJD could be transmitted by transfusion and Dr. Williams walked everyone through how we go to that point and left out a lot of the pain in getting to that point, but the FDA and Dr. Williams are to be complimented for arriving at that deferral criteria and those models. There was a great deal of pain in getting to that point, and they led the way on that.

Two cases of variant CJD have been associated with the transfusion of blood from individuals who later died from variant CJD. This causal relationship is based on mathematical models of

probability and not biological data. We'd love to have biological data for that, but it's not evident.

The lack of biological data continues to confound the issue in our donors. We must note that the identification of these two cases has not changed the picture. We knew many years ago through the animal models that it was theoretically possible to transmit the agent for CJD by transfusion.

Five years ago, FDA developed the model based on potential exposure to the agent. This model continues to be used to defer hundreds of thousands of donors who do not understand why they are being deferred when it appears that both the human and bovine epidemics are over or on the decline phase of those, as you can see from the BSE statistics, the bovine form seems to be under control and we have a limited number of human cases.

The toll of the human epidemic currently stands at 157 diagnosed cases since 1994. There's only been one new human case in the past year.

We believe it's time to begin the discussion of an exit strategy for this deferral. Immense resources, people and dollars continue to be used to update deferral questions, screen and defer donors and respond to questions from deferred donors

and their friends.

These resources could be better utilized in CGMP compliance, developing new screening techniques, better procedures and recruitment of new donors. One severely affected population is the dependence of the military stationed in Europe during 1980 to 1996. Many are just now achieving the age of donation and like my own daughter who was born in Germany in 1998, lived there for two years, eating formula and baby food are indefinitely deferred.

I just had an event on Capitol Hill, rolling out the Ad Council campaign and one of the staffers there who was a teen in Europe, stationed there with her parents, asked if she would ever be able to donate. We proposed that FDA initiate discussions of what would constitute an exit strategy.

The questions that need to be asked are, what requirements should be fulfilled before discontinuance of all or part of the deferrals? What benchmarks need to be met, just as we have used for SARS and testing for West Nile virus. Should we consider discontinuing the U.K. deferrals a certain number of years after implementation of recognized safety measures? Could we decide that former U.S. military dependents have had less exposure than

originally thought and should be deferred for a shorter period of time. Could we discuss the possibility of removing countries which have had no human cases of variant CJD from the deferral criteria?

We raised these questions not as a point of reducing safety of the blood supply, but thinking not only of what can be done to mitigate risk, but what is our total plan after we see that we've accomplished that in a disease that has what appears to be a defined population of carriers and suspect donors.

I want to thank you for the opportunity to address the Committee and we hope to be able to work with the FDA on this in the future.

DR. FREAS: Thank you, Dr. Fitzpatrick. Our next request is from the Consumer Policy Institute, Jean Halloran. Is she here this afternoon?

Okay, we will go on -- my next request is from Dr. Robert Rohwer from the VA Medical Center, Baltimore.

DR. ROHWER: Thank you for giving me this opportunity to make a comment, but before I begin my prepared remarks, I'd like just to second something that Dr. Bailar raised a few minutes ago. It was our own interpretation of our experiment that the

conclusion should be that leukoreduction by itself probably does not provide any risk reduction and that as he pointed out there's 60 percent of the infectivity that still remains in those preparations after a leukoreduction and by definition an infectious dose is the dose required to cause an infection. It's an empirical definition and as a consequence there is in that unit, there's still 3,000 infectious doses remaining.

So at least for a collection that's made close to clinical disease, there's still likely to be enough infectivity to cause an infection and I think we're seeing that in the sheep transfusion experiments of Houston where larger amounts of blood are being transfused and the transfusion frequency in that model seems to be quite high. The incubation times also seem to be quite short.

The issue that I actually came prepared to talk about goes back to the very beginning of our discussion on blood today and involves how we go about doing validation studies and the standards that we should apply to labeling claims for those studies. And I'm going to read that statement.

The FDA has recently approved a labeling claim for removal of TSE infectivity during plasma

processing that is based on single-stepped, scaled down studies using high concentrations of brain-derived TSE infectivity. We participated in a number of those studies ourselves and are responsible for that data.

It has been a consistent finding by our laboratory and now by several others that brain-derived infectivity partitions with the precipitates during alcohol fractionations conducted by either the Cohn or the Kistler-Nischmann processes and is largely removed from the IgG and albumin fractions.

Brain-derived TSE infectivity is mainly associated with insoluble complexes of prion amyloid, cell debris and other particulate matter. The size, distribution of these particulate associations can be reduced by using a post-mitochondrial microsomal supernatant at a loss of 99 percent or more of the total infectivity. Nevertheless, the infectivity is still largely associated with particulates and continues to fractionate in a similar way and that's now been clearly shown in a number of studies.

In contrast, we have shown in this leukoreduction experiment and also other work that I've presented at other times to the Committee in the past, we have shown that blood-borne TSE infectivity

is nearly equally distributed between at least two compartments. Forty to 45 percent is associated with white blood cells. Fifty-five to 65 percent is with plasma, red blood cells and platelet.

We have also shown that the infectivity is not intrinsically associated with purified platelet and we have preliminary evidence that this will also be true for red blood cells.

This means that over one half of the infectivity is associated with plasma. We know almost nothing about the physical form of the plasma associated fraction. We've been working very hard to find out more about the nature of this material, but it's very, very difficult to do this because of the type of titration experiments we have to do to develop this basic data on this very low titer material.

As an example, there has to date been no convincing demonstration of PRP amyloid in either blood or plasma. If an infection-associated form of PRP is present, we do not know if it is in a fibular conformation or some more elemental configuration, or whether it is free in solution or associated with other molecules. There's been no conclusive proof that the most elemental form of the infectivity even contains prion protein. That's my own personal bias

showing through there.

Depending upon its actual form and associations, plasma-associated TSE infectivity might fractionate very differently from brain-derived infectivity which is largely cell associated and/or highly condensed and aggregated.

The concentration of TSE infectivity in the blood of a hamster in symptomatic disease is one billionth that in the brain of the same animal. As a consequence, there is insufficient infectivity in blood for it to be spiked into a process sample for a TSE-removal measurement like those that have been reported to date and were discussed this morning by Hank Baron.

There is, therefore, no obvious way to use blood to demonstrate the same five or six log 10 levels of removal per step that can be achieved with brain-derived infectivity. Nevertheless, at 10 infectious doses per mL, there is sufficient infectivity in a unit of blood, approximately 5,000 infectious doses or in the plasma-derived from a unit, approximately 3,000 infectious doses, to demonstrate up to 3 log 10 of clearance if hamster plasma itself is fractionated.

Even though the maximum level of removal

that is possible could be three or four orders of magnitude less for a measurement on endogenous blood-borne infectivity than for a brain-derived spike, there would be far less uncertainty about the relevance or the removal of blood-borne infectivity than for brain-derived infectivity. For example, high levels of removal of brain-derived infectivity would be irrelevant if the same fractionation steps removed a much lower amount of blood-borne infectivity.

Since concentration of blood infectivity is too low to be used as a spike, it cannot be used to test individual downstream steps in isolation. Rather, one must start the process with TSE infected blood and carry it through the successive steps of the process, measuring the distribution of infectivity between the fractions at each step until one reaches the final product or runs out of infectivity.

One might well run out of infectivity in the first few process steps. This would be a reassuring result. From that point in the process, brain-derived spikes would have to be used to test removal. But at least one would have shown to the limit of practical measurement that relevant, endogenous infectivity was also removed at some point during the process.

If there were significant discrepancies between the findings using blood-borne and brain-derived infectivity, it would serve as a warning that the downstream steps necessarily tested with brain-derived spikes might falsely represent the true removal capabilities of the process.

We have shown in our leukoreduction studies that hamster blood behaves very similarly to human blood in most parameters so far tested. We have also developed a very sensitive and precise method which we call limiting dilution titration for measuring the concentration of TSE infectivity in low concentration samples.

This method is capable of quantitating less than one infectious dose per mL if more than one mL liter of blood is inoculated. We strongly recommend that any blood or plasma-based clearance study include a demonstration that endogenous blood-borne infectivity can be removed to the limit of detection from the unit of equivalent -- from a unit equivalent of blood. This must be done by conducting the process sequentially from the beginning, using whole blood or plasma from a TSE-infected mouse or hamster.

Maximum measurement sensitivity can be

obtained most efficiently by inoculating the pace and pellets concentrated from blood. If infectivity remains to the end of the process, there would be no point in also testing a brain-drive spike. If endogenous blood-borne infectivity is removed to the limit of detection in the early steps of the process, subsequent steps would, of necessity, have to be tested with brain-derived spikes. In this case, regardless of the limitations of brain-derived infectivity spikes, it would have been established that at least a one blood unit equivalent of relevant blood-borne TSE infectivity had been removed by the process.

We also strongly recommend where brain-derived spikes are used, that they are carried through multiple steps in succession with measurements at each step instead of testing one step at a time, respiking at each. This is at variance with the guidance for viral validation studies, but I believe that that guidance is not really appropriate for testing the heterogeneous material that makes up the typical TSE infectivity sample.

While we consider it reasonable to expect that the cell associated component of blood-borne TSE infectivity will fractionate much the same way as the

cell associated and amyloid associated infectivity from brain, over half the infectivity in blood appears to be in some other form. The behavior of this form in the same fractionation schemes cannot be predicted with the same confidence and this uncertainty should be acknowledged in any claim for removal from blood or blood products unless directly tested using endogenous blood-borne infectivity from TSE-infected animals.

Thank you.

DR. FREAS: Thank you, Dr. Rohrer. I have one more request, that's Dr. Merlin Sayers from the Carter Blood Care.

DR. SAYERS: Thanks for this opportunity to speak. My name is Merlin Sayers and I'm Chief Executive Officer for Carter Blood Care. Carter Blood Care is the community independent blood program providing for the blood and component needs of the Dallas-Fort Worth Metroplex and the 26 surrounding counties. We draw something like 275,000 volunteer donors a year and provide service to 150 hospitals and medical institutions.

I have no financial declarations to make. This is a ruthlessly not-for-profit presentation and I think you'll appreciate that when you see the quality of the slides and you hear the anecdotal

nature of the dotter that I'm going to talk to you about.

I have to say by way of a preface that I really don't want to dilute the lofty academic quality of the presentations here, but until Alan Williams spoke, we really had not heard anything from the volunteer donors' point of view and it's worthwhile bearing in mind that some 12 million of those individuals, their candidacy for donation and the confirmation of their own self-assessment of good health is significantly influenced by your deliberations and the responses that you make to the questions raised by the FDA.

So let me tell you what has happened at the Dallas-Fort Worth Metroplex and Carter Blood Care. This illustration shows between 2000 and 2004 to date, the number of donors who have been deferred for variant CJD criteria at Carter Blood Care. Something like 5,000 donors. And that probably, as Alan Williams pointed out, only represents a third of the total number of individuals who have been deferred or lost as a result of these variant CJD criteria. Those that are not shown on these histograms are those individuals who recognize the information that they read in the press, or recognized and understood the

information that we gave them and they essentially voluntarily self-deferred.

Now in spite of all our efforts to ensure that donors do not actually come to the Blood Center to realize that they are deferred for geographic reasons, in spite of the fact that we have really taken significant steps to try and make sure that donors self-defer before they arrive at registration, this next illustration is going to show you -- can you put up the next one for me, please -- that there are still first time donors between 2000 and 20004 who are presenting themselves to donate.

You might well ask why would those individuals present and I strongly suspect that for some of these very significantly motivated individuals, there is an element of confusion in understanding particularly the geographic deferral criteria. And they only recognize that they are indeed candidates for deferral when some of the more arcane aspects of those deferrals have been explained to them at the Blood Center.

So what is our experience then with these individuals that are now permanently deferred for geographic reasons? Let's have the next illustration, please.

What we have here is an accumulative fashion the number of previous donations by donors who are not deferred for the variant CJD criteria at Carter Blood Care. This is cumulative and obviously it refers only to those individuals who had previous donation histories. And as Alan Williams pointed out, many of those individuals were obviously individuals who had had long and devoted previous donation histories.

Before moving on, let me make one point very clear and that is that this presentation is not an appeal for a less safe blood donation, for a less safe blood donor selection system. Let me be quite emphatic about that.

Let me also make the point that nowadays it's not just a question of replacing these individuals with dedicated donor histories. It's not just a question of replacing the individuals who are lost to deferral. Increasingly, donor recruitment has become a question of how best to manage what is tantamount to increasing incredulity on the part of the donors. For many, many individuals, donation has become a confusing and a dismaying experience and if national experience is any extension of the Dallas-Forth Worth experience, some 250,000 donors are now

permanently deferred for geographic reasons and in many of those instances, significant questions have been raised in their minds which we, as blood donors have great difficulty in answering.

We are confronted with donors how deferred who want to know if they should tell their family, if they should tell their dentist. They want to know if they should tell their family physician? They want to know if they should reveal their new permanent deferral status to individuals who are conducting health insurance exams. Some donors want to know if that means their new self-deferral status now confirms the fact that they are no longer on the National Marrow Donor Registry.

Now action which is prompted by observance of the precautionary principle may well be understood in these relatively sterile circumstances, but it is not reassuring to a donor to invoke the precautionary principle when he or she is told that his or her blood is no longer sufficiently safe for transfusion.

If there is no exit strategy that's developed, and if screening does become part of international practice and it certainly sounds as if the National Blood Service overseas will move to screening, once an appropriate screening test is

available, then my request is should screening be part of our conduct here in the States? If donors are screened for prion-based disease, then as early as possible, as soon as is reasonably possible, re-entry programs for donors deferred for VCJD risks should be developed and introduced.

Unless these re-entry programs or unless an exit strategy is developed, we are going to be increasingly confronted with permanently deferred donors whose answers to questions are not well understood and those individuals will continue to become a significant disincentive and deterrent to other individuals in the community who do not want to expose themselves to similar deferral criteria.

Thank you.

MR. FISK: Thank you, Dr. Sayers. We're getting behind on the agenda. Is there anyone left in the audience who would like to make a brief comment before the Committee? Okay, we'll time you for two minutes -- we're really behind on the agenda.

DR. GOLDSMITH: That's fine. Thanks very much. My name is Jonathan Goldsmith. I'm the Medical Director for the Immune Deficiency Foundation and that is who employs me.

I just wanted to say a couple of things on

behalf of our Medical Advisory Committee to the Committee to try and improve the long-term safety of plasma derivatives. And also in terms of some of the comments that have been made today in terms of uncertainties in the blood supply.

We have come out with a statement that makes the following two points. One, there should be a minimum documented level of prion protein removal from all IGIV manufacturing processes. And second, that manufacturers should investigate additional methods to reduce potentially contaminated prion proteins and not be content with the methods that are in place today.

Thank you very much.

MR. FISK: Thank you. Is there anyone else in the audience who would like to make a brief comment?

Seeing none, we'll close the open public hearing session. Thank you for your participation.

(Off the record.)

DR. PRIOLA: I think we'll take about a 20 minute break until -- no, not a five minute break. Let's take a 20 minute break until quarter to 4 and we'll come back and discuss and vote on the questions.

(Off the record.)

DR. FREAS: We have several members that must make airline connections and this is unavoidable, so if you would find your seat, we'd appreciate it.

DR. PRIOLA: If we could have all the Committee Members return to the table, so we can open the discussion. So they put up the questions that we're to discuss and consider and vote on up on the screen. And the first two questions, if you read through them are basically yes or no questions which we can discuss them and it makes it very easy to vote on.

The first one is "are the measures currently recommended by FDA to reduce the risk of transmitting CJD and vCJD by blood and blood products still justified?"

So to open the discussion, I'd like to go to Dr. Salman first.

DR. SALMAN: Thank you. First of all, I want to say that there's no such thing as zero risk, so we have to accept some risk in anything we have to do, including blood transfusion.

I believe like the FDA has taken so much precautionary measures to reduce the risk of transmitting new variant CJD way before we have any type of evidence of the transmission and I think now

we have not to talk about hypothetical situations. We do have some evidence that at least two cases have been transmitted through the blood transfusion. However, as Dr. Will presented, proportionally, even the mode of transmission of these two cases occurred and we agreed on it, is proportionally, this type of transmission is much less likely as compared to the dietary transmission for the new variant CJD.

I think as the current recommendation or the constraint that is applied by the FDA is sufficient to reduce the risk to minimum risk as much as possible for the -- for any type of blood or blood products and to transmit the new variant CJD agents.

So I think you can see my response to the first question. However, I want to say especially related to the question in 3. So we need to be careful as far as like how far and for how long we have to accept this type of rules and measures and my opinion and currently and my estimation, currently, we don't have enough data and evidence to say well, either to stop it or to have a time frame to say when we will stop it, so I believe like we need to accumulate as much as possible data before we could maybe stop this type of measure.

DR. PRIOLA: Dr. Gambetti?

DR. GAMBETTI: I agree. I think though that there are few pieces of information that are missing or I missed in order really to make a complete judgment on this issue. One is the information on the French cases of variant CJD.

We heard a lot about the transfusion, donation, blood donation history of the British cases, but I haven't heard information on the history of blood donation by the French cases. These would, may give us an idea on whether the disease, although the cases are much fewer, but whether the disease may be spread, may spread through blood transfusion in France as well, especially in view of the possibility of banning also cases that receive transfusions from the donor, deferred cases that receive blood transfusion in France.

Another issue that I think is peripheral because I see not much enthusiasm about requiring leukoreduction as another measure to reduce risk of transfusion and I agree, 50 percent or so reduction infectivity is not very impressive and I don't think it's justifiable. Certainly, disease base, that's not justified additional measure based on that, but I haven't heard anything about what -- if leukoreduction is required, what would be the cost involved? In

other words, what will be the costs of these additional steps that I agree is of questionable use.

I haven't heard anything about donors in this country that -- who had surgery in the U.K. and therefore could have been exposed in view of the results of the study on the lymphoreticular system being affected in presymptomatic patients. An individual could be exposed due to surgery by contaminated instruments to variant CJD.

So I think this additional information may be useful to make a final vote on these three issues.

DR. PRIOLA: Dr. Nelson.

DR. NELSON: Yes, this question is simple. It says should we continue the deferral criteria that are currently in place. That's question number one. I don't see how we could not do it, given the fact that there are now two probable causes and given the fact that what we're dealing with is two incubation periods, one from the exposure, the dietary exposure and the second one to that person becoming infective and then donating and the recipient then becoming,d enveloping symptomatic disease.

I don't think we know where this is going to go, but I can't see any public health rationale for not keeping the current criteria in place. However,

I do agree with Dr. Fitzpatrick, that at one point if the risk is minimal or low or doesn't materialize, at one point we need an exit strategy. But I don't think that's now, after this second case. It just doesn't make sense to me. So I'd vote yes on this one.

DR. PRIOLA: And most of Dr. Gambetti's point get more to the second question.

Dr. Allen?

DR. ALLEN: Thank you. Just a couple of brief points. I think we've heard a lot of very important, very useful information today. I think all of us would agree that we still have an awful lot more to learn, that the tests are coming along, but they still don't lt us answer all the questions or begin to answer all the questions that need to be done. We don't have an agent that we can easily work with and identify in all kinds of different specimens. So there's a lot more that needs to continue to be done.

Very specifically, with regard to the question of leukoreduction, if we want to use the hamster model, it clearly reduces by a percentage basis the risk of infectivity. It doesn't eliminate it. Dr. Bailar talked about the proportional reduction that would be necessary. So I don't think leukoreduction for elimination or reduction of TSE is

a justification.

Many blood collection centers, however, are doing leukoreduction for other reasons and that's perfectly fine, but I wouldn't even want to consider doing it for the basis of this alone.

DR. PRIOLA: Mr. Bias?

MR. BIAS: I'll try not to repeat anything anybody else has said. I would agree. We just don't have enough science here to change our current recommendations in terms of lessening them or coming up with an exit strategy.

I was reading the news and getting a lot of information and when the U.K., second case from the U.K. came out and I wanted to just speak briefly to something that I read and we got a lot of information during the open public hearing from the blood collectors about reducing some of the stringent deferral issues and I agree that this is probably not the time to look at that. But I was surprised when I got the PPTA information that they were actually touting in the last paragraph their reduction of logs from plasma products.

When you look at those tests and we're not able to draw any conclusions from the reductions of logs around this table, so my caution to all of us is

that once we open that door and we start reducing standards, the industry is going to take that ball and run with it and I'm just not prepared to face those consequences as a person who's dependent on the blood supply at this time.

DR. PRIOLA: Dr. DeArmond?

DR. DeARMOND: The reason I think that we should keep the deferrals as they are is the second case in Great Britain, the MV case. That opens up the possibility as Bob Will says that there is a second wave of patients that may come along.

Alternatively, that case is very mysterious and raises the other possibility that MV may be protective and actually has kept the disease from getting to the brain and has put it into places where it can be destroyed. But we don't know anything about that.

But it's a possibility of a second wave that means what we have is fine and it needs to be here until we see that, whether a second wave materializes.

DR. PRIOLA: Dr. Bracey.

DR. BRACEY: I must admit that prior to having the second case, I was leaning more towards trying to see if we could develop an exit strategy,

but I think that would be premature now. And in fact, what really bothers me the most is again what I mentioned before and that's making sure that the current checks and balances that we have are working.

I think it would be important for us to get some -- an update on the frequency of BPDs related to this because again, we have two cases. We know that it is transfusion transmitted, but what we do know also is that there are people that are escaping the filter and we should track that and make sure that that works before we pull away any restrictions we have.

DR. PRIOLA: Dr. Creekmore.

DR. CREEKMORE: I agree with Dr. Bracey and many of the others that have spoken here. I think it's too early to make a decision about lessening the restrictions, especially with the second case that has been described.

DR. PRIOLA: Should we go ahead and vote on that first question? It seems that there's pretty much a consensus.

So the question is "are the measures currently recommended by FDA to reduce the risk of transmitting CJD and vCJD by blood and blood products still justified?"

DR. FREAS: I'll call your name. Dr. Gambetti?

DR. GAMBETTI: Yes.

DR. FREAS: Dr. Nelson?

DR. NELSON: Yes.

DR. FREAS: Dr. Jenny?

DR. JENNY: Yes.

DR. FREAS: Dr. Sejvar?

DR. SEJVAR: Yes.

DR. FREAS: Dr. Hogan?

DR. HOGAN: Yes.

DR. FREAS: Mr. Bias?

MR. BIAS: Yes.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: Yes.

DR. FREAS: Dr. Allen?

DR. ALLEN: Yes.

DR. FREAS: Dr. Priola?

DR. PRIOLA: Yes.

DR. FREAS: Ms. Kranitz?

MS. KRANITZ: Yes.

DR. FREAS: Dr. Bailar?

DR. BAILAR: Yes.

DR. FREAS: Dr. Creekmore?

DR. CREEKMORE: Yes.

DR. FREAS: Dr. Bracey?

DR. BRACEY: Yes.

DR. FREAS: Dr. Johnson?

DR. JOHNSON: Yes.

DR. FREAS: And Dr. Petteway, can we have your opinion, not your vote?

DR. PETTEWAY: Yes.

DR. FREAS: Thank you. It's unanimous.

DR. PRIOLA: We can move on to the second question which is "do the recent scientific data on vCJD warrant consideration by FDA of any additional potentially risk-reducing measures for blood and blood products?" And this gets back to what Dr. Gambetti introduced a few minutes ago and one of the things he discussed was leukoreduction.

Now I remember reading somewhere in the briefing materials and you alluded to it as well that a lot of blood producers are already doing that.

And what's the prevalence of that? Is that now a very common practice?

DR. NELSON: I think the American Red Cross and Dr. Page can talk about this, but I think virtually all of the or most of the blood is leukoreduced and there's been a statement of the AABB and others to promote this, based on CJD risk.

DR. PRIOLA: Based on other infectious or transmissible --

DR. NELSON: Based on post-transfusion febrile reactions and other things.

DR. BRACEY: Not a scientific survey, but I would say that there probably are as many as 30 percent of facilities that aren't leukocyte reduced, using leukocyte reduced blood. In fact, largely for economic reasons, folks have begun to move away and some centers, for example, in North Carolina, the Red Cross began to back off of its policy of 100 percent -- offering that.

There are mixed data. It is rather expensive. I can tell you that for a medium sized or I should say a large size hospital, it adds about $1 million added cost to the total budget of $200 million.

DR. PRIOLA: Dr. Page?

DR. PAGE: Dr. Page, American Red Cross. The American Red Cross provides just less than half the red cells transfused in the United States. We originally did have a policy of 100 percent leukoreduction of all red cells, except for autologous. We backed off from that for reasons that were alluded to, but as it turns out now, customers

are ordering and we provide over 90 percent of our red cells as leukoreduced in any event. And the remaining, less than 10 percent include the autologous. So our customers have largely wanted to get universal leukoreduction. It is correct that some don't and I believe it's largely a matter of price.

I don't want to speak for ABC which is the other part, but I believe they've done a survey in that regard.

DR. PRIOLA: From ABC, then Dr. Johnson.

DR. BIANCO: Yes, I'm Celso Bianco. I'm from America's Blood Centers. Dr. Bracey is correct. The American Red Cross with about half of the supply -- here we are talking 7.5 million units or 7 million units in each half. Leukoreduces about 90 percent of the blood. Our members of ABC leukoreduce about 65 percent of the blood. And so if we try to do a calculation for the whole country, it's about 80 percent is leukoreduced. And it's interesting that in certain regions, the blood is totally leukoreduced. In other regions the hospitals and physicians will only order leukoreduced products for a certain population of patients like hematologic patients. They are the ones that benefit the most.

DR. JOHNSON: I think we really have

nothing to do with this. I don't think they should use leukopheresis. The BAC problem is a justification for it. If they're doing it for other reasons, that's fine.

I do not think we should recommend leukopheresis. I think 40 percent decrease is -- when you talk about it in terms of many log reductions, you'd really like to see trivial and we should not bother with that. If we're going change anything in terms of tightening them, they would either be, seem to me to be the other options other than leukopheresis, there may be others, but the only ones I see are decrease in the time over seas in other countries or decrease in the number of countries on the list.

My opinion would be that that probably is not the time right now to do that and therefore my answer to number two, would be no.

DR. PRIOLA: Dr. Rohwer, did you want to address the leukoreduction data? It's your data.

DR. ROHWER: I just wanted to make a couple of other points. We don't believe that leukoreduction by itself can significantly reduce the risk from blood-borne TSE infectivity. However, we're also strong believers in the idea that removal is a

very good option for significantly reducing the risk from TSEs in blood and leukoreduction would be an essential part of any removal strategy because it's required to get rid of this cell-associated component of the infectivity.

What's needed now is a strategy for getting rid of the plasma-associated component of the infectivity. We're working very hard with a company called PRDT to develop such a product, to develop such a device. We know that the Pall Corporation is also working very hard to develop a strategy that they would combine with leukoreduction to do the same thing and there may be other people out there also working on this possibility.

But there are several very attractive features to a reduction strategy, one being that as you go farther and farther back in the disease, before the clinical stage, it's going to get harder and harder, presumably harder and harder to detect infectivity with a diagnostic and addressing the disease in that way seems to me to be problematical at best, whereas a reduction strategy, if it worked, would work hopefully equally well on very low concentrations as well as higher concentrations, realizing that none of the concentrations will ever

get very high in blood itself.

So I guess what I'm -- the message I want to leave is that well leukoreduction by itself does not seem to be the answer. Don't throw out the idea that a reduction strategy might be a very good one.

DR. PRIOLA: Dr. Hogan?

DR. HOGAN: I agree. I think any time you can an 80 percent compliance with anything, as they're currently doing with leukoreduction, that's pretty good. It's already happening. Secondly, I think it's irrelevant if you're only reducing half the risk anyway, so I think that just should be tabled.

Secondly, the issue of changing the deferral from three months to one month, let's say for U.K.. I think that 3 percent calculation that Dr. Williams showed is too much. You're going to lose too many donors. So I think again, I think the current criteria, given the data that we have are adequate. We have two cases, one of which is very atypical, heterozygous and no neurologic disease, maybe his incubation period was 40 years. He was 82 if my calculations looking at the old paper are correct.

I think we need to leave it well enough alone.

DR. PRIOLA: Dr. Bailar?

DR. BAILAR: Perhaps I should add a little bit to what I said earlier about a 42 percent reduction and the continuation of a very substantial risk. The linear model does have some important uses. In particular, it can be a very good basis for proceeding if two conditions hold. One is that the infectivity is low, that the risk is not lumpy, that is that there's a little here, a little there. It's pretty uniformly spread, not one unit here with 5,000 units and then thousands of units with none.

So if the infectivity is low and reasonably uniform and if susceptibility is uniform, if there is no tiny, but immensely susceptible subgroup, the linear model can be right on target.

Having said that, I find the second question a good bit more troubling than the first one. The fundamental problem, as I see it is that we have a very limited kit of tools for identifying risk. We need to expand that kit of tools. I'm glad to hear that a lot of people are working on it, but right now we have a few screening questions and for VCJD we don't have much except geography and time. That's a pitifully small base on which to try to reduce risk, but we use it as we can, but we shouldn't kid ourselves that this is really going to do everything

we want and do it cheaply.

I'm still thinking about how to vote on this second issue, but I'm sure that whatever we say, FDA will continue to monitor this situation and we'll be pushing for improvements in the things I had mentioned, that we really need to do to estimate risk.

DR. PRIOLA: Dr. Bracey?

DR. BRACEY: I think that in light of the fact that we now know that this is most likely transfusion-transmissible that it really does warrant that the FDA would consider additional risk-reducing measures. However, I don't feel that increasing the number of donors deferred to let's say 6 percent is reasonable. We simply wouldn't be able to tolerate that. But there a number of interesting questions, the question of the previously transfused donor, the question of issues related to the differing criteria that we have for source plasma versus recovered plasma.

So in a nutshell, I think that we really do need to ask is there anything else that's within reason that we can do to reduce risk in light of the second case.

DR. PRIOLA: Dr. Schonberger?

DR. SCHONBERGER: As I listen to the

discussion, I wanted to raise the issue that people are talking about a 40 percent reduction in risk, but my understanding is that -- or a titer -- but my understanding is that that relates to whole blood and most of the transfusions in this country are not whole blood, but rather red blood cells and those red blood cells are often washed and plasma eliminated as much to a rather high degree.

So it's not clear to me that the 40 percent reduction is appropriate for most of what is being used in the United States.

DR. NELSON: A washed unit still contains one million blood cells.

DR. SCHONBERGER: But that's what --

DR. JOHNSON: When you talk about 40 percent reduction, you're talking about a 40 percent reduction of risk only if the unit contains one LD-50. If it contains 20, you're reducing it to 8, which is still 8 times more than it takes to kill you. So it's only if it happens to be right on the line that you get a 40 percent -- so we're not talking about a 40 percent decrease in risk. We're talking about a 40 percent decrease in infectivity which is an unknown decrease in risk that we know is less than 40.

DR. EPSTEIN: I think it needs to be

clarified that most red cells for transfusion are not washed, that that's done in selected instances, for example, frozen units that are thawed or certain units for selected patients, for example, with donor antibodies, that the typical packed red cell unit does contain plasma, about 20 to 30 mL, at least 10 mL. So even if you take 3,000 round number residual infectious units in a leukoreduced whole blood, and if there's really only 10 mL is what 20 percent of the unit, right. So you'd still have at least 600 infectious units in a pack of red cell.

DR. BIANCO: You still have a lot of units, but at 10 mL here, would be since the amount of plasma unit is about 220 to 250 mL, it would represent only five percent or less of the total content of plasma. So it may improve the calculation, that you are reducing by one log. But the significance of reducing by one log as we heard may not be relevant in this case.

DR. PRIOLA: Dr. Rohwer?

DR. ROHWER: There is one other important point to keep in mind and that is we titered the blood by the most efficient means of titration which is to put it directly into the brains of recipient animals and there is some current confusion about what the

efficiency of infection is by the intracerebral route versus the IV route, for example.

And it had been sort of dogma for a long time that in rodents it was about 10 fold less efficient by the IV route, but there's been some recent work by Corinne Lazmezas in France using monkeys and assaying blood in a same species transmission by the IV route in monkeys where based on incubation time it looks like there wasn't any difference between the IC and the IV route.

This is something that needs to be looked at much more exhaustively than we have done in the past. We've not actually done these experiments in our laboratory, but we tend to do them now.

DR. PRIOLA: Dr. Hogan.

DR. HOGAN: Was that, in that monkey study, they used brain-derived material, right? Not blood-derived infection?

DR. ROHWER: You're right. What did I say, did I say blood?

DR. PRIOLA: So do we want to vote on issue 2?

Dr. Gambetti.

DR. GAMBETTI: Steve, I think that this Committee should briefly, but consider the possibility

of deferring cases that receive blood transfusion in France in a similar way as the people who receive, donors who receive the transfusion in U.K. are deferred.

DR. PRIOLA: So this gets back at your original comment. Is there any data or tracking of the blood transfusion patients in France? Dr. Will, do you have some comment on that?

DR. WILL: My understanding is that of the seven cases in France, none of them have been blood donors. That is what I gather. The basis of that evidence, I'm not quite sure about because of course, whether they actually tracked to find out as we do whether they all had been to any blood donor centers in France, I don't know. But they're very confident that my understanding is that there were no blood donors in France.

It's also my understanding that in France already transfusion recipients are not acting as blood donors. I think that's correct.

DR. DeARMOND: Bob, were they recipients? Were those seven in France recipients? They weren't donors, but were they recipients?

DR. WILL: I don't know the answer to that question. From our experience that I've already

mentioned we have -- more or less age-matched the French cases, the same age distribution so the chance of receiving a blood transfusion are relatively low. In our series it's 5 out of 149, so France -- I don't know the answer, but I suspect it's not very likely.

DR. PRIOLA: Dr. DeArmond.

DR. DeARMOND: It seems to me without having any data of the patients in France acquired vCJD by blood transfusion rather by ingesting some beef product, I don't see why we would add more to the deferral. It isn't even at the level of a true theoretical risk at this stage. It would be nice to have a little more data on that.

I think the deferrals are doing enough in the United States to prevent, to at least keep the risk of having contaminated blood products to a minimum and the United States is not Great Britain. We don't have the mass quantities of people who were exposed who might be percolating with the disease and at least there's no evidence that we have that here yet.

So I would say that we don't have to add any additional piece of deferral.

DR. CREEKMORE: I'm jumping in on a totally different sort of issue, so is there any more

on that before I get us off on another tangent?

The way I read number two it says, "do the recent scientific data on vCJD warrant consideration" not necessarily warrant adoption, but "warrant consideration by FDA of any additional potentially risk-reducing measures." And I think for FDA to continue to consider other reasonable risk-reducing measures is a good thing and that as long as they are reasonable and they are considered within a cost benefit framework, similar to what was presented in the presentation by our Canadian colleague, so that we can continue to look at what are some other potential options and what are the costs and benefits and use that for the decision making process.

DR. PRIOLA: Dr. Johnson?

DR. JOHNSON: I was going to say exactly what you were going to say except that I already said I was going to vote no on 2. And then I read it again and I don't want to vote no that they shouldn't think any more at FDA. I mean that really is kind of -- that's a loaded -- the way that's written is loaded.

I would vote -- I don't think we've heard anything today that should be instituted, but FDA should consider anything that comes along.

(Laughter.)

They should keep an open mind at FDA.

DR. HOGAN: My sense is even if we voted no, they'd still consider it.

(Laughter.)

DR. PRIOLA: Dr. Allen?

DR. ALLEN: This is beating a dead horse. We can ask Jay for clarification, but I think the FDA will continue to monitor the data. They should. We need all of the new information as it becomes available. I haven't heard anything today that would make me want to seriously recommend that they consider anything additional and on that basis, I'm going to vote no, but with the understanding that the FDA doesn't sit back, as I know they won't, if we make such a vote.

DR. EPSTEIN: I can certainly confirm that we won't stop thinking.

(Laughter.)

I think our objective in asking you question 2 is to see if there was anything on the front burner, in other words, is there something obvious that we ought to be trying to develop now as an additional safeguard.

DR. PRIOLA: So with that in mind, do any of the Committee -- Dr. Jenny.

DR. JENNY: I think the one thing we need to think about is what do we need to know to make an educated decision down the line. Is there data that we want to get that will make a difference whether that decision is made or not in the future?

DR. PRIOLA: Dr. Allen?

DR. ALLEN: From my perspective, in terms of epidemiological data, do we add France, do we add any other -- do we change the deferral window, that sort of thing. I -- if there's any good information that becomes available, yes, we ought to consider it. I don't think it's likely however, that that's going to be the source of new and better information on which to base decisions.

I think we're going to see the next quantum leap which is going to be very important and it will come eventually in terms of the development of tests and using the state-of-the-art tests as they become available, the understanding of our database better and in being able to make more precise recommendations. But I think testing and technology is where the next big advances are going to come.

DR. PRIOLA: Dr. Sejvar?

DR. SEJVAR: I guess just a quick comment. I guess kind of looking at issue 2 from the other side

and this arises just because of how intriguing the second transfusion-related case in the U.K. Neurologically asymptomatic, homozygous, excuse me, heterozygous and just brings up this issue of an asymptomatic carrier state.

It kind of leads one to wonder well, are there people who are going to either be resistant or essentially not able to pass the infectivity. And obviously, at this point we have to go on the assumption that yes, this is going to be transmissible no matter what the state of the host, but maybe those are additional research questions that could be sort of looked at. I don't have any particular recommendation per se, but I mean it's intriguing.

DR. PRIOLA: Dr. Nelson?

DR. NELSON: I guess the data that I'm more concerned about is the appendix and tonsil and other data that suggests that there may be quite a few people who, whether they're infectious or not or whatever, but they may be, have been exposed and may or may not develop symptoms, but the numbers -- the terms of further research and so I would think that those -- that kind of study might be pretty important.

I already mentioned Dr. Will and it would be interesting, this is an anonymous study now, but it

would be interesting to try to link those positive appendices with data that might obtained post mortem from such patients. And it's now anonymous, but we might be able to link people by genetic markers, HLA or something else to find out that when such a person dies and has an autopsy, where is the prion? Is it there? Because it's possible we may be missing some manifestations, particularly we might be missing infectivity as opposed to frank CJD.

I think the surveillance is probably pretty good in the U.K. on variant CJD, but infectivity is what we're really concerned about here.

DR. PRIOLA: I suppose one other thing to consider about the met-val heterozygosity is that's 50 percent, I believe, from Dr. Will's side of the population and so when you have it in a met-val population, it may very well transmit more easily into the met-val population and that's because the PrPs are compatible. I don't know if that will turn out to be true, but it's possible.

I can't remember if it's true in transgenic mice. I think it varies from lab to lab, if I remember.

DR. DeARMOND: It's actually the opposite. The MMs are very susceptible because they have a

higher incidence of CJD beyond the percentage of the population and the MVs almost behave as if they're protective.

DR. PRIOLA: I think I'm just referring if you have the infectivity come from an MV and it goes into an MV, then you've got that match, that's all. So it's another thing to consider and another reason to be cautious for me.

Dr. Bailar?

DR. BAILAR: I think the Committee has read question 2 in different ways. Other people will surely do the same. Do we have the option to re-word the question?

(Laughter.)

DR. PRIOLA: We always have the option to reword the question. It depends upon whether or not the Committee considers the word "consideration" to imply that the FDA will continue to investigate this, even if we vote no and it seems the FDA has said that that will be the case.

DR. BAILAR: Yes, surely they will continue to consider. I think the question that they might have meant to ask is whether anything warrants action.

DR. PRIOLA: Dr. Epstein, could you

clarify?

DR. EPSTEIN: Yes, I think the distinction we were trying to make here is that if an intervention is proposed, we might need to assess it further before moving to action. So what we were really looking for is between questions 2 and 3, whether the Committee Members felt there was a specific action that we ought to further develop as possible or feasible for implementation.

I mean, for example, had it been the sense of the Committee that there really seems to be a value for leukocyte reduction, let's get on this, you would answer question 2 affirmatively.

So again, I mean you have the option to reword the question, but I hope I've adequately explained what we're looking for. This is something that really rises to the level of consideration at this time, and FDA would then take that advice and see if it's feasible to develop that recommendation.

DR. PRIOLA: Dr. Bailar?

DR. BAILAR: If we could take that as de facto revision of the question, I think I would vote no.

DR. PRIOLA: Does the Committee agree we can vote?

All right, so we'll vote on the second question, "do the recent scientific data on vCJD warrant consideration by FDA of any additional potentially risk-reducing measures for blood and blood products?"

DR. FREAS: For the record, there are currently 14 voting members around the table. I'll go around and poll from the opposite side of the table this time.

Dr. Johnson?

DR. JOHNSON: Vote no with the reservations expressed.

DR. FREAS: Dr. Bracey?

DR. BRACEY: I would vote yes.

DR. FREAS: Dr. Creekmore?

DR. CREEKMORE: No, with a revision of the question.

DR. FREAS: Dr. Bailar?

DR. BAILAR: No, with the revision.

DR. FREAS: Ms. Kranitz?

MS. KRANITZ: I vote the same, no, with the revision.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. Allen?

DR. ALLEN: No, with the caveats.

DR. FREAS: Dr. DeArmond?

DR. DeARMOND: No, except as long as they keep thinking.

(Laughter.)

DR. FREAS: Mr. Bias?

DR. BIAS: No, with the revision.

DR. FREAS: Dr. Hogan?

DR. HOGAN: No.

DR. FREAS: Dr. Sejvar?

DR. SEJVAR: No.

DR. FREAS: Dr. Jenny?

DR. JENNY: No, with the revision.

DR. FREAS: Dr. Nelson?

DR. NELSON: No and I hope my vote won't be used in some sort of a political debate in the future.

(Laughter.)

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No, with the revision.

DR. FREAS: Out of the 14 voting members, we have one yes vote and 14 qualified no votes.

Dr. Petteway, would you please give your opinion?

DR. PETTEWAY: No.

DR. FREAS: Thank you.

(Laughter.)

DR. PRIOLA: So I would just like to make sure that by the revision we mean that it's understood that the FDA is going to continue what they're already doing which is the risk analysis for geographical deferrals and time frame deferrals and what not. Is that -- that's what we mean by the revision. Okay.

Well, with that no vote, we basically -- we don't have to say anything about 3 because I think the FDA is pretty clear on what we mean by the vote on 2 and that impacts on question 3.

So are there any other -- before we adjourn, are there any other comments from -- Dr. Hogan?

DR. HOGAN: We wouldn't even be here if it hadn't been for the excellent activities of the CJD Surveillance Unit and I would like to personally thank Dr. Will for all of the work that he and his colleagues are doing and I would urge them to continue to watch these human experiments because I think that's where we're going to get most of our information and I think it will be interesting.

DR. PRIOLA: Thank you, Dr. Hogan. Dr. Epstein, do you have a comment?

DR. EPSTEIN: Yes. I was just curious. There was one yes vote to the question, as amended and I just wonder what specific safeguard that individual had in mind?

DR. BRACEY: Well, the specific safeguard I had in mind was the history of previous transfusions as beyond the U.K. Part of the concern was information, well, you know, the increase infects herd infection rate in Portugal. I'm just concerned about that issue.

MR. BIAS: I would agree with that. Sometimes when we come to these meetings, I'm like what's going on with the rest of the globe here, because we only get the information on Europe and the United States and Canada. So some information on that would be interesting to digest as well.

DR. PRIOLA: Are there any other comments from the Committee or the FDA? Anyone else like to contribute?

Okay, I thank everybody very much for coming. Have a safe trip back. I thank all the presenters and speakers for doing such a marvelous job and this meeting is adjourned.

(Whereupon, at 4:32 p.m., the meeting was concluded.)

**CERTIFICATE**

This is to certify that the foregoing transcript in the matter of: TSE Advisory Committee Meeting

Before: DHHS/FDA/CBER

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represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.