about this after the committee voted.

Then I will review the committee vote and the committee's concerns about labeling, followed by what we did and what we have approved actually as labeling for such a claim.

The rationale for offering TSE clearance labeling is several fold. First, it encourages studies of specific manufacturing processes to determine their capacity for TSE clearance. Although the risk of transmission by plasma products still remains theoretical, that is, we know of no confirmed cases of people receiving plasma products that have come down with variant CJD or CJD, the incubation period, as has been discussed many times, may be prolonged and, of course, blood transmits disease in animals and in humans.

Additionally, we only have one other handle on limiting the risk in these products, and that is donor deferrals for blood and plasma donors, but these deferrals do have their limitations, and that will be discussed extensively this afternoon, particularly the supply impact is increased, and the incremental benefit is decreased as deferrals become more stringent.

I'm particularly talking about especially

the geographic donor deferrals that we have for risk of exposure to BSE.

Published studies can be useful, and they show that TSE clearance is condition and process dependent, that is, one size does not fit all. For example, depth filtration may clear TSE infectivity, but different depth filters and different intermediate products have different levels of clearance. So I will be emphasizing this again.

Therefore, published studies for one product can't be extrapolated perfectly to another product using another process.

Published studies also are not detailed enough for rigorous regulatory evaluation. I don't think any journal would accept a submission that was a couple inches thick.

Additionally, offering this TSE clearance labeling should result in scientifically sound data that permits an estimate of risk reduction by manufacturing, and very important, it improves risk communication to the public. In particular, this allows labeling to describe risk reduction measures.

I just want to review some aspects of TSE clearance in the manufacturing process. Manufacturing processes for plasma derivatives are highly

individual. There are many variations on the Cohn-Oncley process of alcohol fractionation. There are now other fractionation methods that are used, and there are multiple variations in downstream processing and purification of products. Most of these variations have to do with getting rid of aggregates or getting rid of viruses or anything that could cause an infectious disease.

Therefore, rigorous demonstrations of clearance have to be based on the specific manufacturing process, but published studies can prove useful in identifying steps that have a potential for TSE clearance. So for selection of steps to study, I've already said the amount of clearance depends upon the process being studied and the precise characteristics of the intermediate material that you're looking at before and after it undergoes a step in manufacturing.

Some of these variables are a pH alcohol concentration, ionic strength, prior conditioning by other steps, and I'll come back to that last.

I just want to mention a caveat which was alluded to in one of the speakers from the open public hearing, and that is that experimental TSE models might not be optimized because the nature of the

infectious agent in blood and plasma has not been fully characterized.

To review the vote, the TSE Advisory Committee was asked whether the FDA should consider evaluation of TSE clearance studies intended to support new labeling. The vote was 12 votes yes, one vote no.

We had presented a wording that was somewhat generic in nature, and the committee didn't like that. First of all, it was thought that the wording that we had in this labeling that we presented -- and we have something very different now, and that's why I'm not reviewing this in more detail -- but that the wording "remote" and "theoretical" was difficult to interpret, especially by patients and health care providers.

It was also felt that the wording should match the specific details of the clearance in the product and not be just the generic wording saying that these studies were done and resulted in some clearance.

Some committee members felt that vCJD and CJD information should definitely be separated from other information about viruses, and it should at least be separated in terms of formatting in

paragraphs.

There was also a concern about the perception of a double standard. That is, some products with have TSE risk reduction labeling and some will not. This, of course, is entirely dependent upon the data we receive and the quality of that data when we evaluate it.

Lack of labeling would not mean that a product is deemed unsafe or even that a product lacks risk reduction measures, but it would tell you that so far those studies had not been both submitted and fully evaluated by FDA.

These are what we considered to evaluate TSE clearance studies in submissions that have arrived to us. There needed to be a rationale for the animal model selected and the selection of the spiking agent. The spiking agent needed to be characterized and all of the studies needed to be done using actual manufacturing intermediates.

The process used on a lab scale had to be accurately scaled down. The experiments need to be robust and reproducible, and an assay needs to be used that's well characterized for TSE infectivity, although there is a possibility that binding assays or solid phase assays could be linked to bioassays; that

bioassays would not have to be done in every case.

An estimated amount of log's clearance of the TSE by processing steps had to be provided, including a reduction factor and a clearance factor. Mass balance needs to be demonstrated.

Now, there are cases where this is difficult, and we do accept at least explanations and discussion of where you cannot look at mass balance. For example, if a TSE infectivity is removed by a solid column, it's very difficult to assay that column matrix for infectivity later. These are technical limitations of these kinds of studies.

There needs to be a demonstration where it's relevant that orthogonal, or non-orthogonal that should read, or similar clearance steps are or are not additive.

There also needs to be an accounting for the conditioning of infectivity where a prior step, such as solvent detergent treatment may affect the physical state of the TSE agent and, in turn, affect the clearance step downstream.

In addition, our current thinking is that steps with less than three logs of clearance are not considered to provide meaningful amounts of clearance if they are based upon partitioning because

partitioning in general is not an extremely robust method.

So here's a new labeling. It has already been approved for one product. We have other submissions in hand. In the description section, which is the first part of package inserts for plasma derivatives, it reads that additionally the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of TSE considered as a model for the vCJD and CJD agents.

The purpose of this sentence is to characterize the studies as investigational and to introduce a concept that models for vCJD and CJD were studied.

Also in the description section the following statement provides some specificity. Several of the individual production steps in the product manufacturing process have been shown to decrease TSE infectivity of an experimental model agent, and then there's a listing of the TSE reduction steps which states the process that was looked at, for example, depth filtration and the number of logs of clearance.

And then finally the statement these

studies provide reasonable assurance that low levels of CJD, vCJD agent infectivity, if present in the starting material, would be removed.

So the purpose of this whole statement is to state that clearance was observed and to give an idea of the specific amount of clearance for each step, very similar to viral inactivation labeling that these products have, and it provides an estimation of the effectiveness in the context of low levels of infectivity.

In addition, the labeling in the warning section is retained. So the plasma derivatives all carry this warning because this product is made from human blood. It carries a risk of transmitting infectious agents, e.g., viruses and theoretically the CJD agent.

So this captures the still uncertain but still potentially possible risk, and the reduction of risk, if it's based on scientific demonstration is reflected in the description section.

As I mentioned, we have submissions under evaluation. These come in as prior approval supplements or are provided in new biologics license applications, and I also want to say to the audience that future improvements in risk assessment,

understanding of the nature of plasma infectivity and improvements in study methods could provide a basis for additional labeling requests or recommendations.

So the story isn't over. I think that you will be hearing in a moment where industry is on these studies and we do think that we've had a fair amount of interest in these labeling claims.

Thank you very much.

CHAIRPERSON PRIOLA: Okay. Thank you, Dr. Scott.

Our next presenter will be Dr. Henry Baron.

DR. BARON: Thank you.

Good morning. My name is Henry Baron, and I am the Chairman of the TSE Task Force of the Plasma Proteins Therapeutics Association, or the PPTA.

PPTA member companies have generated an abundance of prion reduction data since the last TSEAC meeting of February 2003 that Dr. Scott just referred to, and within the 15 minutes of time allotted for this presentation, there certainly is not enough time to present all of that data.

So what I'm going to be showing you is selected data on certain product categories that are of particular interest to the FDA at this time, and

those are clotting factors and immunoglobulins.

For all of the studies that I'm going to be showing you the data from today, the prion strain that has been used as a spiking agent is the 263K hamster prion strain. It's a well known, well characterized prion strain widely used throughout the domain of prion research.

Now, the first category of products that I'm going to show you data from are Factor VIII/von Willebrand factor products, and as you can see different spiking preparations have been used. I'm going to show you data from three products here. Different spiking preparations have been used for these evaluation: microsomal membranes, purified pathogenic prion protein, detergent treated brain homogenate, and crude ten percent brain homogenate.

These studies also have been performed with different prion detection methods. The confirmation dependent immunoassay, Western Plot immunoassay, and animal bioassay in hamsters, and for each of the studies, at least two to three independent runs have been performed per spike preparation.

Product A in which consecutive salt precipitation steps were evaluated shows you data for microsomes and purified PrP scrapie ranging between

2.5 to 3.2 logs for this spike and up to 2.8 to 3.3 logs for the purified PrP scrapie spike.

Product B in which the three percent PEG precipitations that was evaluated. Multiple runs were used with this spike, and this was evaluated by bioassay as well as by Western Blot immunoassay. The data shown here represents the lowest removal factor in the range of data in the different runs: 2.2 logs by infectivity assay; 3.0 logs by Western Blot assay.

And Product C. Now, I'd like to make a point here. These two products are Factor VIII/von Willebrand factor products of relatively low purity, and when you're dealing with these lower purified Factor VIII/von Willebrand factor products in which it's essential that you have a large concentration of the von Willebrand factor, you're going to get removal levels in this range. You're not going to get a whole lot more.

Now, for some of these products there were other steps that also have removal factors in this same neighborhood. So the additive removal factor would be higher, but with these lower purity products, you're not going to get a whole lot more than this.

This Product C here is a heparin-affinity purified Factor VIII/von Willebrand factor product in

which a PEG precipitation step was evaluated using microsomes and detergent treated brain homogenate. Here in two runs, 3.5 logs. The removal was demonstrated for the microsomes, 4.2 log removal for the detergent solid lines.

If you look at a more highly purified Factor VIII product now, such as this monoclonal antibody affinity purified Factor VIII product, you're going to get higher numbers. Again, the 263K hamster prion strain evaluated using brain homogenate for the monoclonal antibody column and using solvent detergent treated brain homogenate for a DEAE step.

And again, two independent runs were done for spike preparation. The result is you have here, represent the average and monoclonal antibody column, is going to give you a good removal factor of 4.1 logs with DEAE Sephadex, again, 3.5 logs.

So with the more highly purified product like a monoclonal antibody purified Factor VIII product, you will get a higher removal level.

Factor IX products now, again, spike preparations used, microsomes, purified PrP scrapie, and detergent treated brain homogenate. Again, CDI, Western Blot used as prion detection methods, and at least two independent runs per product.

Product A, the manufacturing stage studied here were Planova filters in series, 35 nanometer pore size and 50 manometer pore size, and the result -- and this, again, represents a mean -- 4.1 log removal for this Factor IX product for these two filters studied in series.

Product B, nanofiltration, the YM 100 filter was evaluated using microsomes and purified PrP scrapie. Here is the results for the two runs, 3.3 and 3.7 log removal to give you a mean of 3.5 logs. Purified PrP scrapie, relatively similar results, 3.6, 3.6.

Product C, another Factor IX product in which salt precipitation was evaluated. Again, microsomes in purified PrP scrapie, and again, we're in the same neighborhood for the same microsomes, 3.8, 3.6 logs, a mean of 3.7, and for the purified PrP scrapie, a little bit less removal with a mean of about 3.0 log removal.

Now I'm going to switch over to immunoglobulin products, and I'm going to just show you data from two products, and I'm going to show you specifically a set of data that address an issue that has been often of concern to the regulatory environment, and that is the feasibility of adding

removal factors from independent steps, and whether it is appropriate to offer a calculated removal factor based on evaluation of independent steps as opposed to evaluating the steps, coupled, this whole series of steps, spiking here, and then evaluating what comes out here at the end.

The result in this experiment which evaluated cryoseparation, Fraction I and Fraction II separation, you can see that the additive removal factor for adding up the individual factors for these three steps is 7.1 logs, and it is comparable to the removal factor done when the three steps were studied consecutively, 6.8 logs.

And another immunoglobulin product showing the same kind of data, and this one a depth filtration. Two different depth filtration filters were evaluated in series, and you can see that when the two filters were evaluated in series, you get a log removal factor of 7.2. When you did them individually, 4.5 plus 2.8 gives you a log removal factor of 7.3.

So I think these are two sets of data which show you that the additive calculated removal factors, adding up the factors for different steps do correlate very well with the evaluation when you do

the steps in series.

Now, the numbers that I have shown you are just numbers at this time, and in order for them to have any kind of meaning, they have to be considered in the context of whatever we consider the risk of vCJD to be in the donor population. I'd like to spend the next few minutes discussing this issue.

To date there have been 15 blood donors diagnosed with variant CJD in the United Kingdom, of which nine contributed to roughly 20 pools used to manufacture plasma derivatives. So from 1980 to 1998, the incidence of variant CJD donors amongst the donor population was 50 divided by 1,907,000, which was the number of donors in the U.K. in the year 1997, times 18 years, and this gives us a number. This gives us a number which would give you the incidence of variant CJD donors per million donors per year in the United Kingdom.

Now, I would like to also look at some data which shows the exposure to BSE in the United Kingdom as compared to that in the European Union, and what you see here is that up to the end of the year 2000, which was the year in which -- excuse me -- up until the end of 1999, up until the year 2000. In 2000 active surveillance at the slaughterhouse level

was implemented in Europe.

You had 180,000, roughly, cases of BSE in the U.K. The number of BSE cases in the European Union up to that time was 1,777. So basically what this is showing you is that in the European Union, there was a 100-fold lower exposure to BSE as opposed to that which occurred in the U.K., and all of the U.K. vCJD infected donors contributed prior to the introduction of active testing for BSE.

However, I think it's important to note also that since 2000 when active surveillance, systematic testing at the slaughterhouse level occurred, there was a fourfold increase in the BSE detection due to this active testing.

So I think that what the PPTA is doing now, we're showing you this data because we'd like to use this data to develop an alternate assessment of the risk of vCJD. By using this data we are going to calculate the vCJD, the potentia; vCJD incidence in the donor population in the European Union, and then use those numbers as a model to assess the risk in the United States considering the European Union to be a worse case scenario for BSE exposure and variant CJD than the United States.

And we hope to be able to present this

data, this risk assessment at the next TSEAC meeting in February.

And finally, I'd like to make some concluding statements. I showed you a good deal of data from different PPTA member companies in which different investigative approaches, different spikes, different assays were used, and the use of these different investigative approaches gives confidence that the current systems are working to assure efficient prion removal.

And these efforts made by PPTA member companies really represent an enormous investment in applying the precautionary principle and providing reassurance in the safety of plasma products, and this is an ongoing effort. This is not something that's going to stop in any recent time.

And finally, we feel that balanced approaches are really needed to insure both the safety and the availability of lifesaving plasma protein therapies.

Thank you.

CHAIRPERSON PRIOLA: Okay. Thank you very much, Dr. Baron.

I think that we'll take our 20 minute break here until 11:00 a.m. because we had to absorb

a lot of information here. All of these speakers should be available for much of the day for questions if the committee has them.

So we'll reconvene at 11.

DR. FREAS: Our official photographer is here, and so I would like to ask those who have received their plaques to come up during a break and get their picture taken. Otherwise you cannot leave the committee without an official photograph.

(Whereupon, the foregoing matter went off the record at 10:46 a.m. and went back on the record at 11:10 a.m.)

DR. FREAS: If the committee would return to the table.

Thank you.

CHAIRPERSON PRIOLA: Okay. If we could get started here, most of the committee is back at the table.

And our next set of talks deal directly with the topic that the committee has been asked to discuss and vote on. So our first speaker will be Dr. David Asher.

DR. ASHER: Thank you, Dr. Priola.

Now we turn to our decisional -- gang, can I ask that we take side conversations out into the

hall, please? We're running considerably late already.

Thank you. So thanks very much.

Now we turn to our decisional issue of the day, soliciting advice and posing questions for the committee to vote or to have an opinion from them. After offering the charge, I will review briefly the history of FDA actions to help protect the supply of human blood and blood products against contamination with TSE agents.

Note recent events of concern introduce the scientific program intended to help the committee and then pose the questions. We seek advice on whether recent information regarding variant CJD information of which you're aware warrants consideration of additional measures to maintain the safety of FDA regulated human blood and blood products.

For more than 20 years, FDA has taken precautionary actions and offered guidance to blood and plasma establishments based on the assumption that the infectious agent might be present in the blood of persons with TSEs or during an incubation period of TSEs.

In 1978, Elias Manuelidis and colleagues

reported the first convincing evidence that guinea pigs with an experimental TSE had infectivity in blood, a report later confirmed and extended many times in other animal models. Especially informative have been studies by Paul Brown, Robert Rohwer and their colleagues. Both of them spoke at our last meeting, and I'm glad to say that they're both attending today.

In 1983, FDA, learning that a blood donor had been diagnosed with CJD, encouraged voluntary withdrawal of indate components and plasma derivatives. Nine similar withdrawals followed during the next 12 years.

In 1987, FDA recommended precautionary deferral of some donors with a history of increased risk of CJD, those who had received human cadaveric pituitary growth hormonem, and later added history of dura mater allograft or a family member with CJD.

In 1995, FDA recommended precautionary withdrawals of both blood components and plasma derivatives from increased risk donors, but three years later for reasons summarized on the slide in your handout FDA no longer recommended withdrawal of plasma derivatives when a donor was recognized post donation to have had classic forms of CJD or to be at

risk for them, although retaining previous policy for whole blood and components.

However, there was a greater concern about donors with the new variant CJD, and FDA has continued to recommend withdrawal of plasma derivatives from any pool to which a donor with vCJD contributed, something that has not been necessary in the USA, although the U.K. as we will hear has not been so fortunate.

In January of 2002, FDA recommended enhanced precautionary vCJD policies. Those are still current and are the topic of today's discussion.

Last year we became aware that two Canadian born cows, one resident in Washington State, had been found with BSE; discussed that issue at previous meetings. We also received very troubling news from the U.K. regarding vCJD and blood safety, that a recipient of red cells from a healthy donor later diagnosed with vCJD had himself come down with the disease.

Professor Robert Will was kind enough to share information about that case at our last meeting, and he is here again to speak about a second presumptive transfusion transmitted vCJD infection, the overall situation regarding vCJD in the United Kingdom and other countries and related information.

Not least of which is the recent notification of certain recipients of derivatives made from plasma of U.K. donors that may be at increased risk for variant CJD, and that was referred to in the earlier discussion this morning.

In the handout, you will find a summary of current FDA CJD/vCJD blood safety guidance. Many of you are already very familiar with those policies, and for those who are not, Dorothy Scott will review them later in the program.

The FDA, aware of uncertainties surrounding TSE risks, effectiveness of risk reducing measures and potential to contribute to shortages of life sustaining blood products, is committed to reviewing its blood safety policies frequently. In addressing TSE risks, the agency has tried to take a proactive approach consistent with the findings of the Institute of Medicine regarding government decision making, and that took place for HIV and the blood supply.

As part of that effort, we have tried to review policies regularly and publicly with the TSE Advisory Committee, and in an abbreviated form with the Blood Products Advisory Committee, especially when new information suggests that risks should be

reevaluated.

Since our last meeting in February of this year, significant new information has become available.

FDA has been more concerned about variant CJD than other forms of CJD for reasons listed here. Not only was the neuropathology different, but also there was much more scrapie type prion protein in lymphoid tissue, an obvious potential source of infectivity in blood, and there was a more general concern that because vCJD was an emerging disease, different in so many respects from other forms, that the relatively reassuring epidemiological information that had failed to show actual evidence of transfusion transmitted classic CJD might not be predictive.

The reports of two cases of blood borne vCJD in less than a year has increased our concern.

There has been some good news as we heard earlier this morning. The BSE outbreak may have peaked in many cases, and no further cases have been detected so far in North America since the two were recognized last year.

And the number of diagnosed vCJD cases worldwide is smaller than some models had earlier predicted.

However, troubling uncertainties remain. Evidence from cases of vCJD thought to have been acquired by people in the U.K. who then left the country suggest that incubation periods after dietary exposures might be nine years or more and after transfusion six years or more.

It is clear that as in animal models, blood of an infected person is likely to be infectious for some uncertain fraction of the preclinical incubation period, at least 18 months in one U.K. case and three years in the other.

Furthermore, results of a recent survey of scrapie type prion protein in tissue from routine appendectomies in U.K. suggested that more than 100 persons per million in the U.K. might be in the preclinical incubation period of variant CJD.

We conclude that until uncertainties are resolved better, there's reason for continued concern about the safety of blood donors who were potentially exposed to the BSE agent.

Relevant published information about both the first case of presumed transfusion transmitted vCJD was summarized for us by Professor Will at the last meeting of the committee, and he will discuss the second case today. I summarize information, published

information, for you in the handout.

Taken together, the new information has a number of implications. Variant CJD must be presumed transmissible by blood or at least by non-leukoreduced red blood cells. The heterozygous prion protein encoding genotype, methionine-valine at Codon 129, while probably providing some protection against vCJD as it does for other forms of CJD, does not convey absolute resistance to infection with either CJD or vCJD agents.

A second save of variant CJD affecting persons not homozygous for methionine at the 129 locus is possible. The number of persons incubating variant CJD in various countries is uncertain, but may be significant especially in the U.K. where dietary exposure to the BSE agent was greatest.

The number of persons have vCJD agent in blood may, therefore, be significant. The FDA therefore sees no reason to doubt that recommending geographic BSE blood donor deferral policies was prudent and justifiable and probably remains so.

FDA has recommended CJD and vCJD blood safety policies to reduce the risk that a donor might be incubating CJD of any kind, while not deferring so many donors as to compromise the supply of blood

products. We have acknowledged that the policies cannot eliminate all conceivable risk.

We intentionally are not now offering specific options for the committee to consider, but it might be useful for you to direct your attention to the general kinds of precautionary deferral already in place in order to consider which, if any, are amenable to enhancement, enhancements that might reduce risk sufficiently to justify the inevitable loss of otherwise suitable donors who are a precious resource.

One, deferrals for potential dietary or other exposure to BSE agent, possible enhancements to current geographic deferrals, ignoring the taking of individual dietary histories which are generally thought to be very unreliable would be to reduce the time that a suitable donor might have spent in various countries or to add new countries to the list.

Regarding nondietary BSE exposures, we are not aware of any other U.K. bovine derived injected product similar to insulin that was in general use.

Two, deferral for history of exposure to human blood or blood products from donors potentially incubating variant CJD. The enhancement would extend deferrals to donors transfused in places other than the United Kingdom.

To aid the committee and inform the industry and public as well as our own agency, we have enlisted the aid of a number of speakers. Professor Will as mentioned will review variant CJD and recent events of concern.

FDA's Steven Anderson will again compare blood risks of classic and variant CJD, U.K. and U.S. situations and will comment on the development of risk assessments for recipients of coagulation factors.

Luisa Gregori will summarize her work with Robert Rohwer and colleagues investigating the effects of leukofiltration on endogenous infectivity in a hamster scrapie model and possible implications for human blood safety.

Peter Ganz was to come from Ottawa. Has Peter been able -- okay, good. Peter Ganz has kindly agreed to come to share with us as much as he can regarding variant CJD and Canada's approach to blood safety.

Dorothy Scott will summarize and comment on current FDA policies, and Alan Williams will estimate risk reductions and donor losses from previous and current deferral policies and those that might be expected from other possible policies.

In our open public hearing, Dr. Peter

Page, I believe, will report on the latest results of the American Red Cross study that was summarized briefly at our last meeting by Dr. James Sejvar of CDC, and has been incorporated into Steve Anderson's analyses.

And we're always grateful for other contributions to the open public hearing, as well.

After the program, the committee is asked:

One, to consider whether CJD/vCJD deferral policies currently recommended by FDA to protect the safety of the blood supply remain justified; and

Two, if so, in considering recent additional information about BSE and vCJD, they are still adequate.

If the committee considers any current policy to be inadequate, FDA solicits its advice in suggesting enhancements to existing policies or possible additional policies that might reduce the risk further without jeopardizing an adequate supply of life sustaining and health sustaining blood products.

We ask you please to vote on the first two questions and to discuss the third. As always, we are very grateful to you for your help, and we thank you.

CHAIRPERSON PRIOLA: Thank you, Dr. Asher.

Are there any questions from the Committee for Dr. Asher? Dr. DeArmond?

DR. DeARMOND: It's more of a comment. If we can believe this -- the letter that this person wrote in Great Britain about the son donating blood in the U.S., it seems that the deferrals are fine, but the enforcement of or the actual practice of making sure somebody from a high-risk country doesn't donate blood is the bigger problem at this time.

And it's -- this is all anecdotal, and I don't know how you follow up and make sure that this isn't happening. But it was a little disturbing to realize that Europeans from high-risk countries can come in and donate blood relatively freely, which means, again, people are not following the deferral policies.

DR. ASHER: The donor in question -- and I don't know if the audience has seen the document -- as I recall the situation, is alleged to have given false information on a donor questionnaire in order to donate I believe plasma. And I don't know -- but perhaps as Alan Williams coming in -- I don't know, aside from spotchecking, what one can do to protect against donors who intentionally give false information or leave out information when questioned

on a blood donor situation. The whole system runs on honor.

CHAIRPERSON PRIOLA: Okay. Thank you, Dr. Asher.

Our next speaker is Dr. Bob Will, who is going to update us on the transfusion transmission of variant CJD in the UK.

DR. WILL: Good morning. I'm very grateful for the invitation to come and speak about what is a very difficult issue, both in the UK and elsewhere. I'm going to concentrate on the blood issue, but at the end I will say something about the plasma issue in the UK and the notification of recipients that has just taken place, and perhaps try and balance that with some views from other European agencies.

You have seen this before from David Asher. This is the number of cases of variant CJD worldwide as of today. UK, 149; France, 7; Republic of Ireland, 1; Italy, 1; USA and Canada, and all the ones in blue had potential exposure to BSE in the UK because of a residential history.

I think there's just a couple of things I should probably say about this in view of some of the questions this morning. As far as the other cases

outside the UK are concerned, we believe that none of them were blood donors. As far as the UK cases are concerned, we still believe that the most likely hypothesis is that these cases were caused by dietary exposure to high-titer bovine tissue in the human food chain.

And one reason for that is that the great majority of these cases had no significant past medical exposures. Only five of them had ever received a blood transfusion to our knowledge, and a case control study of risk factors, medical risk factors, has shown no significant additional risk from medicinal procedures in this group compared to controls.

So we do not believe that the evidence that we have today suggests that these individuals have developed variant CJD through medical interventions. Although I am not in a position to discuss this in detail, we have also recently completed a case control study with Hester Ward, which does give some evidence in support of the dietary hypothesis.

The number of deaths from variant CJD worldwide is shown here. There should be an additional orange bit here to represent a case in the

United States that I believe has died this year. It shows this pattern of deaths in the UK with a clear decline, and, as I've said before, we believe that clinical onsets are probably a more accurate view of what is happening in terms of temporal trends in the number of cases.

And you can see this peak in 1999 of clinical onsets, and then a clear decline. The data for the years 2003/2004 are incomplete, but it clearly looks as though there has been a decline in the epidemic of variant CJD in the UK, although I must stress that all of the tested cases to date of clinical cases have been methionine homozygotes. And all of the mathematical models, which I'm going to present shortly, assume that only methionine homozygotes could be infected, and we no longer believe that that is the case.

This doesn't show very well, but this is the numbers of variant CJD onsets, and Roy Anderson modeling of infections of BSE with an incubation period from the peak of the presumed exposure to the peak of the presumed epidemic of variant CJD of about 12 years, which I think is biologically plausible from what we know about other prion diseases.

Now, modeling of what will happen in the

future of the variant CJD epidemic has been carried out over many years, and I think I presented this the last time. The first study done by Simon Cousens in 1997 was designed to show the great uncertainty about the number of future cases of variant CJD that there could be at the very start of what was potentially an epidemic.

And what has happened with time? This is just a selected number of these models -- is that the projections of the future number of cases have become more and more conservative with time, with recent projections suggestions cases of perhaps 4- or 500 in the UK over the next 40 to 50 years.

However, as I've already said, there are a number of assumptions in all these models, one of which is that methionine homozygotes would only be affected. There is also the presumption that there was a unimodal UK population exposure to high-titer bovine tissue in the food chain, and Byrd and Cooper have suggested that there may have been a bimodal distribution of exposure.

So there is great uncertainty about the future still in relation to the variant CJD epidemic in the UK, although I must say that from my point of view, personally I think the very fact that we've had

a peak and a decline in the MM homozygote population means it's less likely that we're going to have such a large epidemic as was originally feared.

The issue of secondary transmission of variant CJD has been a matter of concern for many years, notably since spleen was found to contain PrP by James Ironside and colleagues many years ago. And also, this has subsequently been shown to contain infectivity at a lower level than brain in a variant CJD case.

This is the original study of appendices from samples in the population in which they found 1 out of 8,318 positive, suggesting an estimated prevalence of prion protein in the population of about 120 per million, although with very wide confidence intervals.

And, of course, the concern about this is that these tissues can be positive for a long time during the incubation period, presumptively in humans for many, many years, and that individuals who contain infectivity in the periphery could be acting as blood donors. And it's for this reason that there has been such concern in the UK and elsewhere about the whole issue of the possibility of secondary transmission of variant CJD through blood.

And this is a slide that you have seen already from David Asher showing the more recent study by David Hilton and colleagues in which they looked at large numbers of appendix and tonsil samples, totally anonymized. That was the ethical guidance that was received. Three appendix samples were positive for PrP, leading to an estimated prevalence of 237 per million, again with wide confidence intervals.

Or, because of the age distribution of the sample that they studied, 3,808 individuals age 10 to 30 years might be incubating variant CJD in the UK. So there is a disparity between the observed epidemic and the projections in relation to these tissue studies.

Now, I'm just going to talk about the Transfusion Medicine Epidemiology Review, the TMER study. And just the background is that variant CJD was identified in 1996, it was thought to be a new disease, and we're now confident about that, its future infection with a BSE agent. Some cases, in fact, is blood donors.

And, importantly, I think -- this will be discussed in the next talk -- sporadic CJD is known is to be transmitted from person to person but not through blood transfusion. And the concerns about

variant CJD is it's a new infectious agent with a different pathogenesis. Therefore, there may be different outcomes in relation to blood.

The study involves the National Blood Service in England, the Scottish National Blood Transfusion Service, the Welsh Blood Service, the Northern Ireland Blood Transfusion Service, the Surveillance Unit, and, importantly, the Office of National Statistics. And in brief, because I don't want to go on about this at length, the methodology of this study is really very simple.

What happens is that every time we identify a case of variant CJD that is classified as probable or definite, the details of that individual are circulated to the relevant blood transfusion service in relation to their residential history, and a search is made to determine whether any of them had acted as blood donors.

If they have been identified as blood donors, the recipients of the blood are identified, and the details are then circulated to the Office of National Statistics in order that if any of these individuals die we receive a death certificate.

The ethics of this study, when we originally started it, were that the individual

recipients of potentially contaminated blood would not be informed that they had received such blood. Although as you will know, that decision was reversed last year.

Now, this is the current situation. We have 149 cases of variant CJD, but 147 we have details of. Two of them are currently going through this system, although we know from the families that these two individuals were not said to have been blood donors.

The number who are eligible to donate -- that is, over the age of 17 years -- is 137. There are reported to have been blood donors and actually -- cases where actually donor records were traced -- 19, including one in whom the family had said they had definitely not been a blood donor, interestingly; 16 -- from whom components were actually issued was 16; and we have 50 recipients of labile blood products.

In terms of the blood donors, this is the year of death, and the total number of vCJD cases, the total eligible to donate. And all I'm really trying to show you here is that a number of donations were given over a period of many years, although a low number each year.

And this is the use of these transfusions.

This is the products that were transfused to the recipients, mainly red blood cells and mainly non-leukodepleted red blood cells, because this was introduced relatively late.

Now, I talked about this earlier in the year, but just to briefly go through this. Last December we received a death certificate from one of the recipients, which was received on the 8th of December, which mentioned dementia. All the previous death certificates we had received on recipients who had died had not mentioned any neurological disorder.

And this clearly raised the possibility that this was a case that could have developed variant CJD. The donor to this individual had donated two units at different times in 1996 when they were healthy -- a 24-year old. One unit went to a patient who died of cancer after five months. Platelets were included in a platelet pool, which has not been traced. And plasma from both donations were included in different plasma pools, and the donor died three and a half years later of pathologically confirmed variant CJD.

When we received the death certificate mentioning dementia, we had also received tissues on this case, and also had had a referral from the

relevant clinician.

In 1996, the recipient, who was then age 62, was transfused with five units of red cells, one from the vCJD donor, and in brief developed symptoms and signs that were relatively typical of variant Creutzfeldt-Jakob Disease. The MRI scan was normal, but the patient died 13 months after the onset of symptoms, which is more or less the average for variant CJD. And the post-mortem confirmed variant CJD Codon 129 MM with a Type 2 prion protein in Western Blot.

And I think I'll just briefly show you slides from James Ironside of the pathology in this case, showing the so-called florid plaques on H&E, and with immunostaining appearances that are totally typical of variant Creutzfeldt-Jakob Disease in the recipient.

And the Western Blot pattern showed the Type 2B pattern, which is seen in variant CJD and not in other forms of CJD. And this is just a graphic representing the distribution of the different glycosylation types of PrP. And this is the two samples from this case here in amongst the cluster of variant cases and the other sporadic cases over here. So we are confident that this is a case of variant

CJD.

The statistical analysis is always difficult when there's only a single observation. However, Simon Cousens did do an analysis which looked at the chances of an individual developing variant CJD through dietary exposure in the small population of recipients, and he came up with an analysis of 1 to 15 to 30,000. So we felt that this was a possible case of transfusion transmission of variant CJD, and that case was published in The Lancet earlier this year.

It did cause a lot of concern, and this was one of the newspaper headlines. And one of the reasons I thought I'd put this up is that you may have gathered we received the death certificate on December 8, 2003, and we immediately informed the Department of Health about this issue and there was an announcement by the Minister of Health on December 18th.

We have never and have no intention ever of trying to suppress any information about variant CJD or any other form of CJD. And I think I can assure you that if anything was happening we would make sure that it entered the public domain.

The second case was really as a result of a change in policy after this discovery, because the

decision was made that as of December 2003 there were 17 recipients of the blood transfusions from a vCJD donor who were alive. And the decision from the Department of Health and the Health Protection Agency was to inform all recipients of the risk, together with their general practitioners and the hematologists who had been involved with the blood transfusion.

In 2004, one of these recipients died of a ruptured abdominal aortic aneurysm. There was no history whatever of neurological illness. But because the clinicians were aware of the context in this case, a post-mortem was carried out, which included specific examination of the brain and peripheral tissues to determine whether there was any evidence of infection with variant CJD.

The recipient had received a blood transfusion in 1999. The blood had been donated by someone who was age 27 and was healthy at the time, and 18 months later the donor developed symptoms of variant CJD and died in 2001 with pathologically confirmed variant CJD.

And as far as the recipient is concerned, James Ironside and colleagues, John Bell, carried a post-mortem examination in this recipient, who I stress had no neurological symptoms or signs. Using

immunocytochemistry and Western Blot for PrP, the brain, spinal cord, tonsil, and appendix were negative. However, the spleen and one cervical lymph node were positive, consistent with infection with prion disease.

And just to put it in context, a very important question is using the same technique, so I must stress using the same techniques. What other experience do we have of the neuropathology and the general pathology systemically of other forms of human prion disease and controls? And at that stage, there were 56 other human prion disease cases that had been examined that were non-variant, and 85 non-cases, and all of them were negative in the same tissues using the same techniques.

So we believe that this is good evidence, the fact that they're stating at all that this is consistent with variant CJD.

And this is the spleen showing the immunostaining, which, of course, is much less marked than the previous sample. It may be that this individual was pre-clinical, was incubating the disease, and there may have been accumulation of PrP subsequently in these tissues.

And this is the Western Blot, and the

recipient spleen tissue and in controls, case sample 1 here, case sample 2 here. Variant CJD is a control on the right showing the same pattern which is typical for variant CJD.

The statistical analysis, again, is very difficult. Simon Cousens, again, agreed to do this. And in the absence of transfusion transmission, the chances of one or more in the recipient population, as I've said, making assumptions about age, is 1 in 30,000; the chances of two or more cases, about 1 in a billion, assuming that they're both transfusion transmitted.

However, we also can look at the appendix/tonsil data, which I presented earlier, and if you use that, if it were 5,000 individuals in the UK infected, the probability of two or more cases is about 1 in 80,000. So on both counts it looks as though statistically it is far more likely that these two cases are transmitted through blood than through dietary exposure. And I think for the purposes of public health, we have to assume that blood transfusion is a mechanism of transmission of variant CJD.

This was published, again, in The Lancet. And one important issue was that this individual was

Codon 129 heterozygous. So this is a patient who we believe was infected with BSE who had a heterozygous background, and this contrasts with our previous experience in variant CJD cases where 100 percent of tested cases have been MM.

And this suggests that the projections in relation to the future epidemic of variant CJD in the UK will have to be revised to take this factor into account, although I must stress we do not know that the individual heterozygote was going to develop clinical disease. And there's also a possibility that this individual could have been left in a carrier state. Of course, that's still very important for public health.

And just to summarize the current situation, we've had 32 deaths from variant CJD. There are two variables here -- the time from transfusion to the onset of clinical symptoms in the donor, with the presumption that the sooner before clinical illness the more likely you are to contain infectivity. And then, the survival -- that is, the followup period in this axis here in years.

And you can see that in those that die the great majority died within a very short time, within a year or two of the transfusion, of course, because

of the primary illness for which the transfusion was given. And we have some survive -- some individuals who live for longer before dying. One is the CJD case, and the other is the PrP positivity in spleen, five and six and a half years after the transfusion.

And here we have the surviving recipients, now 18. And you can see that these individuals have survived for a variable period, some up to 17 or 18 years. But the donation was given some 16 years prior to the onset of clinical symptoms in the donor. And the leukodepleted cases are here. And one of these individuals was an individual who received a blood transfusion from the same donor as the pre-clinical case.

The final thing I wanted to comment on -- and I hope I'm not going over time yet -- is the blood donations from variant -- nine variant CJD donors contributed 23 units for plasma fractionation. And with the identification of the second pre-clinical case, the authorities in the UK became concerned about this issue, although, as I'll say in a minute, for some years now we have been importing from the USA primarily plasma for the production of fractionated products.

And the decision was made in September to

-- on the basis of a risk assessment that some recipients should be informed that they may be at additional risk for developing variant CJD because of their treatment with plasma products. And this caused major concern, as one can easily understand, epidemic fears after thousands given CJD alert. And 6,000 get Mad Cow Disease warning. It is feared we may be facing a CJD epidemic.

The basis of this policy to inform these individuals was made by the CJD Incidents Panel and based on a risk assessment carried out by Der Norske Veritas. And I thought what I'd do is just go through some of these issues in brief, although I must stress that I am not a risk assessor or qualified to comment on mathematics.

The CJD Incidents panel has defined an at-risk threshold for public health purposes as the possibility of being exposed to a one percent or greater potential risk of infection on top of the general risk to the UK population that is thought to have resulted from dietary exposure to the BSE agent. That was the basic premise.

On this basis, the levels of likelihood of surpassing the threshold have been categorized as follows, and there are three levels. Number one is a

high -- the amount of potential vCJD infectivity is high enough for the threshold to be surpassed following the administration of a very small dose, e.g. one treatment with Factor VIII, Factor IX, or antithrombin where one vial of product used has been implicated.

Medium -- the amount of potential vCJD infectivity is not low enough to be ignored, but substantial quantities of the material in question would need to be administered before the threshold is surpassed. Several infusions of intravenous immunoglobulin G or large doses of albumin of 4.5 percent from pools that have contained a variant CJD donation. And all of the individual lots and batches have been traced.

Finally, low -- the amount of potential vCJD infectivity is so low that the likelihood of surpassing the threshold can realistically be ignored. Factor VIII products where the albumin excipient used the manufacturing process, and not the plasma concentrate has been implicated, intramuscular normal immunoglobulin for travel prophylaxis.

So that's how the categorization was done, and this was the actions in relation to each of -- each implicated batch of plasma, according to the

likelihood that recipients would have surpassed the at-risk threshold for public health purposes, I stress.

High -- the batches should be traced. Individual recipients considered at risk of variant CJD for public health purposes, and these individuals -- the intention was to inform them of this risk.

Secondly, medium -- this involves tracing batches and assessing the potential additional risk by looking at the volume of material that had been given. And if the threshold was exceeded, those individuals, the intention is or will be to inform them. But if the threshold is not reached, they will not be informed.

And finally, low -- the batches do not need to be traced. Individual recipients do not need to be informed. That's albumin 20 percent, intramuscular, normal immunoglobulin, anti-D, and etcetera. And there is a flowchart, which you won't be able to see very well. I must apologize about this, but this is a flowchart released the 7th of September for vCJD of plasma products that may be affected.

Recipients of UK sourced products down here, which are listed -- hemophilia, von Willebrand

Disease, etcetera. Patients will be contacted. Patients with primary immune deficiency will be contacted. A number of individuals will not be contacted, including those recipients of non-UK sourced products, which has been the position of the UK for some years now. And then there's the middle group in which an individual risk assessment has to be done.

Now, the CJD Incidents Panel recommendations -- there is also some text after this, and I will just read the cite again. I'm sorry, this is not a good way of presenting it, but I think it's very important to get this precise and accurate. For each of the major assumptions underlying the risk assessment, the most precautionary option was chosen.

The uncertainties underlying the assessment of risk are great, and several precautionary assumptions are involved. Therefore, the at-risk threshold for public health purposes is not a precise guide for advising individuals about their potential additional risk of developing vCJD. Very important.

So this is a public health move, because these individuals have been advised not to, for example, act as blood donors or tissue donors, to

avoid recycling of infection within the UK population.

Now, again, I'm sorry about this for people in the back, but this is the -- some of the tables form the Der Norske Veritas risk assessment, which is on the website here. This is a possible infectivity level that is transferred to patients from plasma pools containing a donation from variant CJD patient, and this is the infectivity in ID-50s per year for a range of products.

And one of the ones that comes out here is Factor VIII with -- down at the bottom with one ID-50 after one year's treatment, which is why I think the policy to inform these individuals was introduced.

However, as I've said, all the risk assessment -- the risk assessment contains a lot of variables with a lot of -- a range of potential outputs, and they have decided to use all the worst-case assumptions. And just to show you some of the variation -- I'm sorry this hasn't projected very well. But this is two alternative approaches in the risk assessment, for example, infectivity by a high approach or by worst-case scenario.

And there is quite a lot of difference. There's, you know, two logs difference in many of these assumptions. And I'm sorry, this one is just as

bad -- two alternative approaches for the dose of each product containing an ID-50. And, again, there's marked variation within this, within each product, depending on the assumptions that are made.

And I think finally, which might be more visible, this is a comparatant of the estimates of infectivity in plasma fractions, which, of course, is a very important baseline for making risk assessment. And there are a whole range of possibles here depending upon the assumptions that you make with cryoprecipitate here, Factors I, II, III in dark, and Factors IV and V, these light areas here.

So there's a huge range of possible assumptions you can make about the levels of infectivity before you start. And there's also, which I won't go on because of Hank Baron's talk, the estimated clearance fractions in plasma products -- again, with some variability between two sets of assumptions.

Now, having said all that, I thought I'd better just put it in the context of other European views from official bodies. And this is the French Agency for the Protection of Public Health and Medications. And this states -- this is from 2003, although I do believe that there is a further version

of this from this year, which has come to more or less the same conclusions I think.

The conclusions or recommendations of the report established in December 2000 remain valid. None of the items dealt with -- discussed in this report needs to be modified. No new measure to propose in relation to further reduce the risks of transmission of vCJD by blood products.

And, of course, one of the reasons for this is that the situation in the UK is unique. We have a very relatively high incidence of variant CJD compared to any other country. We do have evidence from the tonsil and appendix study that there may be people incubating the disease, and this may not be true for many other countries.

The measures that were recommended by AFSSAPS in 2000 were as follows -- reinforce measures potentially reducing the infectious load, e.g. plasma leukodepletion in addition to leukodepletion of cellular labile blood products, which has been applied in France since April 1998, and the addition of nanofiltration steps during the manufacture of some plasma-derived medicinal products, continue the validation of processes reducing the infectious load during the preparation of both labile blood products

and plasma-derived products, and maintain close scientific and epidemiological surveillance.

Then, there is the European Medicines Evaluation Agency, which in June 2004 provided a report which had considered the first presumption transfusion transmitted case, but not the second I must stress. And I'm just going to read three of the conclusions from this report.

It is recommended that donors who spent a cumulative period of one year or more in the UK between these periods are excluded from donating blood plasma or blood stroke plasma for fractionation. There is no recommendation to recall batches of information that would have excluded a donor based on his/ her stay in the UK becomes available post-donation, since this is a very conservative precautionary measure.

Secondly, this is an issue to do with the manufacturing process and to do with clearance factors. The rationale for this position is that if, in the future, further cases of vCJD occur in countries collecting blood and plasma for the manufacture of plasma-derived medicinal products, a process previously shown to be able to reduce TSE infectivity will provide reassurance on the safety of

past products and could help to justify continuing fractionation, which seems to be perhaps understandably slightly a different position from that taken in the UK.

And, finally, it is, therefore, recommended that donors who have spent a cumulative period of one year in the UK are excluded. Countries are highly encouraged to choose their national cumulative period limit for plasma-derived medicinal products according to a nationally calculated benefit risk balance, which will take into account the endogenous risk of BSE and the risk of shortages of blood and plasma for the manufacture of medicinal products.

Just to finish, the UK precautionary measures that have been taken -- withdrawal and recall of any blood components, plasma derivatives, or tissues obtained from any individual who later develops vCJD, which was taken in December in 1997.

Important of plasma from the U.S. for fractionation to manufacture plasma derivatives, announced May 1998, implemented October 1999. And perhaps one thing I should say is that the concerns that have been expressed this morning, and a bit later in the morning, are that it is clearly important that

from the UK's perspective and from the plasma recipients in the UK, that the blood that is obtained in the United States is itself at low risk for variant CJD. And the implementation of measures to ensure that such appropriate screening take place is very important.

Look at depletion of all blood components announced July 1998, implemented autumn 1999, importation of clinical, fresh-frozen plasma from the U.S. for patients born on or after the 1st of January 1996. That is, individuals who are presumptively not exposed to dietary BSE, announced August 2002, introduced in spring 2004. Of course, promotion of appropriate use of blood and tissue as an alternative throughout the NHS.

And, finally, transfusion recipients deferred as blood donors in 2004, of course, again with the idea of breaking the potential cycle of reintroducing infection in the UK population.

So, conclusions. I think vCJD now should be regarded as transmissible through blood transfusion for public health purposes, and I think the scientific evidence is now fairly convincing.

One important issue is that precautionary measures in relation probably would have taken years

in advance of evidence of transfusion/transmission in the UK, and, of course, in many other countries including the USA, which Dr. Asher showed the long evolution of such measures here.

Predictions of the future number of cases of vCJD in the UK may have to be revised. And we believe that humans with -- who are heterozygote at Codon 129 PRNP can be infected with BSE, although we do not know whether they will have any clinical expression of disease. And I think difficult decisions will arise if vCJD blood donors are identified in other countries.

I don't have a slide of acknowledgements, but I shall just state that the Transfusion Medicine Epidemiology Review has really been the responsibility of Pat Hewitt and Charlotte Llewelyn from the National Blood Service, who have worked very hard on this for years. And also Jan McKenzie at the Surveillance Unit.

And the final comment, which I think is very important and I always make it, we could do none of these studies without the cooperation of the families of cases.

Thank you.

CHAIRPERSON PRIOLA: Thank you, Dr. Will.

Are there any questions for Dr. Will from the Committee?

DR. BRACEY: In terms of the patients that expired -- the 32 -- are there any autopsy or necropsy specimens that haven't been studied but could be studied?

DR. WILL: Well, it's a very important question, and it relates to the ethics of the study. When we flag people with the Office of National Statistics, we have to go through an ethics process, quite rightly, and the ethics guidance from that is that any individuals who are identified through that process cannot be contacted, and neither can their clinicians.

So we know that the 32 individuals died, but we have no further information on them, including post-mortem results.

Now, whether that ethical position should be reviewed in the light of recent scientific developments is a very important issue. One thing I can say, however, is that we do know that none of those 32 individuals themselves acted as blood donors. So it's a very important question that is under consideration.

CHAIRPERSON PRIOLA: Dr. Nelson?

DR. NELSON: Hearing you describe trying to trace these cases led me to one question. Does the UK have a computerized registry of donors that could be used to facilitate the lookback? Because it seems this would help.

DR. WILL: Well, my understanding is that computerized systems for the blood transfusion service were introduced in the UK many years ago. But I can't exactly remember the right date, maybe around -- actually, I'd better not say. All I can say is that this means that for the variant CJD donors, all of whom are young by definition, we have good access to data and can get followup data.

We are carrying out a similar study in sporadic CJD, but the absence of records in the '80s and '70s and prior to that has made that extraordinarily difficult, because many of these individuals are in their sixties and seventies when they die, and it is found they may have donated blood 30 or 40 years ago.

So the answer is: we have -- there is a good computerized system for tracing donations within the UK, but it is time-limited. It doesn't go back forever.

CHAIRPERSON PRIOLA: Dr. Bracey?

DR. BRACEY: Yes, another question in terms of the -- I guess the 17 recipients that are still alive, 16, whatever the number is. Very interesting information has been presented in terms of some potential -- obviously, they're still under investigational research assays that could be applied to blood. Has there been any thought in terms of, you know, doing those sorts of minimally-invasive assays in that group?

DR. WILL: Well, again, a very important question. Current ethical guidelines do not allow us to contact those individuals. However, clearly, it may be that some of those individuals would want to contribute to scientific research. And we are actively considering exactly how to proceed with this in the light of proper ethical guidelines.

CHAIRPERSON PRIOLA: Dr. Salman?

DR. SALMAN: Yes. The question is about the sporadic CJD. What type of results you are obtaining to parallel the results you are getting with the new variant CJD?

DR. WILL: Well, I don't have the figures to hand. All I can say is that the number -- in that lookback study, we have a very limited number of individuals in which we've been able to trace the

names of the recipients and find out what has happened to them subsequently.

To date, in that study with very limited numbers, we have no evidence of transmission of sporadic CJD in the light of what we have found with the variant cases using the same methodology. But I have to say I think there is a study going on in the United States that's very much more powerful than our study that was reported at the February meeting in which they had fairly large numbers with quite a long followup period.

So our data is very limited, unfortunately, for the methodological reasons I've explained.

CHAIRPERSON PRIOLA: Dr. Sejvar?

DR. WILL: I'm sorry?

PARTICIPANT: When will those be reported?

DR. WILL: Oh. They're going to reported again today.

DR. SEJVAR: I'm sorry. You may have already, you know, mentioned this. But given the ethical considerations, how was the pre-clinical second transfusion case identified or come to autopsy?

DR. WILL: After the identification of the first presumptive transfusion transmitted case, the

decision was made to inform the patients and the doctors of the surviving recipients. So it meant that when the individual died of an unrelated illness there was clearly an incentive with consent from the relatives to carry out a detailed post-mortem to see whether there was any evidence of infection with variant CJD. And that's how it happened.

CHAIRPERSON PRIOLA: Okay. If there are no more questions, we'll move on. Our next speaker will be Dr. Steve Anderson.

DR. ANDERSON: I was going to say good morning, but it's already afternoon. So good afternoon.

My name is Steve Anderson, and I'm the Associate Director for the Office of Biostatistics and Epidemiology in the FDA's Center for Biologics Evaluation and Research.

So today I'm going to talk about comparing transfusion risks for variant CJD and CJD transmission via blood. And at the end of the talk I'm going to mention some of the risk assessments that we're currently developing to look at some of the TSE risks for blood products in the United States.

Animal data have suggested that both variant -- that both CJD and BSE can be transmitted

via blood. Now, I've listed a couple of examples here of animal systems and the types of agents that have been tested. For instance, sheep and BSE -- that's both been done by Houston and Hunter in the same group, as well as scrapie.

Dr. Rohwer's group has looked at hamsters and scrapie. And I believe you reviewed his work in the February 2003 meeting and in the previous meeting as well. And then there was work done in mice with CJD and showing transmission via blood in all of these animal systems with these particular prion agents.

Now, I'm not -- I have slides on the particulars that Dr. Will just spoke of, so I'm actually just going to sort of flash them and say you already -- we already know about these two particular patients in December 2003 and July 2004. And he has explained far more than I know about them.

I'm not going to discuss any of the particulars of the surveillance program, the TMER study that Dr. Will just discussed, but will mention it at the end of the talk when I talk about the little example comparison that we've done.

Now, I just wanted to remind people about CJD and blood epidemiology. Just to remind people that the incidence -- it's a very rare disease. The

incidence is about one death per million population per year. It occurs largely in older individuals and has a long incubation period.

The current evidence suggests that CJD transmission via transfusion is considered a low risk. Now, I think it's important to mention as well that if the transfusion risk was significant, one might expect to see an increase in the CJD rate annually, or the disease might increasingly be seen in younger and younger individuals.

However, the CJD rate has been essentially stable for the last 10 to 20 years in the U.S., and I believe in other countries in Europe where monitoring has been taking place.

And we're going to receive a talk this afternoon on the American Red Cross-CDC lookback study, so I'm not going to go much into the details of this. The current lookback study just tracks 368 individuals who received blood from donors that later were diagnosed with CJD. I've just received an update that it's 118 of the recipients, instead of 116 of the recipients, have lived longer than five years post -- greater than equal to five years post-transfusion.

And approximately 28 percent of those individuals, or 102 recipients in the study, are still

alive. And to date, there have been zero observed CJD infections observed in the study. And I think that's an important concept to reinforce, that if -- it is possible that this event could occur, but at the very least we're looking at something that's a very potentially rare event.

And our interest as well is in -- as a risk assessment person, we're interested in the hemophilia populations that are potentially at risk as well. Those that use -- frequently use blood or plasma derivatives might be at higher risk for contracting CJD, variant CJD, or a number of potentially other prion diseases.

CDC has done a study, and they've talked about this at the previous Advisory Committee meeting -- again, the CDC study was 12,000 hemophilia patients that they looked at, and they also looked at 40 decedents. Again, no observable CJD to date in that patient population.

And the UK also did a similar study, although smaller than this one. They specifically, I believe, looked at 33 autopsies of hemophilia patients in a post-mortem study. Again, no indication of variant CJD or CJD in that population.

I'm just going to breeze through to get to

the comparison. So for our comparison, again, this is just an example. There are a lot of comparisons that we can use. We could look at comparisons among the animal data -- the human data and the animal data.

What we're doing here is we're looking at a comparison between the variant CJD populations that are under surveillance that have given blood, and we now have recipients that have received those blood products, and then the American Red Cross-CDC lookback study.

Again, the numbers -- for our interest, I'm going to -- we're going to keep with 116, since that's what I had in the slide -- 116 in zero observations, and so far 15 in two observations for the variant CJD study.

And if we set this up in a simple matrix and look at it, I've done a very rudimentary statistical analysis, and I'm glad to see that Dr. Will has done -- and the UK risk assessment people have done a nice and actually more precise analysis than what I've got here. So this is pretty crude and rudimentary.

But what we're seeing -- what we would say is that the -- based on this information, there's a small probability this would be actually less than or

equal to 1.2 percent that variant CJD cases occurred by chance. And as Dr. Will just stated in his talk -- and I'll sort of try to remember those numbers -- I believe his population estimates were much more precise, and he estimated that across the population the chance occurrence of two of these types of events occurring through, say, a source like food exposure would be something like one in a billion.

And based on the tonsil study, you could adjust that as well, and that would be -- I believe he quoted a number of 1 in 80,000. So I think the conclusion that you draw from these types of analyses is that it seems clear that these variant CJD cases are arising because of transmission transfusion of variant CJD from donor to recipient.

And I think there are a lot of caveats to doing these types of analysis. That's why we haven't really done a lot of in-depth analyses, because the power in the -- the statistical power of these studies is really limited, and there are a lot of limitations.

The size of the groups that we're looking at are relatively small, only 15 patients in the case of the variant CJD surveillance. The incubation period of the disease is long. And I think that's important given that most blood recipients are very

sick individuals, and they usually have a high mortality rate two or three or five years out. So their chances of survival are -- often exceed the incubation period of these long incubating prion diseases.

All right. So as a risk assessment person, I tend to look at weight of evidence approaches when I'm doing my risk assessments. Now we've got two pieces of important information. First, we had a clue early on that animal transfusion transmission was possible, and now we've got these two cases.

So what we're working with now is that it seems like variant CJD transmission transfusion is a reality essentially, and we've got to treat it like that. This is a very important public health issue that we need to monitor and evaluate very carefully.

So what we're doing at FDA is we're developing risk assessments for blood products in the United States. Specifically, we're starting with Factor VIII, and we did present a preliminary risk assessment for Factor VIII products at the February 2003 meeting of this Committee. We'll probably move on and do Factor IX, and then other important blood products as well as we complete the initial analyses

on Factor VIII and Factor IX.

I think the important thing to take away is that these risk assessments evaluate TSE risk for blood products. They help us identify risk reduction measures. And not only that, but evaluate the effectiveness of those risk reduction measures. So it's part of a plan of reducing the risk, and the public health risk that could arise from variant CJD or CJD possibly transmitted through these products.

I will end with that.

CHAIRPERSON PRIOLA: Any questions for Dr. Anderson from the Committee? Dr. DeArmond?

DR. DeARMOND: How far along are your -- the risk assessment of Factor VIII?

DR. ANDERSON: I would say it's probably midway through. And we've got some initial results from that, and we would say -- I think Dr. Epstein alluded to before that the estimates, preliminary estimates anyway, are that the risks in the United States are significantly lower than they would be for the UK.

DR. DeARMOND: What sort of Ns -- how many individuals, or how are you doing that assessment?

DR. ANDERSON: We're looking specifically for Factor VIII, looking at the hemophilia

populations. So we're starting out with actually back calculations for the potential number of individuals in the United States that could have variant CJD or CJD, and then could donate blood into a plasma pool. And from there we're looking at the plasma processing steps and the reduction steps to the TSE agent in there.

And then, finally, looking at how patients utilize those products, and trying to determine their, you know, annual risk and individual risk. So that's a quick --

CHAIRPERSON PRIOLA: Dr. Nelson?

DR. NELSON: Are you considering the source of the donors of the Factor VIII or blood products? In other words, clearly, there is a greater risk of a UK donor, even in the past. And how are you adjusting your analysis for that factor?

DR. ANDERSON: We're actually including that. We have -- in our back calculations, what we're doing is we have actually a fair number of populations in the U.S. that are potentially at risk. So there's the background risk essentially, potentially in the United States, of BSE risk. So that's put into the model.

And then there are all the populations

that have traveled and meet the criteria for the deferrals that are in this study as well -- military and their dependents, and immigrant populations as well. So it's a pretty -- we're trying to include as much of that information as possible.

I think the important question that came up was: can we measure evasion or people not honestly answering questions? And we could put that in if we had a better measure of that parameter, but we don't have that exactly in it now, so -- I believe our -- the effectiveness of the donor deferral policy, we have a range of 75 to 90 percent effectiveness on that.

DR. NELSON: The REDS study may have some data on that. And, actually, you know, they have looked at people who have -- who test positive who on retest how many have --

DR. ANDERSON: Not honestly answered the questions.

DR. NELSON: Yes. But I don't think they've done it for geographic risks and BSE risks yet. But I think that might be a priority, actually.

DR. ANDERSON: We'll consider it, certainly.

CHAIRPERSON PRIOLA: Dr. Gambetti?

DR. GAMBETTI: Could you just remind us on the -- how, really, the CJD was excluded in that study of the American Red Cross and CDC study -- and CDC on transmissibility of CJD by blood transfusion? In other words, was only -- I understand that there's a considerable number of cases still alive, but was any autopsy performed on those --

DR. ANDERSON: For the lookback or for the hemophilia?

DR. GAMBETTI: The lookback study.

DR. ANDERSON: I think I'll let -- Larry, do you want to answer that? Sorry.

DR. SCHONBERGER: The lookback study is basically looking at death certificates, cross-checking the recipients that are identified who have received a component from a CJD donor, going to the hospital, getting all the identifiers, and then cross-checking with the death index to find out: a) whether the recipient died, and then, b) much as was done in the UK, find out whether there was any neurologic disease identified.

And the actual numbers -- he had it in one table -- greater than three years, which the 116 was greater than or equal to five years.

DR. GAMBETTI: Five. Five.

DR. SCHONBERGER: But in the next table it was -- comparison was greater than three years. And that would give you another -- make it 128 patients, just to give you some sense of how the numbers would change as you increase the period of followup or decrease that period.

The hemophilia situation was done differently. That -- I think DeArmond was -- had volunteered to take any death from a hemophilia patient, with or without any neurologic symptoms, but any death where there was a -- where they would volunteer to donate the brain tissue for detailed exam, looking, in essence, for a pre-symptomatic lesion of CJD in the brain.

And, DeArmond, you may want to comment. I think most of them were AIDS.

DR. DeARMOND: This is before we understood about the spleen and other organ involvement in some of the acquired forms of CJD, variant CJD. But these -- we looked at the patients that had neurological symptoms, and they died either of a Hepatitis-related -- Hepatitis virus-related neurological disorders -- that is, hepatic encephalopathy or AIDS-related disorders. And we didn't see any abnormal prion protein or vacuolation

that would suggest a prion disease. It's a relatively small population.

DR. SCHONBERGER: Right. So these are people, then, who didn't have a clinical diagnosis of CJD who are hemophiliacs, and then having their brain studied by Dr. DeArmond to make sure there was no sort of silent lesion.

DR. DeARMOND: In fact, they did have lesions, but they weren't lesions --

DR. SCHONBERGER: Of CJD.

DR. DeARMOND: -- of CJD. They were the AIDS-type lesions, progressive multi-focal leukoencephalopathy and things like that.

CHAIRPERSON PRIOLA: Okay. Thank you, Dr. Anderson. We'll move on to the last talk of this late morning/early afternoon session, and that's Dr. Luisa Gregori.

DR. GREGORI: Thank you. This presentation will focus on removal of TSE infectivity from blood using leukofilters.

It is known for some time in the literature that TSE infectivity in blood is concentrated in a buffy coat. If we take whole blood -- infected whole blood and spin it around to prepare the three major components -- plasma, buffy coat, and

red cells -- and then each component is titered, we find that there is a level of about 30 percent of infectivity found in plasma, 45 percent in buffy coat, and the rest is the red cells.

This type of distribution was quite a surprise result for many people, because we are used to seeing that TSE infectivity is cell-associated. And this 30 percent here with infectivity was kind of strange, but I'll come back to that point later.

Some one of the first things that we were interested in is to identify the cellular component that is involved with TSE infectivity. The first component, the first cell type that we looked at, were platelets. We did this work with -- in collaboration with Holada and Vostal at the FDA. They are platelets experts, and they came to our lab. And two to five platelets from infected blood, and we noted that these platelets and look at the infectivity, and we found that there was no infectivity platelets.

So we kind of said, "Okay. Platelets are out." Red cell -- they are not really -- there is no evidence in the literature indicating that red cells might be in a -- carry infectivity, and we have a study now ongoing in our laboratory that I think will definitely confirm, and that red cells are not

involved with TSE infectivity.

So that pretty much leaves out the white cells. So the question is: white cells are the only component that carries infectivity. This is one of the bases for the leukofiltration. Red cells seems to be the -- at that time looked like it was the major carrier of infectivity, so the deal was if we remove white cells, and then we remove infectivity from blood.

That's despite the fact that there was quite a significant portion of infectivity found in plasma, as I mentioned earlier. But people was thinking that that infectivity in plasma was perhaps contamination from white cells or cell debris or something like that.

One study -- actually, more than one study that was reported in the literature shows that if plasma from infected blood is centrifuged at a high speed, and the supernatant is tested, there is no significant removal infectivity, indicating again that that type of infectivity might be in a soluble form or in -- not cell-associated I should say.

There were also two studies done, present in the literature -- one by Paul Brown and co-workers, and one by Prowse and Bailey, looking specifically at

leukofiltration. This study has been around for some time. I'm not going to describe them in details. All I want to do at this point is summarize their findings.

For the first study, they used infected plasma from mice infected with TSE and they filtered plasma through a plasma platelet filter, and they found that there was no removal of infectivity by the leukofilter. The second study was done in a very different manner. They tested four whole blood commercial filters, and they challenged the filters with a unit of human blood spiked with PrPres from hamster brain.

And then they looked at the -- what was filtered at the leukoreduced blood in terms of PrPres removal by Western Blot. And in that case also they found no removal of PrPres by any of the leukofilters they tested. So that was the first indication that there might be something going on in there that perhaps leukofiltration might not be removing all the infectivity in blood.

However, many countries had decided to adopt leukofiltration and implemented it as a universal leukofiltration. And one of these countries was Canada, and Tony -- Dr. Giulivi came to us and he

wanted -- he's from Health Canada, and he wanted us to do a study to see if we could show whether we could test whether the leukofilters did remove TSE infectivity.

We were also considering that leukofiltration could not be considered the perfect solution until we actually demonstrated and make a validation study. So we were very glad that Tony came to us, because we could do this experiment with Health Canada.

The validation we decided to do -- we had to decide what kind of challenge to use for these filters. We couldn't think of any spike that we can prepare that would be a valid spike. So we decided to do without spike. We will do endogenous TSE infectivity in blood, and this will be the challenge.

We also, for the same reason, we did not want to scale down the study, so we did a full unit of scrapie hamster whole blood. And at that point, then, we used all of the same protocol and treatment used at the blood centers in Canada. The Canadian -- Health Canada has adopted two systems of leukofiltration, one for whole blood and one for red cells and platelets.

The whole blood is shown here. Here is where usually human blood will be collected. We did

not put human blood. We collected one unit, about 450 mLs, of hamster infected blood. This obviously was pooling, because that -- one hamster has four mLs of blood. So that's about 130 to 140 animals. So the blood was pooled. This was leukofiltered. This is a Pall leukofilter, this online filter.

And we collected leukoreduced whole blood here, and this, then, we continued to prepare red cells and PPP fraction. So this was the first leukofiltration unit that we tested.

We also tested a second one, as I said. This is -- has two filters and is a more complicated -- this is another unit of hamster blood. We first centrifuged this unit, and then the supernatant, as it's called, in platelet-rich plasma was passed through this filter, the platelet filter. And the red cells was passed through the red cell filter. And then we continued to prepare all the rest of the fractions and components.

We did not titer this, so I'm not going to show you data about -- I'm referring to this particular filtration, but I'll focus on the filtration that I showed you earlier on whole blood leukofiltration.

The first thing that we had to demonstrate

to ourselves and to everybody, that the leukofilter that is specified and designed for human blood would perform the same way with hamster blood. We didn't know that at that time when we first started.

So to demonstrate -- to make this demonstration, and to verify that we could actually do this type of experiment, we used the AABB -- the American Association of Blood Banks specifications, and we tried to meet all their specifications. So we collected one full unit, about 250 mLs of hamster infected blood in a few hours. These animals were all at the same clinical stage, and they were obviously pooled.

The blood was processed within eight hours from collection, which is one of the AABB specifications. So we were able to meet the time specification.

We also looked at removal of white cells that should -- it has to be at least three logs of white cell removal. Also, the AABB specification indicates that a leukoreduced red cell component must contain at least 85 percent of the original red cells and cannot contain more than 5 times 10^6 white cells.

So we measured the white cells in hamster blood before and after leukofiltration, and all of the

other fractions. The method that we used is a cell counter calibrated for hamster blood. This cell counter is a HemaVet and has the capability of doing five-part differential.

We also measure the cell count in the leukoreduced fractions by manual count and by flow cytometry. The flow cytometry was done in Health Canada, and they stained white cells with propidium iodide. We did not measure cell fragmentation in microvessels generation. This was one of the concerns that the Scottish National Blood Service had, and they published a paper sometime ago indicating that the leukofilters do not produce this effect.

This is the activity of cell removal. As I said, we had to -- we had to show what kind of white cell removal we obtained with this filter that was used with hamster blood, and also all of the other recoveries. So here are the -- this is a lot of numbers. I'll just focus on a couple numbers here.

Those are the fractions that we tested pre -- whole blood pre-filtration, whole blood post-filtration, PPP, and red cells. This is platelet-poor plasma. And this is the recovery for the white cells, the recovery for the red cells, and the recovery for platelets.

The first thing is the recovery of -- no, the removal of white cells after leukofiltration. It's 2.9, and 3 was our target, so we are close. The removal of white cells -- the contamination of white cells in the red cell component has to be less than 5 times 10^6, and it was.

And, lastly, the other AABB specification is that the recovery of the red cells must be more than 85 percent of the original red cell content, and we obtained 86 percent. So from this observation and data we concluded that this study could be titered, because the cell recovery and white cell removal was according to the specification of the AABB.

And, therefore, we proceed into the titration of the two fractions -- the pre-filtration, the whole blood pre-filtration, and aliquot of the whole blood post-filtration, the leukoreduced whole blood.

The titration was done using the limiting dilution titration method that I'll talk in a minute. More than -- about 100 animals were titered -- were used for each titration. That's about 5 mLs. The titration was completed after 566 days post inoculation, and the brain of every animal was analyzed by Western Blot.

This is something that we routinely do in our laboratory for validation studies, and the purpose of this Western Blot is to -- there are two purposes. One is to confirm the clinical scoring; and, second, is to see if any of the animals that are sacrificed at the end of the study were actually incubating TSE.

Occasionally, we find that some animals were pre-clinical, and we can pick up the PrPres by Western Blot in their brain. In this particular study, there was none of those animals pre-clinical, so there was a complete match between the Western Blot results and the clinical scoring on the animal.

This is a slide you might have seen before. This is the limiting dilution titration method. This is a method that was developed in our laboratory, and this is used in the titration of solutions with very low level of infectivity.

The way it works is rather simple. We have an animal that is the donor. This animal has somehow been infected, so the -- we take the blood from the donor animal, and then we inoculate this blood -- let's say, we take 5 mLs of -- this one animal has only 4 mLs, so this has to be at least two animals to do this.

(Laughter.)

So the incubation -- we inoculate 5 mLs, 50 microliters each, into 100 animals. Then we wait the time for the disease to take its course, and then, at the end, we count the number of animals that are infected. Let's say in this case there are 44, so there were 44 infected in 5 mLs of blood. That's 8.8 infectious doses per mL.

This number then has to be corrected for the distribution that takes into account the probability that one animal received two doses of infectivity. And that usually increases the value a little.

So this is how we did our titration. That's how we do all our titrations for blood or blood components. This is just to show you the distribution of incubation time of all the animals that were in this study. This is whole blood in red. This is the post-leukoreduced whole blood in blue. Those are -- here in gray are the animals that were sacrificed at the end of the study. And they were all normal. And the square -- the triangle one are the animals that died of not scrapie during the incubation.

This is the results. I noticed earlier that in the handout that you have this table didn't come out. I apologize; it was not intended. But this

table is in the publication, The Lancet publication, so you can see it there.

The whole blood -- those are the two fractions that we titered -- whole blood and leukoreduced whole blood. This is the volume we inoculated, the total number of animals that we inoculated, the animals that came down with the disease.

This is the titer that we found for whole blood and pre- and post-leukofiltration. This has been adjusted for Poisson distribution. So what this means -- and this is the fraction distribution of infectivity, what this means -- it means that 58 percent of the total infectivity that we started with was still present in the leukoreduced whole blood.

Or another way to put it is that about 40 percent of infectivity was retained by the filter. And this is about the same percentage of infectivity that we found -- we find if blood is separated by centrifugal force in the buffy coat.

So we think that these two results are pretty much consistent with the removal -- with some part of infectivity being present in white cells, either in buffy coat or stuck to the leukofilter.

That also -- we also think that the post-leukoreduction infectivity is most likely in plasma, and that, therefore, the infectivity in blood is present at least in two forms -- one associated with white cells and one in plasma.

There were also some other conclusions that we draw from this study about the -- we were worried that the infectivity may wash off or be liberated during leukofiltration. We did not find this to be the case.

The implication is that leukofiltration we think is necessary but not sufficient to remove all blood-borne TSE infectivity. In this specific case, we have almost 6,000 units in one unit of hamster blood that I showed you, about 6,000 units of infectivity. At the end, we find more than 3,000 in the leukoreduced blood.

So it -- post-leukoreduction infectivity is not cell-associated, and, therefore, we think there is a need for additional methods to remove TSE infectivity.

And I close with this.

CHAIRPERSON PRIOLA: Thank you, Dr. Gregori.

Are there any questions for Dr. Gregori

from the Committee?

It was very clear. Thank you.

Are there any other -- do any of the Committee members have any other questions for any of the speakers this morning before we break for lunch? It appears we need to break for lunch.

(Laughter.)

So we'll reconvene here. We'll take an hour. We'll reconvene here at 1:40.

(Whereupon, at 12:43 p.m., the proceedings in the foregoing matter recessed for lunch until 1:50 p.m.)

DR. PRIOLA: I guess we'll go ahead and get started with the afternoon session. And our first speaker will be Dr. Peter Ganz from HealthCanada.

DR. GANZ: Good afternoon. I'd like to thank the TSEAC Committee and FDA for giving HealthCanada an opportunity to share some of our recent thinking in the area of variant CJD in risk-reduction measures for the blood system. And thanks for a very, very broad title on the agenda. I'm actually going to focus the talk primarily on variant CJD and not CJD and I also note that Dr. Ron Rogers, we've had a couple of presentations previously at this Committee concerning BSE and some broader TSE issues

in Canada over the years. So I'm not going to retread old territory.

And again, I'm not going to spend a lot of time. I know that you've had a very good overview of many of the variant CJD issues in previous presentations, so I'm not going to spend too much time on background material.

In terms of worldwide numbers of cases, as Dr. Will remarked, there was a case in Canada and again what's of interest is that if there had been deferral measures at the time that would not have been an individual who would have been eligible to donate and that one case is one that is not indigenous to Canada.

Very generally, risk mitigation efforts in Canada certainly mirror those elsewhere. Globally, there are very, very general TSE control measures that have been in place since 1996 and as I mentioned, I think last year, Dr. Ron Rogers sort of summarized some of those control measures very generally for this Committee. There are food chain control measures that have been implemented. And also, there's a very, very active surveillance system, not just for animal TSEs but surveillance for CJD very, very generally. And Canada is very, very active internationally on the

surveillance front.

For the blood system, a couple of points I'd like to try and make with regard to background. Since 1996, HealthCanada has carried out a number of various risk assessment exercises and had consultations and internationally regarding variant CJD risk issues and managing those. In a nutshell, the summary of all of the risk assessments and consultations has been operationally that HealthCanada exercised our precautionary principle, primarily, because we were dealing with theoretical risks and put in place geographic travel and residency deferrals that were again based on theoretical risk of transmission. And again, those needed to be balanced against the loss of available blood supplies.

Also, for the blood system and again, I want to emphasize quite clearly that for reasons and benefits not related to reducing variant CJD risks, HealthCanada issued a regulatory directive in November of 1998, requiring that blood system operators implement universal pre-storage leukoreduction and in fact, as of June 1999, all blood in Canada has been leukoreduced. And again, I am, I guess cognizant of the recent publication which we sponsored that by Gregori, I guess there will be another presentation

later indicating that at least in The Lancet article that 42 percent of the total TSE infectivity from blood may be reduced by leukoreduction. So perhaps in hindsight, this might be a valuable measure.

Now when we went forward with the series of directives that we had put in place, we had a commitment that was made that we would periodically review any new scientific data and consider amending deferral measures, based on new information. And again, we've had some presentations already today concerning data from experiments in animal model systems indicating that there can be transmission via blood and again we've had summaries already, fairly detailed summaries indicating the two more recent published studies showing CJD infection in individuals who received blood components donated from patients who died of variant CJD.

Now with regard to deferral measures in place in Canada, again in August of 1999, we issued a directive and primarily focused on reducing risk from individuals who lived and resided in the U.K. for greater than six months. We did a number of theoretical risk assessments and I believe Dr. Tony Giulivi at one point from our program area did discuss this at either BPAC or TSEAC and based on some of the

theoretical risk reduction numbers, we feel that that particular measure reduced our theoretical risk to levels greater than 80 percent. However, the cost of doing that at the time was about 3 percent of our donor base in Canada. And that was originally predicted and there have been some follow-up surveys and I believe that the actual numbers are pretty close to 3 percent which was really the buffer in the blood system in Canada that we could accommodate. So between our first directive and leading to the present day, there's been a huge effort on the part of our blood system operators, Canadian Blood Services and Hema-Quebec to recruit new donors to basically replenish our donor base.

In September of 2000, based on, at the time there were three deaths due to variant CJD in France. We felt that the risk wasn't equivalent to the U.K. risk, but there was still a risk and we felt that it would be prudent to look at again, geographic deferral for France. That was implemented and again, there was -- the donor base erosion was again -- it was somewhat less, around 1 percent, depending on which part of Canada, whether it was Province of Quebec or elsewhere. And again, there was a slight reduction of 5 percent or so of what we believe in

theoretical risk reduction.

In August of 2001, we again broadened the geographic deferral slightly, and in fact, asked our operators following a very successful and unprecedented donor recruitment effort, asked them to consider whether or not it might be possible to yet further reduce geographic risk reduction, geographic deferral in the U.K., France and also to consider a broader Western Europe deferral and again, that was done and was carried out. And in fact, within the Province of Quebec, based on their donor demographics and that's the area serviced by Hema-Quebec, we have a one-month deferral for the U.K. So we've tightened the deferral here yet further.

All in all, we feel that we have a greater than 92 percent theoretical risk reduction with these kinds of measures and again, there have been obviously consequences in terms of numbers of donors deferred. Also, very importantly, we decided with the directive in August to include individuals who have ever had a transfusion in the U.K. and that includes labile blood components such as platelet, red cells or plasma. And again, that's irrespective of the travel and residency deferral.

So that's really where we are today in

terms of blood system deferral measures. And again, as I indicated in a couple of slides earlier, we are looking at what are the options for reducing risk yet further and are there such options available.

And again, I want to emphasize we don't look at deferral measures very lightly in the sense that it is a rather onerous process to do for the operators and does have consequences for blood supply globally, generally.

One option obviously is to maintain the status quo. The risk reduction measures that are currently in place in Canada could be considered as adequate and we would just assume that we have -- we're at the stage now with our current directives that our system is as safe as it can be, given risks.

A second option is to consider more stringent travel residency donor exclusion policies such as reducing the time spent in the U.K. to less than three months, reducing the time span in Western Europe to less than five years and also to look at whether or not we can reduce yet further the travel residency requirements for France to less than three months. So that -- those are options we're looking at.

Another option is to -- whether or not it

might be prudent and again this touches a little bit on Dr. Asher's slide earlier is to consider in terms of human to human risk, whether or not one could consider excluding individuals who ever received a transfusion in Western Europe, including France since 1980. So that would be a consideration to broaden our transfusion deferral which is currently for U.K. broaden it to include France and Western Europe.

So those are the options that we're currently looking at and also I want to emphasize yet again that any kind of changes such as those in option 2 or 3 would have to consider the potential to create blood shortages, because the risks that we're looking to manage are incremental.

We've had a number of consultations on these various points, certainly with the blood system operators in Canada, Hema-Quebec and Canadian Blood Services. Obviously, a first step to these considerations and moving forward with these would be to look at our existing donor demographic data, particularly concerning options 2 and 3 and I guess ascertain whether or not those data are good enough data for decision making or whether or not a more recent donor demographic survey would be warranted.

The impact of proceeding with option 3 on

the blood donor base and that's the option to debar individuals who have ever received a transfusion of labile components in Western Europe, including France, appears to be minor, at least based on the number of deferrals that were currently, that are currently in place for United Kingdom transfusions.

We've -- similar to the U.S. and many countries, our Expert Advisory Committee on Blood Regulation met late in September and we had an opportunity to discuss a couple of the new recent findings and some of these issues with our advisory committee and I think that there was, and we'll have minutes available on our website in a couple of weeks, but basically we -- there was, I think, some good discussion around a number of these options and I think that there was some reasonable strong opinion that we -- that option 1, the current status quo was probably not acceptable and that were opportunities to move forward.

What about the way forward? Well, certainly we're at very early stages with considering these issues and that we have committed to further consultation not only with the members of the general public and interest groups, but also with the blood operators. We are currently in a situation where both

operators are going to look at their donor demographic surveys yet again, the ones that were carried out initially and again, with regard to trying to tighten the very general geographic deferrals which include the U.K., France and Western Europe. Based on the old donor demographic survey, it appears as if that latter option would have a significant impact on the donor base. In other words, the numbers, particularly for the U.K. for most of Canada, if you were trying to reduce from a three month to a two month deferral, we'd be looking at cost of about 4 percent of our donor base for just a one month tightening in that area and for some of the other options within that broader option, again, the cost to the donor base seemed to be fairly significant.

With regard to an option to debar donors who've ever received transfusion of labile component in Western Europe and France, we again need to -- initial discussions with operators indicate, again, based on what we're deferring now for U.K., it appears as if that would cause a minimal impact in terms of donor base and so that also is being looked at.

I think this is pretty well my concluding slide, but certainly in the discussions to date and our thinking to date, is that the impact of moving

forward with deferring donors who have ever had a transfusion in Western Europe would result in debarring a small number of donors against the benefit of having -- risking the Canadian blood supply being reduced by a small degree below the level that's affording with the current three directives that we have in place.

So that is my last slide and certainly some of this will appear in either on our website in terms of meeting minutes and we'd be happy, certainly, to update as time goes by.

Thank you very much.

DR. PRIOLA: Thank you, Dr. Ganz. Are there any questions from the Committee for Dr. Ganz?

Dr. Bailar.

DR. BAILAR: I appreciate this presentation very much, but there was one comment in passing that really pushed a button. It doesn't have much to do with the burden of Dr. Ganz' presentation here. We do not know nearly enough about possible infective loads in blood products or anything else, nor do we know nearly enough about infective doses.

To illustrate the problem, imagine that you have a unit of blood that has 100 infected doses in it. Reducing that by 42 percent isn't going to

help. There will still be 58 ineffective units. The need here really is for multiple log reductions, not things you would measure in percents this way.

The gap here, I think is in knowledge about both -- about the relation between exposers and infective doses and I hope that FDA and others will be working on this pretty hard so that we'll have a better understanding of how they are related.

The problem is in fact much more general that reduction in risk is simply not linear. It isn't even close to linear with respect to reductions and exposure.

Forty-two percent is fine, but it's a bare beginning.

DR. PRIOLA: Any other comments from the Committee?

Dr. Epstein?

DR. EPSTEIN: Thank you very much, Peter. I appreciate you coming down. Can you just clarify -- I noticed that you've maintained consistency in the deferral period for exposure in France and exposure in the U.K. despite what most people believe to be a disparate risk from food exposure in those two geographic areas and I'm just wondering whether that's been done because of a pragmatic decision just to keep

things simple or whether it reflects some other equivalent measure of risk or benefit?

DR. GANZ: Good question, Jay. Again, I think part of the reason there was at one point we had made the policy decision that if there was a jurisdiction that had variant CJD deaths that the deferral -- that we would have a deferral, based on incidents of variant CJD death. So that's originally how that came about and they were, as I say, at the time three deaths in France and deaths in the U.K., and hence there was an agreement that there should be a deferral measure based on that.

Subsequent risk analysis I think showed that you're absolutely correct. There are differences in risk in those two areas, but we've maintained the deferral period because we were able to, based on blood supply.

DR. PRIOLA: Okay, thank you, Dr. Ganz. We'll move on to Dr. Dorothy Scott, who is going to discuss current safeguards for blood products.

DR. SCOTT: This should be very brief. I'm going to review the current safeguards for blood products recommended by FDA and this is really a lead in to tell you for what Alan Williams is going to tell you and that is how these safeguards evolved over

time. That will give good context for moving forward and responding to the questions that we're asking.

This probably seems like a primer to a lot of you, but I'm just putting it out there at the beginning. These are the donor deferrals for risk of what we call classical CJD. They include, of course, diagnosis of CJD. Also, the two iatrogenic risks in the U.S., receipt of human pituitary growth hormone injections and dura mater transplant. In addition, people are deferred for a family history of CJD in one or more family members. And blood components are withdrawn if there is a posed donation finding that the donor as CJD or, in fact, these risks.

This is donor deferrals for variant CJD risk. Again, it should go without saying, but of course, we have to say it, for diagnosis of variant CJD, for risk of exposure to products that may contain or in theory could contain BSE and for risk of geographic exposure to BSE. So I've put these in two different categories.

Risk from products may include the receipt of transfusion in the U.K. from 1980 until the present, or injection of bovine insulin that was sourced from the U.K. between 1980 and the present.

The geographic donor deferrals I'll go

into in the next slide, but this includes travel and residence in certain countries with BSE or exposure to British beef on military bases in Europe. The current donor deferrals are for greater than or equal to three months' residence in the U.K. between 1980 and 1996; five years or more in France between 1980 and the present. That's because France also had BCJD cases and they had a fairly large importation of British beef; or six months or more on certain military bases between 1980 and 1996, and that's because of the British Beef to Europe Program.

In addition, there's a deferral for five years' residence or travel in Europe from 1980 to the present, again, reflecting the risk of exposure to BSE. And this deferral is for blood components for transfusion only, therefore source plasma or plasmapheresis plasma is not included in this donor deferral, except for France, as you saw in the previous slide.

The decision to do this was based on the demonstrations that model TSE agents are partitioned or removed during plasma fractionation and that was evidence from published studies, but more than that, the European risk of variant CJD has been low and it appears to continue to be low. They had a very small