have a lower incidence or prevalence of variant CJD, very few cases across Europe compared to even France, and then also the amount of beef products that they received is much less. So, the relative risk there is much less.

All right, so the next component is the percentage - we had to figure out the percentage of donors that actually traveled to these countries for a duration or a period of time that they would have been exposed. So, this slide is actually incorrect, I didn't give an updated slide, but this is approximately 7.2 percent of U.S. residents had a history of travel to the U.K. and Europe during the 1980s and 1990s. Three percent of those individuals were military and dependents, hence, we are treating those separately in the equations that we are doing. They also tend to spend approximately two years, one year, they have more sort of defined periods of time that they were in the United Kingdom or in Europe.

Of blood donors that were questioned, 1.7 percent traveled to the U.K. during the time period 1980 to 1996 for a three-month period, and then .2 percent for a five-year period since 1980, and then .7 percent traveled to Europe since 1980 for a five-year period.

The duration of travel. So, we have information from U.S. surveys that were conducted in blood banks and blood organizations, and we have information on travel history and duration of travel, and Alan Williams has presented this, from the FDA, has presented this in previous meetings, so I'm not going to in depth into it, and he'll probably actually touch on it this afternoon as well in his talk.

But, travel history and duration of travel was taken from that information and incorporated, so we could get the number of days and years that people resided or traveled to these three areas of the world, U.K., France and Europe. That was included in the model.

What we assumed was that blood donor travel history is the same for plasma donors. Again, plasma donors are known to have less of a probability of having traveled, or less of a history of travel to U.K. and Europe than blood donors, but right now we have the best information for blood, so we are assuming they are the same.

Just sort of moving on quickly, talking about plasma donation, so a plasma donor walks in, we want to know something about their age of donation, because that's related to variant CJD rates, so most

of the individuals that donate are under the age of 35, I believe that's about 70 percent of donors, and that's really the group that's largely affected or most affected by variant CJD. So, the median age, remember, for variant CJD is 28 years, so there's a lot of overlap and a lot of potential for risk in the U.S. from these groups, because they so overlap in their demographics.

The probability of variant CJD donation per plasma pool, we've calculated that. The quantity of ID50s, again, what we are doing here is, the quantity of ID50s we are getting in from the previous model, our estimates of quantities of ID50s from blood and animal studies, and then the probability of donor deferrals. So, this all goes into the plasma donation.

The probability of donor deferrals is quite important, because we think that that's an effective risk reduction strategy and probably knocks out about 90 percent of the risk or more. So, that's an important component of all this.

So, just to give you an idea. This is some of the representative data we are using. This model uses estimated age-specific source plasma donation rates. So, we characterize all donors by

these characteristics, and, for instance, this is about 70 percent of the donors fall under age 34. People over 35 represent about 20 to 30 percent.

Some of the other data we use for the model is the age-specific variant CJD rates. Again, we are plugging this all in to see the overlap between these two age demographics of donation and variant CJD rate in these populations.

The probability that a variant CJD donation will be in a plasma pool or the probability of variant CJD per plasma pool, what we are doing here is, we are using a mathematical equation, a binomial distribution, to estimate the number of variant CJD donations per pool. Basically, the assumption is, is that the risk is very low, the variant CJD prevalence in the United States is very low, so the chances of getting one or more donations in a pool is very small. The chance of even getting one donation in a pool is small, but it is possible.

So, this equation, basically, gives us the probabilities. We can plug it in for zero donations, which, you know, would probably be something like 99 percent or more, but you'll have a few pools that will have donations, and then we can run the probabilities, plug in one, run the probability, two, what's the

chance of having two donations, three donations, very small probabilities once you get past one, of having more than one donation per plasma pool, unlike the situation with Factor XI this morning.

All right. The quantity of agent, I'm just going to say this is data from this morning, so I'll refer you to that from the earlier presentation., all assumptions that you've seen before.

Again, the probability of donor deferral, we assumed that the universal donor questionnaire, with the questions on travel history, are about 90 to 95 percent effective in eliminating potential donors that may have been exposed to BSE through travel history to the U.K., France or Europe.

All right, so processing, I'm not going to say much about this, because this is very similar to Factor XI. The effects of processing do reduce - potentially reduce the amount of variant CJD infectivity. I think it's important to emphasize the processes, like Dot had just mentioned, processes are going to vary for each different product. You use different sort of methods of purification. So, specific reduction is going to be based on processing steps, and I haven't presented a complete picture here.

What I'm going to do is present some of the information for Factor VIII. So, high purity product, for instance, is an immunopurified product, and then intermediate uses some other steps, like alcohol precipitation, chromotography, et cetera.

And, the levels of reduction we're assuming for Factor VIII at this moment in time are given here. So, a minimum of three, most likely of five, a maximum of six logs of reduction for Factor VIII, and then a much lower profile two, three and four, for intermediate purity Factor VIII.

We get on to utilization. Again, we're interested in probability and quantity of exposure that influence - probability and quantity that a person will be exposed to the variant CJD agent is really influenced by the amount of product that they are using. So, if it's a one time or sort of an incidental use for surgery, like Factor XI, there's less of a risk, but we've got a number of patients that use these products, Factor VIII for instance, constantly. It's a chronic use type of situation, and there are also degrees of severity of disease, so very severe disease for, I believe, about 60 percent of the population, and the remaining population is less severe disease, and these patients that are taking the

most product are the severe patients and would be at higher risk if there is a risk for variant CJD exposure.

I thought I would just present this, this goes back to Doctor Salman's question about variability and uncertainty. This is actually a good example of variability, so we are looking at utilization of products. This comes from a paper by Jeanne Linden's group in New York, where the mean utilization of Factor VIII was predicted at 200 - and you can say about 240,000 units, but there are percentiles around that utilization as well that we can do. So, that represents - we know that information, so this is true variability.

So, episodic, just to note, if you are treated on an episodic basis about two and a half times less amount of product you are using and being exposed to. Again, what we are doing is, we are not only doing Factor VIII, but Factor IX, immunoglobulins and albumin in this larger risk assessment. So, the concepts for utilization for these products is very similar. We are interested in probability and quantity of exposure, and that's influenced by utilization, processing, and a number of different specific, product-specific steps that go into the

manufacture and use of these products.

Again, I think I've just covered most of those points in what I said.

Many of the concepts in this model are very similar. You know, probability of variant CJD, the probability of contaminated pool, effectiveness of screening questionnaire, all of those are sort of the common components of these models, and then what's going to vary are the plasma pool size, the reductions that we see, product package size, amounts dispensed, and then utilization by patients. Those things are going to vary, but these are going to pretty much stay the same.

So, to sort of move on. Again, more data are needed, and we've talked about these data needs, and I think I'll leave that for the Committee to discuss, and then I just again wanted to thank all these people. I have a limited list of people. Hong Yang, though, has been doing most of the modeling, and so she's done an extreme amount of work just in sort of, you know, developing this model and getting the Factor VIII and several other models up to snuff.

And then, we have a lot of people providing technical assistance, and a lot of people that I haven't mentioned. Again, I have to say that

I'm really pleased by the compliments that we've received, but, you know, it is Steve Anderson sort of the face of this, but underneath it all there is this whole effort by a large number of people that really need recognition as well.

So, I thank you for your time.

CHAIRPERSON PRIOLA: Okay, thank you very much, Doctor Anderson and Doctor Scott.

We are going to have a discussion and vote period after lunch, but I want to give you an opportunity to ask any pressing questions right after these talks.

So, Doctor Salman, do you have a question?

DOCTOR SALMAN: Thank you, Doctor Anderson, it was a very good presentation, but just a couple points for clarification.

In your model D, you are saying the output will be annual predictions?

DOCTOR ANDERSON: Right, based on utilization of the product, but it could be different because things like albumin are used more for a surgical procedure.

DOCTOR SALMAN: So, I assume, just listening to the methodology, you are taking the entire cumulative data, and then you try to divide

them by the number of years? How you will get annual prediction, that's what I don't know how you will get this.

DOCTOR ANDERSON: I'm sorry, what?

DOCTOR SALMAN: How you will get the annual predictions, when you are dealing with a cumulative data of several years, unless if you assume like the exposure are equal among all these years, is that right?

DOCTOR ANDERSON: Right now, the model is assuming - you mean for the U.K. prevalence, for instance?

DOCTOR SALMAN: U.K. prevalence or any of this.

DOCTOR ANDERSON: >From the period from 1980 to 1996.

DOCTOR SALMAN: Yes.

DOCTOR ANDERSON: We haven't done, right now we are assuming equal risk throughout those entire years, from 1980 - for each year. Right now, it's equal. I think what we need to do in the model that's taking a lot of time is, we'll actually link it to the BSE prevalence. So, it will be different, and we'll link it to the BSE prevalence and epidemic, and then, you know, it will be a more realistic representation

of the risk.

DOCTOR SALMAN: And, that's taking me to the second question about the BSE, you are taking relative risk, which I think is a good indicator for France versus U.K., and versus Europe, but these are whatever is the output from the surveillance data. There are other countries, specifically, in Europe, in which they have much, much higher cases, but they have poor surveillance, and you are actually penalizing countries in which they showed result, where the other countries they don't show results, such as East Europe. I can tell you, if I'm traveling in East Europe I will be at much higher risk there to be exposed to the BSE agent as compared to France or Switzerland.

DOCTOR ANDERSON: Right. I mean, I would agree with you. Right now we haven't gotten to the refinements in the model. I mean, right now we are making large blanket assumptions, but, eventually we'll refine those estimates.

I think a good source to potentially do that could be the geographic-based risk assessments, but, you know, the information on those countries that aren't doing surveillance are really poor, but you can also consider other factors in risk, as far as do they

have food chain controls in place, do they have surveillance, et cetera, and then link it to what's been determined by the GBR, the geographic-based risk assessment.

DOCTOR SALMAN: I really believe, like if you take the GBR classification that will be much better, and associate that with your calculation of relative risk.

DOCTOR ANDERSON: I just want to say, I mean, I like getting these ideas from people, because it tells us what direction we should really be going, and what you are saying is, we need to refine these estimates as much as possible. It does take a great deal of work to do that, but we are putting that effort in.

So, it just takes time, you know, we've got bundles of data out there to sort of go through and integrate in.

CHAIRPERSON PRIOLA: Are there any other questions from Committee Members before we break for lunch?

Okay, so let's break for lunch until 2:00, and come back with questions and discussion.

(Whereupon, the above-entitled matter was recessed at 1:04 p.m., to reconvene at 2:00 p.m., this

same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2:19 p.m.

EXECUTIVE SECRETARY FREAS: Okay, Doctor Priola, with your permission we are going to resume and starting with the open public hearing.

And, I would like to ask, I have not received any requests to speak in the second open public hearing, is there anyone in the audience who wishes to address the Committee at this time?

Yes, Doctor Baron.

DOCTOR BARON: Thank you.

My name is Henry Baron. I am an employee of ZLB Behring, a major producer of plasma protein therapeutic agents, and I'm also the Chairman of the TSE Task Force of the PPTA, the Plasma Protein Therapeutics Association, and I just wanted to make a comment about the risk assessments and the exposure assessments that we've seen today.

I think that there was unanimity, as far the fact that the models being used to generate an outcome in these assessments appear to be valid. I'm no expert about that, but it certainly - they certainly look like good models to me.

Where the problems seemed to occur were in

the data gaps that led to some of the assumptions, and if there were two assumptions that had a huge impact on the final outcome of the assessments those were the ones involving the estimation of the prevalence of vCJD in a given donor population, and the estimation of the amount of infectivity in the blood of a vCJD patient. And, these are the two areas with the highest degree of uncertainty.

Now also, clearance factors were indicated as a critical variable as well by Doctor Scott and also by Doctor Anderson, and I think that there's less variability there, even in view of some of the caveats demonstrated by Doctor Scott, because of the fact that even though people are doing these studies in very different ways the data seems to converging in the same direction.

But, I would like to bring us back for a second, if the Committee would consider this, to a question that Doctor Gambetti asked when looking for ways to fairly rapidly address one of the main data gaps, and that was the one that involves the amount of infectivity potentially present in the bloods of vCJD cases. And, he asked the question to Steve DeArmond, who seemed to give an unqualified no, there doesn't seem to be anything that we can really do in a short

amount of time.

And, I would just like to suggest that there could potentially be something that could be done in a short amount of time if the FDA could make it an aggressive part of its agenda to try to obtain samples of blood and/or plasma from known vCJD patients in the U.K., these samples could be analyzed in a relatively fast amount of time by one of the laboratories currently implementing and employing the CDI immunoassay, which has an extremely high degree of sensitivity as far as human prions are concerned.

So, I think that this is not an approved test, as you had asked earlier, Doctor Priola, it's not an approved test, but it is, nonetheless, the endogenous infectivity experiments which have been used to be the basis for the current estimations, or the current assumptions are not approved tests either. It's a research tool, but it's a highly-effective and highly-sensitive research tool, that I think could give us some reasonably realistic and relevant answers about the potential or the amounts of potential infectivity in blood.

And, that's what I wanted to say. Thank you.

DOCTOR SCOTT: I would just like to comment

on that. I think it would be useful for everybody to understand what these sensitivity and specificity of those tests are for blood of infected animals.

DOCTOR BARON: As far as blood of infected animals is concerned, there has been no study done with the CDI, as far as I know. Now, Steve DeArmond might have some further comments to make upon that.

The sensitivity of those tests, as far as brain material is concerned, is that the CDI detects less than one ID50 per ml of brain homogenate, so you would have an answer at least as far as the ability to detect less than so much infectivity, as demonstrated in tests with brain homogenate.

As far as the animals are concerned, the problem is also what antibodies you are using with the test. The test that we've employed for the human prions uses antibodies that capture antibody, that only reacts with human PRP.

Steve, do you have any further comments that you would make?

DOCTOR DeARMOND: Not specific. All I can say is, there are multiple new ways of enhancing the sensitivity of the detection tests that our lab have, but Aguzzi's lab and other labs are using, and the most remarkable part about it is that they show

positivity even when the pathology is negative, that is, there's no vacuolation and when immunohistochemistry is negative.

And, what I was trying to say this morning is that today, because of these newer developments, and as I say, it's not just our group, it's multiple groups have done this, we are in a new era of detecting abnormal prion protein.

DOCTOR BARON: If I could just add that while we haven't tested human blood, because we haven't had access to those samples, what we have done is, we've taken variant CJD brain tissue and formulated it into different preparations, including microsomes, caveolae-like domains, and purified PRP scrapie, and spiked that at the human plasma, and I can say that human plasma does not interfere with the ability of the CDI to detect those preparations of human prions.

EXECUTIVE SECRETARY FREAS: Thank you very much, Doctor Baron.

Is there anyone else in the audience who would like to address the Committee during this open public hearing?

Seeing noone else, Doctor Priola, In turn the meeting over to you.

CHAIRPERSON PRIOLA: Okay, so this is the discussion part of Topic 2, where the FDA wants the Committee to consider and comment on the U.S. risk model in regards to assessing risk for TSE contamination and exposure via U.S. plasma derivatives.

So, the comments are just as in the - just as for the first topic, that is, do we have any comments on the model per se, and is there any additional information that is needed to improve the risk estimates for the various plasma derivatives?

Doctor Bracey?

DOCTOR BRACEY: In have one question, and that is, unlike the U.K., there seems to be sort of a greater variance in terms of variability, in terms of how plasma products are made in the U.S., and, perhaps, Doctor Petteway could comment on that. Are there, I understand that there has been a move, perhaps, by some to increase the number of apheresis donations, and, therefore, perhaps, the volume in a given lot of product might be greater.

What is the trend, and what is the uniformity, and, you know, is the U.S. product that different?

DOCTOR PETTEWAY: Well, in general, cone

fractionation uses ethanol, pH, temperature to precipitate proteins along a train that's then purified.

There's a significant difference in the way that those steps are coupled together and not coupled together. One company may take three steps and make three fractions, fraction I, II and III, all in one process step, and that has one set of consequences for partitioning. Another company may separate the fraction I part of it from the fraction II plus III.

So, in general, for the data that we have, where different companies have used different processing to look at removal, as Hank Baron said, they all converge and they all coincide, and as you move down the trunk you remove prion.

That said, I think as Dorothy Scott said, they also differ significantly beyond the trunk. So, the trunk is one aspect, but, perhaps, some of the most important removal steps are in the purification processes, and they are very different from company to company. So, they really have to be looked at independently.

And, if you are going to look at them as a composite, then you have to look at, say, for all

immunoglobulin products, then you have to look at a composite of data from different companies.

And, actually, I think that industry has presented that sort of data here before.

CHAIRPERSON PRIOLA: Doctor Hogan?

DOCTOR HOGAN: Yes, I'm going to come back to this question again, and I really don't know the answer to this, I'm not an epidemiologist or a statistician, but if you are looking at prevalence rates, that's a population-based figure, and I still think you need to think about, or add to your model, or at least consider, what percentage of a certain prevalence might donate. That is, if only 7 percent of the 28-year olds are going to donate, why would you expect 100 percent of those patients to have CJD, vCJD, would donate?

So, I don't know, is that a useful tool to put into your model, or am I just confabulating?

CHAIRPERSON PRIOLA: Doctor Anderson, do you want to comment on that?

DOCTOR ANDERSON: Can you repeat that?

CHAIRPERSON PRIOLA: Could you go to the microphone?

DOCTOR ANDERSON: Sorry.

DOCTOR HOGAN: Essentially, what I'm asking

is, when we look at corneal donor data -

DOCTOR ANDERSON: Sure.

DOCTOR HOGAN: - and there's two ways of looking at it, that everybody that has CJD donates, or the percentage of people in a specific population would donate, that is, the corneal donor population is less than 1 percent of the total population.

DOCTOR ANDERSON: Right.

DOCTOR HOGAN: So, you don't look at all corneal donors, you look at 1 percent of the population.

DOCTOR ANDERSON: So, the question is, is there a way for us to narrow down the population that we are looking at that's at risk for variant CJD in donations?

DOCTOR HOGAN: That is, you say there's a prevalence rate of vCJD, what percentage of that population, given the ages or whatever, might be expected to donate? You can assume 100 percent for worst case scenario, but what's the real world?

DOCTOR ANDERSON: Right. We are trying to adjust for that as much as possible by including age specificity for variant CJD rates and then donation rates. But, I can't, beyond that, really sort of narrow it any further. I mean, we are open to

suggestions in doing that.

CHAIRPERSON PRIOLA: Doctor DiMichele?

DOCTOR DiMICHELE: In think I might know the answer to this question, but I feel like I need to ask it anyway.

There's also an issue that we are going to be discussing later on, and that's the whole issue of Euroblood and the four million units that sort of have come into the United States, primarily, in the New York area.

And so, I was just wondering if transfusion acquired variant CJD needs to be included in the model.

CHAIRPERSON PRIOLA: Doctor Anderson?

DOCTOR ANDERSON: We can do that, and that's probably something that we can consider in the future. We are not considering - I mean, I haven't incorporated that concept yet in the model, but certainly something that we can do.

CHAIRPERSON PRIOLA: Doctor Belay?

DOCTOR BELAY: Related to that, I was a little bit worried about the 90-95 percent effectiveness of the donor deferral policy. That seems to be the assumption in the model.

My recollection was the 90-95 percent was

removal of the person time exposure in the U.K. or other European countries, rather than the risk of exposure.

So, the actual risk of exposure that's reduced by the donor deferral policy could actually be smaller.

DOCTOR WILLIAMS: You're correct. They are really two different concepts. The deferral for geographic risk by our calculations, given the overall potential geographic exposure, removed 91 percent of that risk.

I think what Steve was referring to in the model was, actually, something like the predictive value of the question itself, to remove those folks who, for instance, for the U.K. had a three month or greater geographic exposure.

I believe the model does not cover that residual 9 percent risk for those who had a shorter geographic exposure.

EXECUTIVE SECRETARY FREAS: Those comments were made by Doctor Alan Williams.

CHAIRPERSON PRIOLA: Any other comments from the Committee on this issue?

Is there a consensus of the Committee that this model is - the Committee is as satisfied, in

general, with this model as the one presented earlier this morning for Factor VIII, since they are relatively similar with these differences, donor addition and what not? I see nodding. Okay.

One more chance, any other comments?

Doctor Belay?

DOCTOR BELAY: Yes, Doctor Steve Anderson maybe already is thinking about this issue, but I didn't see it on the slides so I just wanted to mention it, and that is, I think the risk assessment should be stratified by the time that the donor deferral policy actually came into effect. In other words, the risk before 1999 and after 1999 is dramatically different, and the risk assessment should accordingly be stratified during at least the two time periods, although there are some nuances and differences in terms of the time period that the different donor deferral policies were instituted.

DOCTOR ANDERSON: Right.

I can tell you right now that we are focusing on one year, which is the current year or one of 2003, 2004, and trying to get the model set for that period, and then the idea would be to sort of move back and look at, you know, previous time periods, like before these mitigations were put in

place and the donor deferral policies, et cetera, and look at the risk for these products at those times at well.

So, right now we are just sort of starting where we have the most information and developing the model, then we'll sort of probably do a retrospective look at previous years as well.

DOCTOR BELAY: Right.

Obviously, the bulk of the risk would be pre-1999.

DOCTOR ANDERSON: Sure.

CHAIRPERSON PRIOLA: Doctor Schonberger?

DOCTOR SCHONBERGER: One other refinement, perhaps, is the issue of when they actually were visiting the U.K., and you talked about refining it per the epidemic of BSE, or having it proportional to the epidemic of BSE, but Doctor Belay has also mentioned preventative measures that could influence exposure of humans. I think the U.K. instituted their preventive measures for humans, at least, was around 1999, figure a couple years to make it effective, so that, in fact, even though the peak may have been '92-'93, it may well be that the peak human exposure, given the preventative measures, may be a year or two earlier than that.

So, you might want to take that all into consideration.

DOCTOR ANDERSON: I think we'd really like to do that, but we don't have travel - that type of travel history. We are getting this from survey data, so, you know, that type of survey information would have to be collected, and that's a pretty large undertaking.

DOCTOR SCHONBERGER: Yeah, I can imagine.

DOCTOR ANDERSON: So, we don't have a year of attribution for the travel, which is unfortunate, and that would certainly help in doing the types of things that you are talking about.

DOCTOR SCHONBERGER: Yeah, that came up in part because of this recent Japanese case that was only there for a month, and it happened to be 1989, which of all the years that might be the year, because that was the first time that the U.K. was starting t put in the preventative measures to protect human exposures.

DOCTOR ANDERSON: Right, and prior to, I think, you know, yesterday or the day before, we weren't really thinking about under three months as a risk.

DOCTOR SCHONBERGER: Yeah, exactly.

DOCTOR ANDERSON: I think we'll have to reconsider that as well.

CHAIRPERSON PRIOLA: Doctor Belay?

DOCTOR BELAY: Last point. I think this current risk assessment focuses on blood derivatives, right?

DOCTOR ANDERSON: On blood?

DOCTOR BELAY: Blood derivatives, not blood components.

DOCTOR ANDERSON: Correct.

DOCTOR BELAY: Yeah, but we know blood components, particularly, before 1999, could potentially be highly risky, because -

DOCTOR ANDERSON: Right.

DOCTOR BELAY: - there was no donor deferral policy.

DOCTOR ANDERSON: Right.

DOCTOR BELAY: So, in fact, in most of the patients who potentially would have been exposed as a result of blood transfusions would probably be exposed to blood components collected from people who have visited to the United Kingdom before 1999.

How are you addressing this issue?

DOCTOR ANDERSON: We aren't addressing that at this point in time. I mean, that's something we

can certainly do in the future. Yeah, I can't really add much more to that. So, it's definitely something that we can consider in the future, but at this moment in time we are not doing a risk assessment on that topic.

DOCTOR BELAY: That's, obviously, a real risk than a theoretical risk for blood derivatives, that's basically what I'm trying to point out.

CHAIRPERSON PRIOLA: Doctor Allen?

DOCTOR ALLEN: This gets very difficult, and I think what I hear you saying with your cautious statements is, we really need to look at how reliably we can collect the data, how much effort has to go into collecting and analyzing that, and what are we really going to use it for as we move further back.

And, I think those are very important considerations, you know, from an epidemiological perspective what you've heard expressed is right on target, but I think unless you've got a good way to reliably collect the data it makes it very difficult to -

DOCTOR ANDERSON: Yeah, you are correct, because then we went into issues of, you know, recall-wise as you go further back. I mean, who can recall, you know, where they traveled, you know, a year ago,

two years ago, three years ago, and the further and further you go back what you ate, the types of behavior, the activities, things that you did, that all becomes much more difficult, you know, the further back we go.

And so, that's some of the challenges that we are going to be facing if we sort of go in that direction. So, I think it's important to do, because, you know, we have had these deferrals and other policies that we've put in place relatively recently, in the last three or four years, but again, just collecting the data and the information, and getting our hands on it, is really difficult.

DOCTOR ALLEN: And, what you've just expressed is the real conundrum that faces all of us sitting around the table, as well as the Blood Products Advisory Committee, the FDA in general, in terms of how do you set policy that is reasonable, because, you know, I'm very concerned that we not do anything that is going to be disruptive to the supply of blood. On the other hand, we want to make it as safe and good as possible.

And, we need to be very clear in terms of every step that we take to enhance the safety of the blood supply, that it really is effective, so that I

think this kind of model, the studies that will emanate from it, are extremely important, but we always have to be trading off.

DOCTOR ANDERSON: Right.

Well, we are well aware, I mean, of the issue of balancing this safety versus supply, and so, you know, we can incorporate supply issues into the future models as well, because, you know, we have developed some minimal supply models, and, you know, do more of a risk-risk tradeoff type of model, as we're considering other deferral policies, et cetera, or other policies that might affect supply.

So, that's something that we can do in the future.

CHAIRPERSON PRIOLA: Doctor Telling?

DOCTOR TELLING: Could we review what we know about the etiology of this Japanese case? I think it would be useful for the Committee to visit this, it seems to me germane to this discussion.

CHAIRPERSON PRIOLA: Comments on the Japanese case?

CHAIRPERSON PRIOLA: Comments on the Japanese case?

DOCTOR SCHONBERGER: In just wrote an e-mail on it a couple days ago, I'll try to remember

what I actually said, but I think the patient was in his 40s, that the onset was like in 2001, December I think, and the patient died three years later in December of 2004, 36 month duration. What we've learned is that there was a visit to - oh, just got my memo here -

DOCTOR ALLEN: Instant messaging.

DOCTOR SCHONBERGER: What I wrote here was that the CJD Surveillance Committee in Japan confirmed the case as vCJD as of February 4, 2005. The month of onset was December, 2001, and the month of death was December, 2004, so that's good. I am aware of only four vCJD cases, I wrote, with a longer duration of illness, so it's not the longest illness that ever occurred here. The vCJD case patient had been classified officially earlier by the Surveillance Committee as a probable sporadic CJD case, because of the report of the patient's developing an EEG finding more characteristic of sporadic CJD. So, this report indicated that late in a very long vCJD illness an EEG, more similar to that of the classic CJD, does not rule out vCJD, a fact that may not have been previously appreciated.

The patient is classified as definite, based on pathological Western Blot and

immunocytochemistry findings. There's been genetic analyses performed, and they revealed no PRNP mutation. It also revealed the presence of the codon 129 met/met homozygosity characteristic of all food-borne vCJD cases to date. A presumed exposure of the case patient to the U.K. in 1989, which was a one-month exposure, they did not say - have a history of what he ate or anything, but it suggested an incubation period of, roughly 12 years.

This probably, if it's true that that was the source, then I was saying that it suggests that one does not need cumulative exposures lasting for a year or more as some people have postulated was responsible for some of the cases.

And, more information from Japan should be forthcoming, and the source of this information is Doctor Yoshikazu Nakamura from Jichi Medical School, who is a member, as I understand it, of the CJD Surveillance Committee in Japan, and he helped us write a couple articles on dura mater, the dura mater epidemic that they are having, so we had just e-mailed him and asked whether he knew about this case, and that's what he answered.

CHAIRPERSON PRIOLA: Doctor Bird, did you have a comment that you wanted to make about something

that came up earlier?

DOCTOR BIRD: Yes, I did, just to remind the surveillance data from the United Kingdom relate to tissues that were removed at operation 1995 to '99. So, although the paper was published in 2004, it was a retrospective study, relevant to the period 1995 to '99, which is important.

CHAIRPERSON PRIOLA: Thank you.

Are there any other comments from the Committee for FDA? So, is FDA - oops, sorry, Glenn?

DOCTOR TELLING: You mentioned the John Collinge had done some studies on tonsil biopsies, what time periods did those tissues cover?

DOCTOR BIRD: I'm not absolutely sure, because as far as I'm aware those results haven't been published, but I think they are fairly similar towards the end of, you know, 1999-2000, so it's about the same sort of time period. But, it was a prospective collection of tissues for the prion unit.

CHAIRPERSON PRIOLA: Is FDA satisfied with the discussion on Topic 2? Okay.

I know we have a break scheduled here, but we just got back from lunch, so with the Committee's permission we'll go ahead to the speakers and take a break after that.

So, this will start a new topic, Topic 3, which has to do with the risk reduction aspect of all these models. That's the potential deferral of blood and plasma donors as a consequent of a history of transfusion in Europe, and the first speaker is Doctor Alan Williams.

DOCTOR WILLIAMS: Thank you. It's my pleasure to chair this third session.

This session can really be viewed as a continuation of the last TSE Advisory Committee meeting held October 14th, where the Committee heard an extensive set of presentations regarding to development of FDA policy related to interventions related to potential BSE vCJD exposure. And, although the Committee voted that the measures currently were adequate and did not recommend any additional changes, there were some threads of discussion in the course of the meeting that we wanted to pick up on and continue in a little more focused fashion in this session.

Specifically, some more discussion about history of transfusion in countries other than the U.K., specifically, France and other BSE countries of Europe.

Fortunately, I don't really need the slides for this intro, but the goal of this session is

that FDA seeks the advice of the Committee whether the recommended donor deferral for history of transfusion in the U.K., which is currently 1980 to present, should now be expanded to include history of transfusion in France and other BSE countries of Europe.

We have several data presentations in this session. The first speaker was scheduled to be Doctor Jean-Philippe Brandel, who is a Neurologist with the Epidemiosurveillance Network, however, he, unfortunately, was not able to travel, and his talk will be shared by two FDA speakers. The first will be a presentation on vCJD in France by Doctor Pedro Piccardo, who is with FDA, and the second will be risk of vCJD transmission by plasma-derived medicinal products, risk assessment in France, and this will be addressed by Doctor Steve Anderson.

The next talk will be deferral - I'm sorry, estimates of blood-borne vCJD risk in the U.K. and other European populations. This will be by Doctor Sheila Bird, with the Medical Research Council, Biostatistics Unit, Institute of Public Health, at Cambridge University, and then I will round out the speakers by addressing some of the risks and benefits of deferring donors transfused in France and other BSE

countries of Europe, potential impact on blood and plasma supplies.

Because I do want you to see the questions, I'm going to just take a second and flip to those slides. The first question for the Committee is, based on the available scientific information does the Committee recommend deferral of blood donors transfused since 1980 (A) in France, or (B) in other BSE countries of Europe?

Then, as a separate question considering the potential for infectious agent clearance, as part of the fractionation process, a separate question, based on the available scientific information does the Committee recommend deferral of source plasma donors transfused since 1980 (A) in France, or (B) in other BSE countries of Europe?

Thank you very much.

CHAIRPERSON PRIOLA: Okay, thank you, Doctor Williams.

I think we'll move on to the first part, so Doctor Piccardo will be giving part one, and the second part will be given by Steve Anderson, about variant CJD epidemiology in France.

DOCTOR PICCARDO: Okay.

So, as was said, unfortunately, Doctor

Brandel cannot be here, so I have to present for him. Unfortunately, for me, I did not have the chance to talk with Doctor Brandel about these slides, so I will make the best I can, try to be objective on this presentation.

The whole issue is about an overview of vCJD, the situation of vCJD in France. Okay.

So, there are nine patients with vCJD in France, eight died, five were diagnosed with definite vCJD and three with probable vCJD, and one of the cases is probably vCJD and is still alive. The age of onset is - the mean is 33, and between 17 and 52, and the mean duration of disease in months was 20 years.

What you see here is the distribution of cases according to year, and according to onset, and this is between 1994 and 2004, and according to death between 1996 and 2004. I think that the only thing we can conclude from this slide is that probably because of the small amount of cases is that there is no pattern or no trend.

Okay. So, the diagnosis of vCJD patients in France, the five definite cases had typical neuropathological data, just to remind you that to make the diagnosis of definite you need the neuropathology, and florid plaques, and the Western

Blot analysis showed a type 2B according to a specification of Parchi and Gambetti. As you know, different - I mean, there are basically two groups that have a slightly different version of how to classify PrP, and one is John Collinge's group, and the other is Parchi and Gambetti, so this was classified as 2B, type 2B, according to the Parchi and Gambetti specification, and there are four probable cases, and to make it probable cases you need the clinical consistent with a vCJD case, plus the MRI that showed the typical posterior thalamic sign, and positive tonsillar biopsy shown by positivity for PrP by immunohistochemistry or Western Blot analysis.

Genetic analysis was done in all these cases, and in nine out of nine cases were met/met homozygous for the 129 polymorphic site on PrP, and there were no mutations detected.

Actually, this slide was not provided by Doctor Brandel, but we decided to include just a few slides to exemplify what we mean, and this is the MRI of a patient with vCJD, sorry, with sporadic CJD, that show high signal on the basal ganglia, and this is the classical or typical MRI for a patient with vCJD, that shows this high signal, pulvinar signal, or in the posterior thalamus.

And, what you see here is, basically, a case of sporadic CJD with a typical vacuolation, and usually patients with sporadic CJD show PrPres, or PK-resistant PrP that could be of approximately 21 or approximately 19 kV of the non-glycosylated isoform. Patients with vCJD that show in the pathology this typical florid plaque, usually show a pattern that is slightly different that is notorious for the presence - for the over-representation of the de-glycosylated PrP isoform as shown here.

Actually, this slide was provided by Doctor James Ironside, and this slide was - these two slides were generated at the Indiana Alzheimer's Disease Center, working for the WHO.

The other thing is that patients with vCJD, with clinical vCJD, that are positive, usually there is immunhistochemistry positive for PrP in tonsils.

Now, talking about, once again, specifically, about these nine patients that were recognized in France, these patients had no specific medical risk factor, so therefore there was no history of human growth hormone treatment, or dura mater graft, or neurosurgery, were not blood recipients, or treatment with albumin, immune globulins or clotting

factors. Well, no other risk factors, for example, there was no family history of dementia or CJD, or contact with CJD patients, or contact - frequent contact with animals or animal products that - are considered to at risk, there were no professional risk factor, no special diet, and traveling the U.K., except for short stays for three patients.

And now, what about, once again, we go out of the nine cases, two cases with vCJD happened to be blood donors. The first patient provided 14 donations between 1993 and 2003, that result in 13 transfusion of red cells and one transfusion of platelets, and the recipients, five are still alive, and nine are dead.

The second patient provided two donations in 1984, and the two - resulting two transfusions of red cells, and two transfusions of plasma, and seven donations between 1996 and 2002, that resulted in five transfusions of red cells and three transfusions of platelets.

Okay, what about risk for vCJD in France? And, the sources of exposure to BSE of the French population could be bovine carcases and other beef products imported from the United Kingdom, endogenous BSE in French cattle, or travel to the U.K. It has also been recognized that the distribution of the

incubation period and age-specific susceptibility happens to be similar or the same to that seen in the U.K. population.

And, continuing with the risk factors, the predicted number of vCJD cases in France by birth cohort and gender, according to this publication, the total number of vCJD cases would be up to 33 cases, and 67 percent in the post-1969 birth cohort, and the number of cases would be equal to the number of infection, meaning that very few cases would be censored by death, meaning that if they are patients they will tend to die in that birth cohort due to vCJD, and not to other causes. And, no expected cases attributed to travel in the U.K., which is something that is not very clear to me.

And now, I'll pass on the podium to Steve Anderson, who is going to present the risk assessment, the French risk assessment.

DOCTOR ANDERSON: All right, I'm going to talk about the risk assessment that was done in France. You'll notice these slides are a little bit starker than the other slides.

Okay, this risk assessment, there were actually several iterations of the risk assessment and reviews and comments made on the document. The report

is a December, 2000 document, "Risk Analysis of Variant CJD Transmission By Blood and Blood Products, and Recommendations," again, a number of different iterations to this French document.

The French document and risk assessment actually estimates numbers of cases of variant CJD based on the Ghani model, statistical model, and I discussed that a little bit earlier. I presented earlier a few starker estimates from that, but they are using a more realistic hypothesis or sort of the middle level hypothesis, that there is a mean incubation of the disease of 30 to 60 years, and you can predict 150 to 6,000 cases in the United Kingdom.

Earlier this morning, I think it was at the 230,000 range, at the upper end.

Again, there's a 20-fold lower level of exposure to the risk of BSE. That sort of relates to the relative risk that I was talking about for our risk assessments, 20-fold is about a 5 percent level compared to the United Kingdom, and that's based on consumption of bovine products, and then the number of cases of variant CJD in the U.K. versus the number of cases in France.

So, what they estimate is, the total number of cases in France would be six to 300 in the

next 60 years, and if you remember what I told you this morning, is that since the number of cases in the U.K. are sort of decreasing Ghani's most recent estimates suggest the number of cases in the U.K. are also decreasing, but what the French are doing is, they are keeping this assumption based on the earlier, more sort of conservative estimate, and using that in their estimate of risk for France.

And, what they are doing here, here are some of the estimates of the blood of these 300 - I'm sorry, assumptions that they are using in their risk estimates on the blood of these 300 subjects, currently asymptomatic, is infected throughout the incubation period. That's seen in several risk assessments. Blood donors are random sampled the French population. We also assumed that these are very sort of standard risk assessment assumptions. Asymptomatic subjects are restricted to the general population, and the prevalence of pre-clinical incubating disease is approximately in the blood donor population is 8.3 per million.

And then what they do, what that works out to is a maximum of one blood donation is predicted per 120,000 that could be infected with variant CJD agent.

And, this is the risk for the transfusion

product, assuming no significant reduction in infectivity occurs from the donor to the recipient. This is for blood product.

Working assumptions on infectivity of blood. They are using animal models as well. I think the important thing here is, not to sort of get confused, you are seeing a lot of numbers here, 20 to 30 infectious units, that would correspond approximately to ten to 15 ID50s, because their one infectious unit is defined as a minimal infectious dose capable of transmitting the disease at 100 percent level, essentially. So, this is what they are assuming, 20 to 30 infectious units per ml of blood.

And, they don't do a correction for the intracerebral route, which is probably a more efficient route compared to the intravenous route, so they are assuming intracerebral and intravenous are equally infective and capable of transmitting the disease.

The infectivity in blood, again, they are assuming, very similar to what's in the literature, 50 percent of the infectivity is in plasma, 30 percent in buffy coat, so this is the number they are working with.

Now, they also do leukodepletion in France

and so infectivity in the plasma, what they do is estimate it at not more than ten infectious units per ml, and that's intravenous, and that corresponds, essentially, to five ID50s per ml of blood.

Here are some further working assumptions in their risk assessment, just calculating residual infectivity in plasma-derived medicinal products. Some of the things that they follow are the volume of the plasma pools, every single pool is infected by at least one donation. The extraction yield for the protein, for instance, if it's Factor VIII then you have a range of, you know, 120 to 160 units per liter of plasma, they are assuming, you know, the lower end of that as far as the yield from these proteins that they are purifying.

The extraction yield for the proteins is at the lower end. Cumulative reduction factors resulting from the manufacturing processes, so you can - I believe these processes they believe are additive, although they don't add for reduction factors that have similar mechanisms, so they only allow for adding reduction factors for different processes. It can't be two ethanol precipitations, it's got to be, you know, two specific processes, like ethanol precipitation and chromatography, et cetera.

Total dose of the product received by a yearly patient is at the maximum dose regimen, so if it were a hemophilia A patient they would assume that they are receiving the maximum dose, if they had severe disease and were, say, on prophylaxis. So, that type of sort of the worst case for the treatment scenario.

Now they walk us through a number of different reduction steps that could occur during the processing of these different products that I'm going to show you a list of at the end, near the end of the talk. So, for cryoprecipitation, and these are of the assumptions that they are making for the levels of reduction associated with the process, so, for instance, cryoprecipitation and the cryoprecipitate, they assume zero levels, zero logs of reduction. But, up here for ethanol precipitation of fractions I and III in the supernatant the reduction factor is approximately three logs. Again, you can just go through these, four logs for ethanol precipitation of II and III in the supernatant, et cetera. So, they have a number of assumptions for different types of processes and allow for the variation in the processes, and their level of reduction accomplished with each.

Again, just going through more of the processes. For instance, absorptions in chromatography, for instance, two to three logs of reduction, et cetera, so these are very sort of straightforward hypotheses. They don't allow for any reductions due to, I believe this was detergent, enzyme or heat treatments.

So then, they go through a number of example calculations. They are going to present one here for Factor VIII. The smallest pool necessary for fractionation is approximately 4,000 liters. That, I think, sort of corresponds to about 20,000 donations, 20,000 donations of recovered plasma that is.

The extraction yield is about 100 units of Factor VIII per liter of plasma. The cumulative reduction factor, they assume a range which could be as low as four logs, and it's between four and seven logs or a max of up to seven logs, so between four and seven logs of reduction in their model for Factor VIII.

Again, the yearly dosage that somebody might receive on Factor VII, they assumed the maximum dose regimen would be as high as 500,000 units, and given that theoretical residual infectivity in that product, if they receive all infected, contaminated

product, would be 2.4×10^{-2}, or as low as 2.4×10^{-5}.

All right. So, what they do here is, they present sort of a tour de force of all these models, and they are just presenting results. So, for Factor VIII, they are presenting this sort of as three logs of reduction, greater than three logs of reduction the risk is $10^{-3.21}$, Factor IX it's 10^{-5}, as far as levels of infectivity. Now, this is, remember, levels of annual infectivity, so what would be sort of typical for annual usage of these products.

And, what they are trying to show here, I think, is that there's a hierarchy of risk, some products are certainly riskier than others, as far as - and that is dependent on the types of processes and the utilization of these products and the number of other product specific processes.

So again, just albumin, again, down at the $^{-3}$ logs of ID50s, as far as risk, Hepatitis B down to $^{-3}$, you have some that are even lower, and $^{-7}$ et cetera. So actually, what they've done is, a lot of simple calculations, but on a lot of products, and they give you at least this general range of risk for each product, so you know sort of a hierarchy of which products are the riskier, and which are less riskier.

So, what they are saying here in their

conclusions, that the residual infectivity value given for each product must be considered as sort of indicative, or you might say relative, and it's not an absolute value, and although absolute values are imprecise the risk hierarchy, again, they are focusing on this risk hierarchy. The interesting thing out of this model is that they give you the risk hierarchy that you get from this model for the different products is more robust, and you can take more meaning from those, at least the relative risk from one product to the next.

And, none of the plasma-derived products has been judged as bearing a risk that would warrant its withdrawal.

Risk assessment in France, the measures taken in France, so they have permanent deferral for blood donations for previously transfused individuals, permanent deferrals for people that lived in the United Kingdom or British Isles, equivalent to one year between 1980 and 1996, and they also have mandatory plasma leukoreduction, plasma for fractionation undergoes this process, and you get just - I'm not sure exactly what that means - oh, removing down to or a minimum of 10^4 or 10^6. These are two different types of process, plasma for fractionation,

removes less cells, plasma for therapeutics remove more of the leukocytes per liter of cells.

Some of the other measures taken in addition, improvement of - and I'm not sure what LFB processes are, I assume those are the manufacturing processes for the production of these products, and they recommend TSE validation studies for the fractionation steps that are performed for these various different products, and then revision of the recommendations on the use of plasma-derived medical products.

Boy, they keep on going.

And then, they go into nanofiltration, which is a new technology for reduction of risk. Before 2000, they talk about for Factor XI and Factor IX, using these 15 nanometer filters, now you are using a combination, you are sort of hitting the products first with a larger filter, and then following it up with a smaller size filtration device, and that's just an improvement over the previous purification schemes for those products.

TSE validation for these processes, these are the numbers and the levels of reduction that they are achieving. So, for albumin precipitations of fractions I, II and III, you are getting greater than

2.8 logs of reduction, et cetera. For the rest of these, and then they are looking at polyvalent IV immune globulin in Factor IX, and through nanofiltration with a 15 nanometer filter you are getting greater than 2.7 logs of reduction.

So, these are validated processes, and then they use those in their risk assessment to estimate risk. Validation again for Factor VIII, with nanofiltration you are getting the greatest, greater than 3.3 logs, von Willebrand factor, 3.9, et cetera.

All right, and that's it.

CHAIRPERSON PRIOLA: Okay.

Doctor Allen, I'm not sure it's entirely fair to ask too many questions, but go ahead.

DOCTOR ALLEN: Going back to one of the earlier slides, it talked about a mean incubation period of 30 to 60 years.

DOCTOR ANDERSON: Yes.

DOCTOR ALLEN: I wondered if the context seemed to be that, perhaps, that was a population-based incubation period with, perhaps, the out years ranging from 30 to 60 years? I don't know.

DOCTOR ANDERSON: Um -

DOCTOR ALLEN: I mean, 30 years as the low end of the incubation period is incredible.

DOCTOR ANDERSON: Right, and that would give you the lower estimate, but if they used a shorter incubation period I believe the numbers would go up, and they'd get more cases, basically.

CHAIRPERSON PRIOLA: Do you know why they picked that 30-year lower limit?

DOCTOR ANDERSON: I think in the study they just presented a number of different scenarios, like 30 to 60, you know, ten to 20, et cetera, if I remember correctly. And so, and there were different case predictions from those studies.

DOCTOR JOHNSON: The mean age of onset of variant CJD is 29, it didn't work, and I think the longest incubation period on record are the kuru patients at 40 now. So, I don't know where they got 60. Those numbers seem just way off base, I agree.

DOCTOR ALLEN: Yes. I guess I was assuming that if they looked at a fairly short, you know, controlled incubation - controlled exposure point, and then you follow the population through that, they are saying by the end of 30 years - I don't know, I just had trouble - I think there's probably a problem in interpretation here.

DOCTOR JOHNSON: At the end of 30 years they'll all be gone, or maybe as long as 60 years.

DOCTOR JOHNSON: Yeah, that was -

DOCTOR JOHNSON: Yes.

CHAIRPERSON PRIOLA: Doctor Belay?

DOCTOR BELAY: You say they permanent defer from donating blood patients who have been transfused?

DOCTOR ANDERSON: They did, yes.

DOCTOR BELAY: Did they do that for plasma donors, did they defer them from donating plasma, do you know?

DOCTOR ANDERSON: I don't know off hand.

DOCTOR BELAY: Jay, do you know?

DOCTOR ANDERSON: I don't think we know.

DOCTOR BELAY: That's one of the questions that we are asked in the document.

DOCTOR ANDERSON: Yeah, and I don't know what their policy is off hand.

CHAIRPERSON PRIOLA: Doctor DiMichele, did you have a question?

DOCTOR DiMICHELE: It was, actually, for Doctor Piccardo, and it was just the slide went by so quickly, I was wondering if we could re-clarify the second donor, how much that donor had actually donated, and the implications with respect to the recipients?

DOCTOR PICCARDO: That I can read to you.

DOCTOR DiMICHELE: Okay, yes, please.

DOCTOR PICCARDO: Second patient?

DOCTOR DiMICHELE: Yes.

DOCTOR PICCARDO: Two donations in 1994, and that was two transfusion of red cells, two transfusions of plasma, and the recipients are two are still alive, one dead, one to be confirmed. You don't have to take notes, I'll be happy to give you this.

DOCTOR DiMICHELE: Oh, okay.

DOCTOR ALLEN: Can you?

DOCTOR PICCARDO: Definitely, I will give you these. Okay? Do you want me to keep on reading, or should I just make the copies?

DOCTOR DiMICHELE: Okay, I'm sorry, of all of them, how many recipients are potentially still alive then from the two donors?

DOCTOR PICCARDO: >From the two donors, two, two are alive.

DOCTOR DiMICHELE: Oh, so just two.

DOCTOR PICCARDO: Two, yes.

DOCTOR SCHONBERGER: The first had five alive.

DOCTOR DiMICHELE: Five alive, yeah.

DOCTOR SCHONBERGER: So, there's five there alone.

DOCTOR PICCARDO: Let me see, of the second patient, yeah, second patient, recipients two still alive, recipients two still alive -

DOCTOR DiMICHELE: Okay, so a total of seven, okay.

DOCTOR PICCARDO: No.

DOCTOR DiMICHELE: A total of nine? Okay, never mind.

DOCTOR JENNY: Were any of the recipients of that blood tested? Do we know?

DOCTOR DiMICHELE: So, it was nine?

DOCTOR PICCARDO: I'll make you copies.

DOCTOR DiMICHELE: In think there was another question.

CHAIRPERSON PRIOLA: Yes, Pedro, Al Jenny had a question for you.

DOCTOR JENNY: Do we know if any of the recipients of the blood from those individuals were tested when they died, after they died?

DOCTOR PICCARDO: In don't have that information. If any of the recipients have been tested you say, that is the question?

CHAIRPERSON PRIOLA: It might be unlikely, because isn't it true that often - I mean, the transfusions are given to people in dire straits

frequently.

DOCTOR PICCARDO: Or, who are dying.

CHAIRPERSON PRIOLA: Right, so by the time these look-back studies are done that's probably not.

Doctor Johnson?

DOCTOR JOHNSON: Yeah, isn't the 1994 case the one in which there was a series of letters back and forth in Lancet about the body-building auto mechanic who was taking injections of pituitary hormones? I mean, I know they said no pituitary hormones, but isn't that the same case, that's the 1994 case in France, I think, the first case, the first French case. It was reported then, there was a letter afterwards saying that he'd been taking some kind of pituitary hormone extract that was approved by the FDA of France for a while and then taken off the market.

DOCTOR BELAY: I don't know, the question is whether or not the first case in their slide refers to the very first vCJD case or the first vCJD blood donor, I don't know.

DOCTOR JOHNSON: I know there was a pituitary hormone.

DOCTOR DeARMOND: But, wasn't the pathology variant CJD in all of those cases?

DOCTOR JOHNSON: Yes.

DOCTOR BELAY: Yes.

CHAIRPERSON PRIOLA: Doctor Bird, do you have a comment?

DOCTOR BIRD: Just a clarification, that the two French vCJD cases who had been blood donors were the 8th and 9th case, so it was certainly not the first vCJD patient in France. The blood donor cases are France's 8th and 9th cases.

EXECUTIVE SECRETARY FREAS: Could I just clarify one thing for the record. If we get permission we, of course, will give the slides to the Committee member and to the public, we cannot give it just to the Committee members unless we have permission, because it's not in the public domain at this time.

CHAIRPERSON PRIOLA: If there are no more questions - whoops, there, Mr. Bias.

MR. BIAS: I don't know if this is a question, it sounds like we are asking a lot of questions, we are not getting a lot of answers, so I'm not even sure we are going to be able to answer the FDA's question, based on the information we've been given here.

But, it was nice of them to tell us how

many logs per product that you needed to remove - or that they consider safe, so you won't have to figure that out. That's good.

I don't know if I have a question, it's just that there seems to be a lot of missing information, and I'm not exactly sure we are going to be able to give you a confident answer without getting some of those questions answered.

I was also disappointed, and I guess LFB is the fractionator in that country, but we've written them several times about product lines that are finished or partially produced there and then shipped to the United States for sales, and we've been able to get very little information out of them as the manufacturer, which doesn't bode well in terms of building confidence in terms of this question that the FDA is asking.

CHAIRPERSON PRIOLA: Let me - what's your name, sorry?

DOCTOR WEINSTEIN: Weinstein.

CHAIRPERSON PRIOLA: Doctor Weinstein.

DOCTOR WEINSTEIN: Could you clarify that, because there aren't any licensed products, as far as I'm aware, LFB plasma derivatives, was this personal importation, is that what you are referring to?

DOCTOR ANDERSON: Are you talking about the ZLB?

DOCTOR WEINSTEIN: We are talking about LFB, the French company, a different company, LFB, not ZLB.

MR. BIAS: But, still my comment is, we don't seem to have all the information we need to answer your question.

CHAIRPERSON PRIOLA: Doctor Schonberger?

DOCTOR SCHONBERGER: Well, I was just going to comment that if in France they don't accept as donors people who have received blood in their own country, it's not clear that we should be. That's my comment, I guess.

CHAIRPERSON PRIOLA: The gentleman at the microphone, could you identify yourself, please?

MR. JACKMAN: Yes. My name is Dennis Jackman. I'm with the ZLB Behring, and I'm trying to answer Val's question, possibly, in some ways referred to as ZLB incident, actually, there was a donation from a single French donor in 1996, who then subsequently developed variant CJD. He was the 8th so-called French donor that went up in one batch of a European product which had been recalled, and there was notification given around the world on that.

Beyond that, what LFB has done, I think you are trying to get answers to questions beyond that, whether other products might have been imported possibly under personal importation or other aspects, that would be something only LFB would know, and so we can't answer that any further.

So, just to clarify, I hope that clarifies a little bit.

MR. BIAS: Thanks, that clarifies it in terms of ZLB, and your excellent service to the community, it doesn't clarify it in terms of them answering questions that we might have about their processes over there, which makes the FDA's question loom pretty large if we can't get answers out of them.

CHAIRPERSON PRIOLA: Doctor Bracey?

DOCTOR BRACEY: In noted that when the Netherlands had the rejection of people that had been previously transfused, there was a loss of about 8 percent of the donor base, and I think it would be important for us to know in France what the impact on the donor base has been, so that we can make an assessment of the tradeoffs.

CHAIRPERSON PRIOLA: Okay, if there are no other comments or questions we'll move on to the next speaker, and that's Doctor Sheila Bird, who is going

to talk about estimates of blood-borne variant CJD risk in the U.K. and other European populations.

DOCTOR BIRD: Thank you very much, Madam Chairman.

I'd like to talk about the BSE cascade through human dietary BSE exposure, primary exposure, to blood-borne vCJD exposure.

When we think about human dietary exposure, we have to consider U.K. exports of bovine carcasses, 60 percent of which went to France, U.K. exports of contaminated feed for cattle, and U.K. exports of infected livestock.

These last two featured large in the European Union's Geographic BSE Risk Assessment, which was concluded in 2000, by which the European Union regarded that all member states bar two were GBR III, in other words, BSE likely or proven at a low level. And, that classification applied to member states that had not had any clinical BSE cases. But, that geographic BSE risk assessment was part of the underpinning for the obligatory post-mortem BSE testing that was introduced on the 1st of January, 2001 in the European Union.

You've heard earlier this afternoon about the work of Marc Chadeau and Annick Alperovitch, just

published in January of this year, which suggested that in dietary exposure in France is about 1/20th of the U.K. dietary exposure, and that that dietary exposure in France was mainly through U.K. exports of bovine carcasses, 60 percent of our exports having gone to France, and, therefore, that would suggest that in other member states they would account for two thirds of the cases that one might be projecting for France.

U.K. human dietary BSE exposure raises the issue that we would in dietary cases expect a male predominance of 58 to 60 percent of dietary vCJD cases being male, on account of male's greater consumption of contaminated - of the likely implicated foods.

And, indeed, as you see here, variant CJD cases presumed dietary in the United Kingdom have been 152 to the end of 2004, nine in France, as you heard earlier, and there have been seven other vCJD cases, two in the Republic of Ireland, one in Italy, one in Saudi, one in Japan just announced on Friday, one in Canada, and one in America.

When it comes to blood-borne vCJD exposure, we need to consider U.K. versus France, versus other exports of pre-clinical or sub-clinical infections of variant CJD. By pre-clinical, I mean

patients who might ultimately go on to develop clinical disease. By sub-clinical carriers, patients who potentially, even if no matter how long they lived, might never actually manifest clinical disease, and not only exports of individuals, but exports of contaminated blood and blood products.

I'd like to take you through a brief history of vCJD and BSE from 1980 to 1999, to remind you that BSE was announced in November, 1986, variant CJD on the 20th of March, 1996, although the first onsets of variant CJD were in 1994, and the first diagnoses in 1995.

The United Kingdom's BSE projections have been too low, largely because we assumed that later cases would be due only to maternal transmission, rather than continued exposure to contaminated feed. We were wrong, France protested, and the projections in various ways were revised.

Variant CJD projections, again, as you've heard, have been generally newsworthy, initially they were vast, and have been coming down until the latest surveillance data, which have put them up again, and I'll talk a bit more later about the geographic BSE risk assessment.

This shows abattoir removal of spinal

cords, so abattoir workers were the guardians of the public health. The BSE controls after November, 1986, remember, that highest infectivity is in brain, spinal cord and the dorsal root ganglia, which nestle closely against the vertical column. So, the first action of the - Food Committee was to introduce a slaughtering compensation policy to ensure that the carcasses of BSE affected cases, clinical cases, did not go into the human food chain, which they had been doing for about two years, and in August, 1988 also we introduced the ruminant food ban.

It was over a year later before the specified bovine offal's legislation was introduced, which removed brain and spinal cord, and some other tissues, from all slaughtered cattle, irrespective of BSE infected or not.

Over the next six years, there were some amendments to our specified bovine offal's regulations and inspections by the State Veterinary Service, particularly, in 1995, which eventually persuaded us that we were not doing a good job at the abattoirs and, in fact, we could not do an adequate job, so that the use of mechanically-recovered meat from vertical column walls ended in December, 1995.

Variant CJD announced in March, 1996 the

recovery of head meat was ended in March 1996, our over-thirty-month scheme, whereby cattle slaughtered over the age of 30 months would not enter human food or animal feed chains introduced from April, 1996, and from August, 1996 a reinforced feed ban, which was supposed absolutely to protect our cattle from contaminated feed. It has not. We have had BSE cases in cattle born after the 1st of August, 1996.

And, the rest of the European Union introduced its reinforced feed ban from January, 2001 and they, too, have had BSE cases in cattle born after January, 2001.

Human surveillance of CJD was reactivated in the United Kingdom in 1990. The remit of the CJD Surveillance Unit was to alert to any changes in the age-specific incidents, occupational distribution or dietary correlates of CJD that might alert to humans having been affected by exposure to BSE.

Presentation, if it happened at all, was considered more likely to be atypical, but, therefore, couldn't be described in advance.

And, of course, the CJD Surveillance Unit sadly fulfilled its remit spectacularly well, ten cases of variant CJD were announced on the 20th of March, 1996, characterized by young age at onset,

longer clinical course, distinctive neuropathology, and methionine homozygosity, which applies still for all clinical cases.

The very next day, the French were going to ban British beef. Our Ministry was still reluctant to release data, and they phoned calls to pass on data from the dam-to-calf experiments that had already - that were already showing 10 percent maternal transmission risk in the last six months prior to BSE onset in the dam.

That information was used by Roy Anderson and colleagues in their seminal paper in Nature on the transmission dynamics and epidemiology of BSE, according to which mean BSE incubation period was five years, and they estimated the U.K. had had 1 million BSE infections. We now know that was an underestimate by a factor of three, we had over 3 million.

In order to be BSE affected, what you observe as clinical cases is a convolution of the BSE incidence curve, the incubation period, and the age-specific slaughter or export pattern.

Now, the BSE incidence curve depended upon access to contaminated feed, to maternal transmission, and possibly to another exposure, though no other exposure has been definitively identified.

Age-specific slaughter pattern for cattle is different for dairy versus beef herds, and it was assumed, wrongly, that it was irrespective of whether the cattle were BSE infected or not.

So, BSE projections in the United Kingdom were essentially back calculations from clinical cases, and that procedure led to serious underestimation of our BSE infections. The back calculations assumed no under reporting of BSE cases after the thought on compensation policy in 1998, wrong, no diversion of BSE cases into the over-thirty-month scheme, implausible, no differential survival of BSE infected, wrong, and no exposure except maternal after August, 1996, wrong.

Beware, therefore, that variant CJD projections, which have, of course, been very newsworthy, have also, essentially, until recently, been back calculation from clinical cases. That we cannot rely upon with this disease. The projections have been reined in from vast 200,000 to under about 400, and are now on their way up again because of the surveillance data.

Our own work considered dietary BSE exposure by birth cohort, because we were interested as to whether differential dietary exposure of itself

would explain the young age of variant CJD cases. It does not.

These were the dietary results for the U.K. Shown separately here for the 1980s, exposure in terms of bovine oral ID50 units in the 1990s, you'll see that exposures were actually greater in the 1990s than in the 1980s for each of the birth cohorts. The youngest birth cohort was, of course, being added to by birth. The oldest birth cohort being depleted by deaths. But, it was, in fact, the middle birth cohort, those born in 1940 to '69, who had been most exposed to BSE infectivity, but most of the cases had not occurred in that birth cohort.

The work just published by Marc Chadeau and Annick Alperovitch used, essentially, the same approach, but based on U.K. exports of bovine carcasses to France, and this shows the cumulative exposures for the U.K., dietary exposures for the U.K. versus for France, and you can see that the French exposure is, indeed, about 1/20 of that of the United Kingdom.

The reason that I say that dietary exposure does not sufficiently explain the young age of the variant CJD cases, this slide shows for the first 112 vCJD onsets in the United Kingdom the period

of birth for those born 1940 to 1969, and you'll see that there were 21 of those 47 were actually born 1965 to '69, whereas, the age distribution predicted by our dietary exposures was shown in the middle column, which you can see is a very poor fit to the age - the periods of birth of the actual cases, and only became a good fit when we incorporated the idea put forward by Valleron, again, vive la France, that age-dependent susceptibility decreased for exposures beyond the age of 15. And so, the work that Annick Alperovitch and Marc Chardeau have just published for France incorporated our estimate of a .06 exponential decay in susceptibility, and then one can get the age distributions to match that of the cases.

So, we think it is not dietary exposure, and this raises the specter that sub-clinical BSE infections may be differential by birth cohort. What's happened to those exposures in the older birth cohort that have not materialized as clinical cases, and we do not know that they are not blood or operation transmissible, even although they may not materialize as clinical disease.

And so, I'll go rapidly over this, because you have seen this already, that the French projections, that France will have a further central

estimate of about 33 variant CJD cases, and on that basis the United Kingdom might be expected to have about 20 times more, around an additional 600.

Let me turn now to this rapid post-mortem testing, introduced first in Switzerland. Switzerland tested all of its fallen stock, and 5 percent of its normal slaughter, in 1999. In that year also, the United Kingdom tested 4,000 cattle in the over-thirty-month scheme, and found 16 of them, to our horror, positive. So shocked were we, that the next year we tested 10,000 and found 40 positive, unfortunately, confirming what we'd seen the year before.

France and Ireland had also started testing of risk stock and found that their late-stage BSEs were being considerably underestimated by their veterinary surveillance.

In 2000 also, there was a comparison of four tests for rapid-post-mortem testing, three of which were approved for use throughout the European Union, in the program that started on the 1st of January, 2001, which obliged all member states to test all cattle born - coming for slaughter at 30 months or above, and to test risk stock age 24 months and above.

That surveillance, from the very first year, showed that BSE positivity is ten to 15 times

higher in risk stock than in normal slaughter bovines - in bovines slaughtered over the age of 30 months, and in order to understand BSE in the country you need to consider the threesome of the clinical cases, plus their BSE test positives in risk stock, plus their BSE test positives at normal slaughter, and both of those surveillances should be comprehensive, unlike they appear to be in the United States for risk stock.

Because here, compare in the first four months only of 2004, the European Union's BSE surveillance in member states, the old member states other than the United Kingdom, which had about 36 million adult cattle compared to the U.S.'s 45 million, and in four months the European Union tested 400,000 risk stock, and you are talking about having tested 200,000 in eight months in a larger herd, which suggests that on a European basis you are testing between one in four and one in five of what we would consider risk stock.

In white, for the member states other than the United Kingdom, you can see that the BSE positive rate in risk stock was 245 per million tested risk stock, whereas, in normal kill the rate was 16 per million tested, in other words, about 15 times less.

Whereas, in the United Kingdom in the

first four months of 2004, still our test rate in risk stock was about four times higher than in other member states throughout the European Union. And, in the new member states who had just started rapid-post-mortem testing at this time, they had no clinical cases, but they had 12 cases, late-stage BSE test positives.

And, indeed, the implications of the U.K. testing in this over-thirty-month scheme in 2000, when we had 40 positives in just over 10,000 tested, in that year between 600,000 and 700,000 cattle five years of age or over, had gone through the over-thirty-month scheme. So, although we were credited with 40 BSE test positives in that year, we probably had 2,700 go through the over-thirty-month scheme. So, unless your testing is comprehensive, you need to multiply up, adjust for your sampling fraction.

Briefly on scrapie, where the European Union in 2002 set up a TSE testing scheme in 60,000 adult sheep per member state, and 6,000 fallen sheep per member state, and also did genotyping of a sample of 500 adult sheep per member state, again, within the first year of that surveillance we found four TSE positives in what had previously been considered to be the scrapie-resistant genotype. So, this post-mortem testing is revising our understanding of scrapie

epidemiology. Also, it's leading to a reappraisal of the ARQ/ARQ genotype, which accounted for nearly 40 percent of the positives, although it had been considered to be only a moderately-susceptible genotype. So, one fails to understand TSEs adequately by looking only at clinical cases.

And so, to post-mortem testing in humans, you've heard already about the two blood-borne cases in the United Kingdom. Let me remind you that the first of those was detected, essentially, because we had a study that was flagging recipients of vCJD implicated blood, and the death certificate, copy of the death certificate was sent to the CJD Surveillance Unit and had a sort of query dementia, an astute physician had been concerned about the clinical course of this patient, had persuaded the family to agree to a post-mortem. The post-mortem was not done on the basis this was query CJD. Had we not had that surveillance and that study in place, we could have missed this case, methionine homozygote, born pre-1940.

And, the second patient, the aortic aneurysm, abdominal aortic aneurysm case, again this was a patient who had received vCJD blood, the general practitioner had been alerted to this fact. It's not

clear whether the patient had been, but there was a medical legal post-mortem. So again, another special reason for there to be a post-mortem which discovered this sub-clinical case in a patient who was heterozygote at codon 129.

And again, the testing for abnormal prion and tonsils, appendix, that you've heard about, this was unlinked anonymous testing of stored tissues, those stored tissues relate to 1995 to '99, even although the results were published in 2004, and the subjects whose tissues they were were mainly, predominantly, age ten to 30 years at operation.

A positive was found in the first 8,000 tested, when we had expected that there would only be likely to be one positive in 40,000, on the basis of that calculation from clinical cases. So, this study was not done to be powerful in terms of an estimate of prevalence, this study was done to give the opportunity to falsify the assumptions that went into the back calculations from clinical cases. And again, spectacularly fulfilled its remit, unfortunately, because we have three positives in just over 12.5 thousand, two of them atypical and subject presently to genotype.

So, there is a conflict, again, just as in

the animal studies, between clinical cases and surveillance, essentially, tissue testing or post-mortem testing. And, that conflict is reflected in the latest estimates published by Clarke and Ghan in the Journal of the Royal Society, again, in January of this year, where based on back calculations in variant CJD cases only they would be projecting only a further 70 cases in the United Kingdom. If you take into account the surveillance data, then the numbers are hugely uncertain, affecting conflict between cases in surveillance, anything from 32 to 4,000 additional cases.

And, a model which makes the assumption that we are dealing with sub-clinical carriage would estimate that we could be dealing with, in terms of prevalent infections in 2004, anything - a central estimate of about 5,000 prevalent infections, but a range from 1,000 to 13,000. So, vast uncertainty. We don't know whether these sub-clinical infections would be transmissible in blood. We would be prudent, of course, to assume that they could be.

Therefore, I suggest that the United Kingdom in particular needs to limit human vCJD transmission, but we also need to acquire key data, and in order to do that we need to consider

attributable testing for abnormal prion, particularly, at autopsy, people who come to autopsy under the age of 55. And, we also need to approach those who have been alerted that they are at vCJD risk recipients, to ask them to consider giving permission in life for post-mortem testing in the event of their death, because otherwise we will not have evidence from vCJD informative tissues, and I would on that caution you about the interpretation of the hemophilia data in the United Kingdom, what we need to ask is how many men with hemophilia were subject to post-mortem from 1995 onward, or had testable operative tissue, and should we be doing, essentially, unlinked anonymous testing in those to find out whether there was sub-clinical carriage of variant CJD. That has not, to my knowledge, yet been done, but your discussions today persuade me of the importance of doing so.

Reminding you again of the rural analogy, experimental BSE in scrapie transfusion risks in sheep, infusing when the transfusion was made halfway through the incubation period in the donor sheep, have given rise to transmission rates of between 10 and 20 percent in sheep.

And then, if we look at the vCJD transmission risk in humans in the U.K., and we

consider only those who are five-year survivors, we have had 17 five-year survivors of vCJD implicated blood transfusions, two of whom we already know are clinical or sub-clinical carriers, but five of those 17 there was no autopsy, and so if you reduce that denominator from 17 to 12 you are looking at the current evidence in man is of a transmission risk between 10 percent and 20 percent, which reemphasizes the need, in my view, that we in the United Kingdom should be testing without consent at autopsy for sub-clinical variant CJD, because then we would be able to have surveillance data by age group, by gender, and by genotype, and if we did identify sub-clinical variant CJD then we could alert the recipient network, in terms of recipients of blood products or tissues surgical network, needle stick network, maternal transmission network, and those recipient networks would then be alerted in order to prevent onward transmission and to contribute key data to document their exposure risk.

And, that comes from their giving permission in life for post-mortem testing in the event of their death, because, ultimately, at the bottom of this slide what we need to consider are how many post-mortem detected sub-clinical variant CJDs do

we have in those who were vCJD exposed at least five years previously, divided by the number who were subject to post-mortem and/or who were exposed at least five years ago. So, we need a relevant numerator and a relevant denominator, and you need to be hearing about that in all future talks, or asking why we can't provide you with numerators and denominators.

So, in terms of detectability, if you take a worst-case scenarios of 10 percent transmission risk, if we, for example, conducted 500,000 tests on operative tissue, and if in 2004, as opposed to in 1995 to '99, it was still the case that about 1 in 5,000 of those was positive, we would be looking at 100 sub-clinical vCJDs, 10 percent of those might have been donors with an average of about four recipients, 40 recipients, about a quarter of those 40 recipients will survive to about five years, for at least five years, so we would have ten recipients of implicated blood who were five-year survivors, and if you had a 10 percent transmission risk one of those might, indeed, develop vCJD. So, we would have one viable blood-borne vCJD transmission. That's not the worst case, it's just a worse case, and even if screening were to cost us 200 pounds per tissue, that's about

$400, then the cost of that sort of surveillance is a 10th only of the cost of the over-thirty-month scheme to prevent one cattle to human variant CJD, dietary, vCJD, over the next 60 years, no species barrier for human-to-human transmission species barrier in the second case.

Now, clearly, if transmission risk were 100 times less than my worst case, then we couldn't afford to reduce them, but we are in the scenario that, perhaps, we need to consider that detector now.

Thank you.

CHAIRPERSON PRIOLA: Thank you, Doctor Bird.

Are there any questions for Doctor Bird from the Committee?

Ms. Kranitz?

MS. KRANITZ: If I understood you correctly, if you suspect that there is maternal transmission in BSE, what do you feel the risk is of maternal - human maternal transmission?

DOCTOR BIRD: It is a risk which we need to be alert to. We know that vCJD is blood-borne, and whenever you have a blood-borne disease you have to consider the possibilities of maternal transmission.

It is early yet to think in terms of the

finding of a clinical case. If, for instance, only one in ten vCJD mothers was anyway capable of transmitting, who delivered a baby in the last six months of her incubation period, then we probably have had fewer than ten such deliveries in the United Kingdom as yet, and the incubation period for vCJD, as you've heard, is probably on average 11, 12 years, and so it's too early yet for us to know.

And, we could be looking at, you know, one potentially at-risk child so far, which is not, you know, a core that statisticians hail, a denominator of one, and so it's really very uncertain at present. We have to be alert to the possibility, and we can't rule it out.

CHAIRPERSON PRIOLA: Doctor Telling?

DOCTOR TELLING: So, we hear a great deal about with respect to scrapie, a great deal about, albeit apocryphally, the potential for environmental transmission, or at least mainly apocryphally.

What about your rather alarming numbers for the existence of the BSE epidemic after these measures were put into place, what about the role of environmental contamination in sustaining the epidemic in the U.K.?

DOCTOR BIRD: In the U.K., we think in

terms now of the third wave of our BSE epidemic, the first one before the ruminant feed ban in August, 1988, and then the second epidemic between August, 1988 and the introduction of the reinforced feed ban on the 1st of August, 1996.

So, the BSE cases that were born after the 1st of August, 1996 are what we think of as our third wave of the BSE epidemic, and in terms of such cases the United Kingdom is now probably at about the peak of BSE cases coming through from that third wave, and there are about 60 to 80 a year. So, it's very low level.

There are at least a third of those cases that you can definitely say were not due to maternal transmission, and the current - I mean, the U.K. veterinary epidemiologists are trying to set up a sort of case control study, not only in the United Kingdom, but would apply to born after the reinforced feed ban also in other European member states, to see whether it is still some residual contamination at feed mills or in transport of materials in ships or whatever.

So, one can't rule out the potential, but the geographic distribution of the third wave of cases is distinctive from both of the first two waves, which argues a bit against environmental contamination.

DOCTOR TELLING: Can I ask a second question?

CHAIRPERSON PRIOLA: Go ahead.

DOCTOR TELLING: So, a second question relates to scrapie genotype, scrapie susceptible genotypes, and I ask this because there was a lot of attention given several years ago to the possibility of BSE infection in sheep, and I notice you talked about the ARQ genotype.

What is your thought about the possibility of those cases actually being BSE in sheep?

DOCTOR BIRD: Well, in the European Union any TSE positive in the scrapie resistant genotype had to be reported and has been subject to experiments and passaging in mice. And, as many of you will be aware, that surveillance program covered goats as well as sheep, and in France they detected a field case of BSE in a goat, and that detection was in 2002, but the definitive results of the mice studies have just come through. And so, about a week ago was the announcement that, yes, this is a field case, the first that we are aware of.

I don't know, I'm afraid, to what extent there has been passaging of any of the positives in the sheep. There have also been some odd positives in

the sheep, not necessarily just in the ARQ/ARQs, and that particular genotype is highly variable between member states, the sheep in different member states.

CHAIRPERSON PRIOLA: Doctor Johnson?

DOCTOR JOHNSON: Yeah, I just thought it needed to be clarified for Ms. Kranitz and others that this is variant Creutzfeldt-Jakob Disease that's being discussed, and that there's a lot of epidemiological data that would show that there's no vertical transmission, or horizontal transmission, of the sporadic disease that we see here in the United States.

CHAIRPERSON PRIOLA: Doctor Belay?

DOCTOR BELAY: I'm just trying to understand the last slide that you showed us, where you said potentially there could be one avoidable vCJD transmission via blood.

How are you proposing to identify the donors? You said testing operative tissues, are you saying that anybody that goes into some kind of surgery should be tested? I'm trying to understand.

DOCTOR BIRD: Well, for example, if we would - if in the United Kingdom we were doing attributable testing when somebody had their appendix removed, or when they had their tonsil removed, and if

we found 100 positives in 500,000 such tests, then we would know who those positives were.

Remember that in the United Kingdom patients who have received at vCJD risk blood have been alerted, and so, I mean, if we found a tonsil positive or an appendix positive they would be in the same category of requiring to be alerted in terms for the public health.

We are not doing attributable testing at operation at present. I'm raising the issue as to whether we should be.

DOCTOR BELAY: So, you have to notify the patients that they are positive and that they should not donate blood?

DOCTOR BIRD: That's correct.

DOCTOR BELAY: All right.

DOCTOR BIRD: Yes.

CHAIRPERSON PRIOLA: Doctor Salman?

DOCTOR SALMAN: This is, again, for clarification. As far as your birth cohort, are you saying like due to this type of study, like the dietary is not as important a factor in the transmission of new variant CJD? Is that what you are saying?

DOCTOR BIRD: No, I'm saying that dietary

exposure is a very important factor, and for the - so, for example, this was based on the dietary exposure, the average age at onset in the youngest birth cohort was 21.8 years of our 64 cases - yes, the 64 cases, and based on the dietary exposure data we simulated onsets, and the average age of our simulated cases was 21.3 years. I mean, very good, directly from the dietary data.

But, when we did exactly the same thing for the middle birth cohort, the agreement was insufficiently good, that was illustrated, so in the older birth cohort it's not just dietary exposure, and we suspect that there is an age-related susceptibility to, as it were, progression of that exposure. Okay? So, we are getting less clinical cases than their dietary exposure would suggest.

DOCTOR SALMAN: That's in the old cohort.

DOCTOR BIRD: In the -

DOCTOR SALMAN: Old cohort only.

DOCTOR BIRD: - exactly, in people who were born before 1970, and it's even more pronounced in what I've called the oldest birth cohort, those born prior to 1940.

DOCTOR SALMAN: I have another question, and this is merely just, I wonder what's your

speculation about Germany, why Germany would not see any case of new variant CJD, why you think that, and giving the number of BSE cases, giving the exposure, giving the dietary there, giving the number of tests they are doing, or testing they are doing, and no clinical cases, what's your -

DOCTOR BIRD: Germany has had - Germany has a large herd of cattle, and it has done - and it has a low BSE rate per million tested in its risk stock. So, it has a much - it has had a much lower level BSE epidemic than France has had.

DOCTOR SALMAN: I thought the opposite, actually, just recently for the last couple years Germany is much higher than France.

DOCTOR BIRD: So here, for example, Germany, now these are the data in 2003, for the whole of 2003, Germany has about 6 million adult herd, cattle herd, it had 13 clinical BSE cases, 20 cases in risk stock, and 23 cases in normal slaughter. It's BSE positivity rate in risk stock was 80 per million tested, whereas, France's rate was 300 per million tested.

DOCTOR SALMAN: But, the denominator, as you said, the denominator for France is 11 million, as compared to Germany's 6.2 million, the adult cattle.

DOCTOR BIRD: Yes, but that would mean that if France was operating at the same level as Germany, then in its risk stock France should have had less than 40 cases. France has had 87 cases. It has considerably higher level of epidemic in its own herd than Germany has. Germany has a very low level of BSE.

CHAIRPERSON PRIOLA: Any other comments, questions, for Doctor Bird?

Okay, thank you very much.

We'll move on to the final speaker in the session, and that's Doctor Alan Williams.

DOCTOR WILLIAMS: Thank you.

Both the slides and the speaker will be somewhat less colorful, but there are a couple of additional concepts that we wanted to bring to your attention to support the discussion.

First of all, just very quickly, because most of you have seen this many times before, just to review the current FDA recommended policies with respect to donor deferral.

In guidance to industry issued in January of 2002, which updated prior guidance, FDA recommended that individuals who had greater than or equal to three months residence or travel in the U.K., between

the period of 1980 to 1996, be deferred indefinitely. Similarly, individuals with greater than or equal to five years residence or travel in Europe for whole blood donors, but specific to source plasma donors, donors of source plasma, this would only apply to France based on some of the relative risk considerations that you've heard earlier several times.

In addition, deferral for individuals who spent greater than or equal to six months on certain U.S. military bases in Europe that were supplied with U.K. beef in the commissaries, deferral for transfusion in the U.K., from the period of 1980 to the present and receipt of bovine insulin sourced in the U.K. after 1980.

Now, at the October meeting you received a comprehensive review of certain FDA recommendations and their development, and the Committee did not provide additional recommendations but there were discussions in a couple of areas that I wanted to probe just a little bit in this talk.

The first is the predictive value of the donor questions to exclude TSE risk. This is, again, an instance where the donor screening process is the only intervention currently available to potentially

reduce risk from an infectious disease agent, so it's an important question, just how well these screening measures work for us.

Second is to consider the feasibility of deferral for history of transfusion outside of the United Kingdom.

So, first to address the donor question itself. Of course, there are very limited data, as in many things in this field. True validation of the donor screening process is complex and expensive for many reasons, one of which is the outcomes depending on what the gold standard is, your outcomes tend to be very rare, particularly, if you are trying that to a specific post-transfusion adverse event.

Secondly, most of the deferral of donors actually takes place before that donor appears at the blood center, based on educational information, conversations with the blood center, and just overall knowledge of the donors themselves. So, then what you see as far as on-site deferral of donors based on administered questions is really only a fraction of the total deferral that occurs.

Thirdly, it's a difficult venue in which to conduct studies, because the finding of alternate information related to a donor's eligibility has

operational implications. So, it is a difficult area in which to conduct studies, but that said there have been many successful epidemiologic studies conducted with the blood community.

Another factor is understanding of the questions, and I just wanted to acknowledge that in collaboration with the Donor History Task Force, which is sponsored by the American - the AABB, formerly known as the American Association of Blood Banks, there's been major progress over the past five years to take a hard look at the donor questionnaire itself, which for many years had simply been additive in terms of adding new questions without any thought for their coherence as an overall questionnaire.

Each of these questions has been looked at for content and subjected to cognitive study, either by one-on-one cognitive interview, or focus groups, or both. So, I think there's been a major improvement of this, and in terms of the full-length donor questionnaire I think there are major improvements occurring.

Trying to get at the very difficult estimate of what would be the false negative donor response rate to some of the risk questions, there are several studies that begin to address this, but none

of them really give a complete picture.

The NHLBI sponsored Retrovirus Epidemiology Donor Study in the '90s conducted some anonymous mail surveys post donation to donors who had been accepted for donation, had donated, and then received a mail survey afterwards, which, basically, reasked some of the screening questions.

And, the study found that through that survey one could document between a 2 and 3 percent overall deferrable risk, i.e., positive responses to questions by donors after successful donation that would have resulted in their deferral, had they given the same answer at the time of deferral. That's a cumulative factor.

For individual risk, this ranged from .1 to .5 percent, but all of the risks were represented, including things like IV drug use, and clearly for some of the less well focused questions, like needle stick or body piercing type questions, that rate goes higher in proportion to the vagueness of the question.

There were parallel findings and some similarly designed studies, Canadian Blood Services did one, also there was one done in Hong Kong, several other types of study formats. Blood centers frequently, in the course of notifying donors of

positive infectious disease test results, combine that with a study to determine what risk factors the donor might have had that contributed to that positive test result, and there are numerous studies for known infectious agents like HIV, HCD, HTLV, et cetera, that show that a high proportion of donors who successfully donated and were found to be test positive, in fact, had the risk factors that should have requested in their deferral. So, there clearly is a level of false negativity, although it's very hard to quantitate.

One other thing I'll mention, it's not on the slide, but getting at it from a different area one can look at risk factors measured in the general population versus risk factors which result in deferral in the first time donor population, and one example that's been used before is the Dallas Household Survey of HIV Risk Factors, when those risk factor prevalences were compared between general population surveys, albeit limited, to first time donor deferrals, the risk reduction was about 20 fold. So, I think in keeping with the estimates put forward by Steve Anderson in his model, a 95 percent efficacy rate of the screening process, is a reasonable estimate.

There's one additional measurement, which

does provide some information, and I think this information addresses some of the confusion that arises when you ask a very complex donor screening question. Manufacturers are required to report to the FDA any deviations which are discovered after the collection of a product that was, in fact, distribution. These are known as Biological Product Deviation Reports, used to be known as error and accident reports.

But, keep in mind in looking at the information that these are only reported to the FDA when an implicated product is issued, so that if an error was discovered in the course of a collection, but the product was still in house, that would be useful information, but that's not sent to FDA and collected.

The most common cause of BPDRs is what's known as post-donation information, information that becomes known after the fact, after the donation, and the most common PDI for 2003 was variant CJD travel, reflecting the complexity of the question.

Where does the post-donation information come from? Generally, it comes from subsequent donation, where a donor who had a false negative screen at one time is found at a subsequent donation.

Some time it's from the donor calling back to the blood center, and sometimes, occasionally, from a third party.

When was the deferral known by the donor? Generally, it was known at the time of donation, but not provided for one reason or another. This isn't necessarily, you know, lack of truthfulness on the part of the donor, it may reflect the quality of the question or attentiveness of the donor or some other factor. About 92 percent of the time it was known at the time of donation but not provided, and about 8 percent of the time not known at the time of donation.

I don't need to reflect on all of these numbers, this is simply total BPDRs reported to FDA for 2001 through 2004, the percentage of those which are post-donation information, and the percentage of PDIs which are due to variant CJD travel. I put this up mainly just so you can get a feel for the numbers that are involved. They are in the thousands, but I think another eye opener is just anything considered in the context of blood donation or plasma collection gets large really fast, just simply due to the large number of donors. There are approximately 9 million whole blood donors, approximately, the same number of plasma donors, so the deferral itself results from

400,000 to 500,000 donors deferred in each category. So, it's really major impact of some of these deferrals, and the numbers that you see reflected in PDI 1/100th of those total numbers.

So, in summary, estimates of the predictive value of donor screening are crude, I'll say very crude. However, based on available data false negative self-report of donor eligibility may be in the 3 to 5 percent range of donors deferred on site and may be higher in relation to complex questions.

Okay. Switching to a different concept, the current FDA recommendation is deferral for transfusion in the U.K. from 1980 to present. There have been a handful of recent developments, not that many since the last discussion of the Committee. There have been two probable variant CJD transmissions by transfusion, which I think most importantly reflect the capacity in humans, similarly to the animal models, to have an incubation period with circulation in the blood prior to clinical disease, and the numbers here, I think as Dave Asher summarized, would be on the order of 18 months and 36 months for the two cases.

There were recognized prior donations by variant CJD cases in France. I'm not sure this is

contributes that much scientifically, but simply opens your eyes if some of the variant CJD cases were donors.

There's also known to be donor deferral for any previous transmission. France, the policy goes back to 1998. We don't know what the donor loss is related to this, but I would propose that it's probably not too much different from the losses estimated by the Netherlands, and as you'll see some estimates for the U.S.

The Netherlands put the policy into place in December of 2004, with an estimated 8 percent donor loss.

So, what are the range of possible policy extensions, if any? First, would be a consideration of transfusion in France since 1980, again, looking at that relative risk relationship.

Second is transfusion in any BSE country in Europe since 1980.

And, the third, any transfusion since 1980.

The donor loss estimates, I believe you saw quickly at your last meeting, they are based on, again, the survey data for travel among donors. We used as an assumption, because the longest period of

travel that we had available was five years or greater, we used this as an estimate of long-term, lifetime exposure.

For U.K. travel, that was .4, there should be a percent there, estimating that about 5 percent of donors were transfused, we estimated donor loss already taken place of about 2 per 10,000 donors.

Similar calculation for France, we did not collect any data specific to France, but what we did do was get lifetime travel to countries and then established a ratio between travel to France versus travel to the U.K. That ratio was .7 for France to U.K., so we simply inserted that with a donor loss estimate of 1.4 per 10,000.

In considering source plasma donors separately, there are no even crude calculations of donor loss, but we would expect it to be somewhat less because history of transfusion is an age-specific relationship, and the plasma donor population is somewhat younger than whole blood donors.

Estimating history of transfusion anywhere in Europe, exclusive of the U.K., similarly, .7 percent times 5 percent estimated transfusion history, loss of about 3 per 10,000 and the same comment for source plasma donors.

So, overall, the donor loss, again, if you multiply by 9 million individuals it can create a larger number than one might think, but compared with some of the other donor deferrals comparatively smaller.

For overall transfusion, and I know you saw this slide at the last meeting, one reason I wanted to show this is probably more than considering history of transfusion between countries, it's important to understand the distinction of donations versus donors. These are data, again, from the NHLBI RED study, this is percentage of donations given by transfused allogeneic donors, overall has dropped a little bit over the years, but we use the figure of, roughly, 5 percent of donations come from transfused donors.

It hasn't been calculated on a donor basis, but if you look on a donor basis it's going to be, roughly, in that 7 to 7.5 percent range, because you get different rates of donation for donors of different ages. So, it's important to keep those two constructs in mind.

This one, similarly, percentage of donations, and this just gives an example of the more frequent history of transfusion among older

individuals, as high as 11 to 11-1/2 percent, and among the college-aged group well under 2 percent for an overall mean of about 5 percent.

Now, in considering the three potential extensions for transfusion, it's important to consider the Euroblood program, as was mentioned earlier. The reason it's important is, certainly one could, you know, recommend a policy independent of considerations of the Euroblood program, but it would potentially set up an asynchrony if one were to defer for time spent in Europe with individuals in the U.S. who were transfused with blood derived from Europe who may not be traceable. So, I did want to give you some observations about the Euroblood program. All of these were derived from testimony provide by the New York Blood Center and the Greater New York Hospital Association in the 2001 era, when the deferrals were being discussed.

The program began in the early 1970s, and at its peak represented about 1/3 of the New York area red cell supply, and approximately 2 percent of the total U.S. red cell supply.

Euroblood was provided to over 200 New York metropolitan area hospitals over the 30-year period of existence, approximately, well over 4

million components.

In the absence of a massive look-back effort, Euroblood recipients currently living in the U.S. are largely untraceable. A couple of comments related to that. One is that it is known that the five-year mortality following transfusion is well above 50 percent, may, in fact, be as high as 80 percent, so many of these individuals are not living, and that mortality we'd actually say is generally unrelated to transfusion. It's simply that it's people who aren't well, who generally receive transfusion.

And a second is, look-back efforts are notoriously inefficient, that even if you conduct a look back two to three years after an implicated unit of blood is identified, your likelihood of finding the recipient goes down over time, and it tends to be a very inefficient process.

A final comment is, the Euroblood program ended in the months prior to the October, '02 implementation of FDA deferral recommendations, which was Phase II, and the pan-European deferral for travel and residence.

That brings us to the questions.

CHAIRPERSON PRIOLA: Are there any