asymptomatic, or latently incubating people that will never become symptomatic, will never become ill. They are infected, but they'll never become ill.

We don't know the size of that population, but these models don't actually capture that, so that's one of the issues that we're trying to resolve, and so what we've chosen is another strategy, is to use surveillance data. So, the most recent surveillance data that's come out, and this is a study by Hilton, et al, and it's a surveillance study of tonsils and appendices, and what they've done is, they've identified three positive samples, samples from three different patients were positive in a total of 12,674.

And, what they estimated in that paper is that gives you a rate of about 237 positives per million individuals in the U.K. population. If we walk that down to estimates for our model, what we assumed was that we would have one positive individual in 4,224, just a strict interpretation of this data.

So, I wanted to provide somewhat of a rationale for us using this data, and I think these data, for us, are very compelling, first of all because they are surveillance data, they are not modeling data, there's not much more modeling done o

them. There's not much more analysis done on them, so they really represent what we consider real data of possible incubating cases. So, we think this data are actually capturing some of the incubating cases that won't progress to illness, as well as those cases that will progress to illness.

Now, we know this is somewhat of a conservative approach, but again, the uncertain estimate of the prevalence I think sort of necessitates that we take this approach and use these numbers.

Again, the modeling data sort of mostly estimate clinical variant CJD cases and won't really capture those asymptomatic cases. And, I think it's important to emphasize that the non-clinical or asymptomatic infections probably have the similar potential for transfusion transmission as somebody that's going to progress to clinical illness. So, I think that's sort of our reasons for using this data.

So, you may want to circle this slide, because this is going to be a point that we may want to discuss later on in the discussion.

Again, this is just a summary of the different types of data in the United Kingdom that have been presented, mathematical modeling results are

out there in the literature and surveillance studies.

In the United States, I think I'm going to not discuss this, because we are going to discuss this point more fully in the second presentation that I'm going to be giving, so let me just move on from there.

All right. Now, I've just discussed, in our Factor XI risk assessment we're interested in the probability of exposure, and prevalence of variant CJD determines the number of variant CJD donations per pool. So again, if we take that Hilton data, and we look at it, again we are getting one positive in 4,225 individuals, we'll round it up, or down, and what that actually breaks down to is, we consider processing for 20,000 donations, so a pool of plasma donations in the United Kingdom, the average size of the pools that were used to make Factor XI was about 20,000 donations, and in that what we would expect, just applying these numbers, is that we would have approximately 4.7 donations on average per pool. So, not just one, but we've got almost five, so that's a significant amount. Not only do we have nearly 100 percent of the pools predicted to be contaminated, but we also have this larger number of donations going on, so about an average of five times more infected material going into those pools.

And, what I did was, I just wanted to show how we actually arrived at calculations in the model, and what we did was, we just adjusted, these are numbers per million, 237 per million, coming out of the Hilton study, and the range on that, with their 95 percent confidence intervals, was 49 to 692. We, basically, just divided these by 50, because it's 1 million up here, 20,000 down here, that's dividing by 50, and we get a mean of about five donations or variant CJD donations per pool of 20,000 donations, and the range on that went as low as zero and as high as, potentially, 14, although this is a much less likely event.

So, that's how we actually sort of took this data and adapted it for our uses in our model, based on the 20,000 donations going into a plasma pool.

All right. Our next question then is, we've got this probability, and we've got a little information on quantity, we wanted to get more information on quantity. So, in general, what's the quantity of TSE agent in the starting plasma pool, the amount of infectivity per donation in pool had to be calculated, so we estimated infectivity in human blood derived from animal data. So again, we are using

animal data to draw these conclusions.

We also wanted to estimate the number of TSE donations per pool, and we've done that using the Hilton data, and it's just important to remember, the higher the prevalence and incidence of the disease the greater the chance of multiple donations in a pool.

All right. So, you may want to circle this slide, too, because these are some of the major assumptions we are going to be talking about in the talk. So, this goes to the Factor XI risk assessment, how did we calculate the quantity of variant CJD ID50s that were present per ml of plasma, and what we did was, we used animal studies, and we used what's called a triangular distribution, because this is a probabilistic risk assessment. We are not using just ten ID50s and calculating things out, we are saying, minimally, there could be .1 ID50s per ml of blood, but we are estimating, well, most likely from the data that we've seen that there are ten ID50s, but we actually suggest that there could be a maximum of 1,000 ID50s.

I just wanted to sort of summarize some of the data sort of verbally, so what we did was, I think some of this data is also described in the risk assessment, but we also relied on Doctor Paul Brown's

data to make these estimations. That's why we are assuming our most likely is around ten, because his estimates came up in 1988, I'm sorry, 1998 and 1999, with an estimate of ten to 20 ID50s per ml of blood, and then also Bob Rohwer's group at the University of Maryland also did some more studies, there's were in the range of two to 20 ID50s per ml of blood. So, we have a heavy emphasis down towards the lower range, but we are acknowledging that there are some experiments done by Paul Brown and others that are sort of up at the high end. So, we still have to sort of incorporate that into our estimate, so we did that with this distribution.

All right. The second part is, what fraction of the infectivity in blood is associated with plasma. We assumed based on experiments by Luisa Gregori in Bob Rohwer's lab at the University of Maryland, that 58 percent was associated with plasma, very similar to the Paul Brown estimates of around 50 percent or slightly higher than 50 percent. But, we chose 58 percent as our estimate.

The other thing to do that we did was, we adjusted for the efficiency, and there is a reduced efficiency for intravenous units versus intercerebral ID50s. So, what we've got up here at this point is

intercerebral ID50s. These were determined by injecting blood into animals, but what they think is that there is a five to ten-fold reduction in efficiency via the intravenous route, because we are looking at blood we are interested in that intravenous infectivity, so we adjusted any estimates downwards by about five to ten-fold, and that's based on information from, I believe, Paul Brown's lab, and also from a paper from Kimberlin in the late '90s.

So, you may want to circle this, and we can come back to this and discuss it as part of our assumptions that go into the model.

The next part of the model that's very important, and I would say that what the sensitivity analysis showed us, I'll sort of tilt my hand right now, is that the variant CJD prevalence was the most important factor in determining risk. This is one of the second most important things. So, we are sort of emphasizing this quite a bit, and that is, what's the log of reduction that could occur during processing, and this reduction is based on the various processing steps, and I believe the previous presentation walked through several of those various steps in the reduction levels achieved.

I think it's important to remember that

there's variability in the processing and the levels of reduction achieved. But, based on information we had, we assumed for Factor XI, again, this is a Factor XI risk assessment, that the minimum reduction could be as low as zero, the most likely level of reduction could be as high as two logs, and this would - the counterpart would be about 99 percent reduction, and then as high as four logs. So, about 99.99 percent reduction in the amount of infectivity.

Now, sort of a caveat that I would put, or an explanation here, is that we never assumed that infectivity is totally eliminated. We assume it's greatly reduced, but we assume that there's never 100 percent elimination, just to keep that sort of conservative aspect in our estimates.

Finally, moving on to the last part of the risk assessment, what's the dose that people actually receive of the product and of variant CJD ID50s during their surgery or treatments with this product? And, what we have to consider is package size, whether it's a vial or other type of product, the vial size. If you have multiple vials coming from multiple different pools, that has an influence on risk. The number of units in those vials, the ID50 then per package, whether it's a vial, or unit, or whatever your unit of

interest is, how often the product is used, in this case for Factor XI it's used individually or two or three times during surgery. But, there are people that use other sort of plasma derivatives that have multiple or chronic need for use of these products, and they are at higher risk if there is a risk associated with that product.

Again, utilization may vary by severity of the disease. We saw in some of the Factor XI patients being treated, some were very mild, needed very little of the product, some needed a lot. Again, those that probably need a lot are at higher risk of variant CJD transmission than those that received lower amounts potentially.

Again, in our estimates of utilization I think it's important to try to be as precise as possible, since this is an important aspect of exposure assessment.

Okay. So, what did we do for Factor XI? Okay, so for the Factor XI risk assessment we looked at utilization of the U.K.-manufactured Factor XI in the U.S. by patients. Now, what we did was, we looked at the scientific literature to get an idea of the dosing. We looked at also other sources of information for dosing, and what we came up with is

three possible scenarios. And, what we try to do is sort of have representative scenarios, an extreme scenario, something that's more in the middle, and then something that's at the low end, just to give you an idea of risk, and that's what we are doing. This is sort of a low estimate. A patient might receive one treatment, a 60 kilogram patient might get 50 units. That would total about 3,000 units of product. Scenario two, somebody might receive 9,000 units and then 15,000 units if they get three or more treatments, or they are particularly a large patient, heavier, et cetera.

So, these are the three scenarios that we use representing the extremes that we saw in the literature.

Again, so to do the risk characterization part. I just wanted to say some general comments again about risk characterization. This is the integration of the exposure assessment component, or dose, and then the dose response information to estimate risk. And remember, we don't have a good estimate of the dose response relationship, so we are probably going to apply a sort of more qualitative estimate to that, to our risk.

TSE dose response information again is,

that information is lacking, so it's not possible to precisely estimate the risk, and that's a severe limitation here. I think it's important to emphasize, though, what I'm doing here is what we call a TSE risk assessment, but we are really characterizing exposure. So, it's really sort of almost the end of the exposure assessment stage, we go a little bit further, but not much. So, I just wanted to give that clarification.

We can draw some limited qualitative conclusions about risk. So, if we know the exposure is extremely high, you can say, well, you know, there is a risk there. If it's extremely low, then we can say, well, there's very little risk there. So, I think we can draw some sort of qualitative comparisons by looking at these types of models.

I think you may want to circle this slide, too, because this contains a summary of all of the different parameters that went in and the different statistical distributions. So again, the number of variant CJD donations per pool of 20,000 donations, we estimated a minimum of zero, most likely of two, which works out to a mean of five donations per pool, and then a maximum of 14, 20,000 donors in the pool, 200 mls - I'm sorry, 20,000 donations in the pool, 200 mls per recovered plasma unit, these are the variant CJD

ID50s and on and on.

Again, we also have the log reduction in there, and that's an important factor in driving the risk and the risk estimate, and then we also have information on the yield of Factor XI from the pool. Again, these numbers are all feeding into our risk of what the patients are actually receiving.

So, this is the final result of actually all the effort of doing the model. What we've got is our three scenarios of 3,000 units, 9,000 units, 15,000 units. We also did a calculation for 1,000 vial, and what the risk was for that, and then per unit of Factor XI. So, these are all Factor XI, and then these are the exposure estimates based on our risk assessment.

So, for instance, you see a number for 3,000, six times 10^{-2}, or .06, for 9,000 it's .17, and then for scenario three it's .28. I think at this point I'll sort of just put an aside in and say that, so how do we really interpret this information? And, I think it's important at least to put some guide on this information. So, this is an ID50, and if we sort of did a strict interpretation of the linear dose response for the ID50, I think as Anna or Doctor Molesworth or Soldan described, what we would get is,

we would get .28 units would equivocate to about a 14 percent risk, so we would reduce this by 50 percent, because it's an ID50, that would equate out to a risk of about 14 percent.

So, if we had 100 individuals that all received this dose, you might expect 14 of those to potentially become infected with the disease. Now, that doesn't mean that they are going to become ill, and I think we also have to remember that this is an animal ID50, and there are all the caveats of uncertainties that come along with this estimate. And remember, this is based on animal data, the units of infectivity per ml of blood are based on animal data. We also have the logs reduction, and that's based on data - some data, but a lot of uncertainty there, and on and on. And, we have all these assumptions going into this model that have extreme uncertainty. So, I would caution anybody sort of looking at this and trying to do a direct interpretation.

I think I wanted to draw people's attention to this, which we didn't actually try to do, but 1,000 units, as the earlier presentation, this equates out to .02, so this would equate out to about a 1 percent risk, if we are using the U.K. approach to this.

And again, I think the other aspect of this that's very important is to look at these, we not only have these measures of central tendency so we are using the mean, but we are also giving you the fifth percentiles and the 95th percentiles. These express the uncertainties within the model.

Now, the other big uncertainty that's not really - that we can't express because we don't know the uncertainty there, is again, this sort of translation of what's an animal ID50 in comparison to a human ID50. So, we can't capture that in these estimates, so that's not there.

And, other estimates of things that aren't in the model and their uncertainties aren't there either. So, there is extreme uncertainty again in these estimates.

All right, so let me go to the next slide, which talks about models and uncertainty. I just wanted to say that I think you have to keep these models in perspective. I do this all the time, and, you know, I try to keep this in perspective. I don't say, this is an absolute, people are going to get ill, blah, blah, blah. That doesn't mean - necessarily mean that. A model reflects a mathematical approximation of reality. Our model may be inaccurate and may not

actually approximate reality very well. As we get more data, it will, and we'll have less uncertainty, but there is extreme uncertainty.

Now, the predicted risk, you have to remember on this model, is a product of uncertainty in the data and the assumptions, so we not only have the data that are uncertain, but we also have assumptions that we make are uncertain.

What we are doing is, we are using a probabilistic model approach. We use statistical distributions to capture the uncertainty that we know about, again, there's unknown uncertainty in here that we have to consider, and then what we do is, we use what's called the Monte Carlo method, it randomly chooses values from the distribution, so we have distributions going up and down the model, and what we are generating at the end is another distribution, which is an aggregate distribution, a product of all those distributions. So, it's just important to keep this process in line, as to what we are actually doing.

So, we repeat this, we choose randomly from each of those distributions, repeat this process thousands of iterations, and we get this huge aggregate distribution at the end for the risk.

Let me just remind people that this is the estimate, these are the distributions we are generating, these are summaries of them, so that's what we are doing, we are actually generating a summary of the distributions that the model generates.

All right, so let me just sort of quickly move on. Uncertainty arises from this lack of information. Uncertainty also arises, another point is a model uncertainty, so the model could be highly uncertain, it could be incorrect, so there's uncertain there. Express uncertain outcomes from the model using measures of central tendency, and then the uncertainty with confidence intervals.

Then, sort of moving on quickly, we've mentioned sensitivity analysis, and that was mentioned as a question in the previous talk. We actually did do sensitivity analysis. I wanted to explain what that is, so sensitivity analysis determines what factors in the model have the greatest influence, and we actually do that by varying parameters in the model by percentages, for instance, 25 percent, 50 percent, and so on.

And then, we observe those - the impact of each of those portions of the model on the risk estimate, so this can be done for multiple outcomes,

so we could do this looking at our ID50s for any of those particular scenarios. We can do it for potential illness if we had a dose response curve, et cetera, and infections as well.

And, what it does is, sensitivity analysis identifies factors in the model where additional information would improve the risk assessment, so we know those things are really driving the risk estimate and they are highly uncertain. So, if we get more information and we prove particular aspects of the model, we can improve the final estimates.

So again, for the Factor XI risk assessment, we specifically did a sensitivity analysis, two major factors influenced risk. There were certainly more, but the number of variant CJD donations per plasma pool, of large influence on the risk.

I wanted to put in, this doesn't necessarily apply to Factor XI in the U.K., but it does apply here, that for the United States the risk reduction measures that we have in place are the donor deferrals that get at this prevalence and try to prevent individuals that are potentially infected with variant CJD from getting into these plasma pools.

The second factor that sort of drives

risk, second most important, is the log reductions of the variant CJD agents during the manufacture of the product. Again, we have risk reduction measures, and we look at the processing, and then try to predict the levels of reduction, but again, you know, a good risk management strategy, I think that was being alluded to earlier, is that if you can get the reduction even greater than you'll reduce the risk even further. So, we think that this is a very valuable step in reducing risk.

So, and I think it's important that these processes be validated so we know, you know, what the level of risk - you know, what level of agent is being reduced and quantify the level of reduction that's occurring during these processes.

Let me just sort of quickly move on. There's model validation. I think we were sort of getting to some of these issues about epidemiological data and not having epidemiological data. In emerging situations, and I would consider variant CJD much like that, epidemiological data on outcomes may not be available. Certainly for this new emerging issue of hemophilia infectors and plasma derivatives in risk we don't have any indication of cases coming from that, so it's very hard to sort of estimate those risks.

So, we do that using these risk assessments.

Now, lacking that data, formal model validation may not be possible, and we sort of acknowledge that up front. But, it's important, I think, to anchor the components of the model with data, so maybe the endpoints we are uncertain of a little bit, but if we can get some of this intervening stuff that are used to predict that risk, then we can have a more certain estimate of the final outcomes, and that's very important.

So, for instance, we have - we are gaining more information and at times know the levels of TSE clearance for specific products, we know about utilization, those pieces are incorporated into our model. But again, and this is what gave us sort of the impetus to put in the surveillance data for the variant CJD prevalence, is that empirical data and epidemiological data are much preferred over risk assessment estimates and model estimates.

I'd probably get fired for that from the risk assessment group for saying that.

So, the objectives of risk assessment, I think it's a useful tool in decision-making. What we are really doing here is, we are determining, is there a risk with this risk assessment, what's the magnitude

of that risk? So, I think it's a very useful tool for sort of starting, at least, visualizing what that risk is, and then what the impact of risk reduction measures are, and we can get to that in future risk assessments as we develop this risk assessment further.

An important part, as people were mentioning, I think, you know, about the amount and quantity in human blood of this agent, you know, to identifying gaps and research priorities, and this can be a useful tool for saying, hey look, if we had this information we would know more about the risk. So, it's very important as a tool for doing that, so we have to really consider that carefully in looking at the results of these risk assessments.

So again, the uncertainties, I think everybody on the Committee certainly knows about all of these things, you know, prevalence in the U.K. and the USA, amount in the blood, and plasma, et cetera, so we have a number of data gaps and a number of data needs.

Conclusions of the risk assessment, so potential exposure to variant CJD manufactured in the U.K. and used under IND was estimated in the risk assessment that we've done. It's possible that the

product manufactured from U.K. plasma may have been manufactured from plasma pools, and the model actually predicts that, that it was manufactured from plasma pools that may have contained or did contain plasma donations from an individual that was incubating variant CJD.

Again, to date, no recipients of plasma derivatives in the U.K. or elsewhere have been diagnosed, again, but given the potentially prolonged incubation times those cases may be out there, but may yet to be identified.

And, I wanted to acknowledge the people that are part of this process. I don't do this process alone. I have a lot of help from other people and the area experts. So, there were a number of people at the Centre, and this is a limited list, a lot of people that aren't listed here also contributed.

So, I thank you for your time.

CHAIRPERSON PRIOLA: Are there any questions for Doctor Anderson from the Committee?

Doctor Salman?

DOCTOR SALMAN: Well, I appreciate all the precaution and the explanation of the model. I think it's very well done.

My question, and it's maybe very general, is, as you explained in the beginning the first step in the risk assessment process is the hazard identification. And, it seemed like, by just looking at that, you came up with a conclusion it's almost there is no hazards. And so, the process after that, and I think you explain it very well, is mainly characteristic or characterizing the exposure, rather than risk assessment per se.

My concern is the table you presented, because that really is not characterization of exposure, that merely is you are talking here about risk assessment, okay, and I think we need to be aware, as you said, is the gaps in the data and the assumptions you went with in all the process.

Most of the time is, when you have the first step, hazard identification, to lead you to that, there is no risk, then you stop there, but I think it's, and you did it, I would say, very nicely, is you followed that to maybe characterize the exposure, and I think we need to differentiate between the two.

The other thing is, the data presented in that table, I believe, is related to the variability rather than the uncertainty.

DOCTOR ANDERSON: Well, it's actually probably a little bit of both, so you are correct.

DOCTOR SALMAN: The 5 percentile and the 95 percentile, that's related to actually the variability within your point estimates, rather than the uncertainty in your point estimates.

DOCTOR ANDERSON: I guess what we can do is, it actually captures both, and what we could do is, we could go to another level of modeling, which is to separate variability and uncertainty and really even hone in on what those components are, and how they contribute to those estimates.

But, we didn't do that, and, perhaps, later on we will. But, you are correct.

CHAIRPERSON PRIOLA: Doctor Gaylor?

DOCTOR GAYLOR: Yes. I've gone through the risk assessment each step in great detail, as Doctor Anderson knows, and I agree with the framework that the FDA has used here. It appears that they've included all the important factors and elements, and as has been said over and over, the problem is not the framework of the risk assessment, but the data, the numbers that we plug into it. They are both assumptions and data uncertainties.

You had a slide near the end of your talk

where you had two major factors that influence risk. I would add a third one to that, and that's the ID50 per milliliter of plasma is another major factor.

And so, I agree with the approach. The bottom line that I come up with at this point, with the estimates that are available, and assuming that the animal ID50 applies to humans, you come up with risk estimates varying from near zero up to as high as 50 percent. That's a pretty wide range, and you say, well, how useful is that going to be to the regulators and decision-makers, but that's where we are at. The risk, based on the data, and the assumptions, could be quite high, could be as high as maybe 50 percent, but equally likely as zero percent. So, we have a wide range of uncertainty here.

DOCTOR ANDERSON: But, I think, if I can just comment, I think one of the things we can do, in effect, is reduction, and so we can reduce the level of the agent that people are being exposed to, and then we can do further validation studies to see, are we actually affecting, do we ever get down to near zero as far as the amount of agent that's in these products, even if it comes from a contaminated batch or a batch that has a donation or five donations in it.

So, I think one of the areas of focus for us is really to sort of emphasize that. You know, log reductions really can have a potential impact, and I think that's - we don't have control over the prevalence of a product that was manufactured in the U.K., and the other way we control it here is, the donor deferrals. And so, I think the value of the risk assessment is, we can look at those different mitigations and then try to predict what impact they'll have on risk, and then you can determine, well, is that an important benefit or not.

And so, I think that that's sort of the value. I agree, we are highly uncertain as to our risk estimate, so -

CHAIRPERSON PRIOLA: Doctor Gambetti?

DOCTOR GAMBETTI: In want to compliment you, because it looks to me a very complete and clearly presented study.

There is one point that I would like to have some clarification. According to your calculation, it looks like you have the likely scenario is five donors were affected by variant CJD in that pool of blood from which Factor XI had been extracted.

At the same time, you also made the

statement that no symptomatic, or no patient with variant CJD, was demonstrated to be one of the donors. So, is that the assumption that we are making here, that all those five potential donors remained asymptomatic?

DOCTOR ANDERSON: Potentially, or they could become symptomatic at a later time and not be caught by the system.

DOCTOR GAMBETTI: We go from '87 to '99, so the least time here, assuming the incubation time, the common figure for the incubation time for variant CJD, is about ten years, so there would be time, at least for some of those to have become symptomatic.

DOCTOR ANDERSON: And, some have, and they've been traced back, but not to Factor XI.

DOCTOR GAMBETTI: In beg your pardon?

DOCTOR ANDERSON: Some patients have been identified and traced to other products, just not Factor XI, specifically.

DOCTOR GAMBETTI: So, there could be less than this five?

DOCTOR ANDERSON: Again, I would say that that's an assumption based on the current prevalence estimate that we are using, based on this surveillance data. But again, I don't really know of those five

what proportion of those will actually progress to clinical disease.

So, it could be that all five of them will, but what I suspect is that, you know, 90 percent of them won't and maybe one will. So, I think there's a large sort of population out there that's potentially infected in the U.K., but they won't ever progress. And so, that's part of this calculation at this point in time, and so I think the U.K. and others are using an estimate of what happens if we get one infected donation per pool, but we are sort of saying, well, that's fine if you are predicting based on the number of clinical cases, but if you want to expand that and include the non-clinical or latent cases then we have to allow for this possibility that there could be more than one infected.

DOCTOR GAMBETTI: In agree, I agree, that is correct, but at the same time -

DOCTOR ANDERSON: So, we don't know what that estimate really should be, and it could be five, or it could be less, and we acknowledge that there are limitations to the surveillance data.

DOCTOR GAMBETTI: No look, my question, I understand all this, my question centers on the fact that probably those hypothetical five are all, or most

of them, remain asymptomatic, so probably come from that pool of patients who never really developed the disease, so it's a special pool of patients that may be different from those who have gone and developed the disease. And, probably with those five we are dealing with the pool of patients who never developed the disease.

Is that right? Is that the assumption?

DOCTOR ANDERSON: I would say that that's at least my working assumption, so, yeah, that's my thinking on it.

CHAIRPERSON PRIOLA: Doctor Allen and then Doctor Hogan.

DOCTOR ALLEN: I guess my question is sort of a corollary of Doctor Gambetti's. The Hilton data, obviously, were very important in your establishing your presumed risk up front. Have you, or have our British colleagues, examined the similarities between the population that went into the Hilton data and the population of blood donors in the U.K.?

DOCTOR ANDERSON: I think I would leave that to - can either of the -

CHAIRPERSON PRIOLA: Would either Doctor Molesworth or Doctor -

DOCTOR BIRD: If I could just comment on

that.

CHAIRPERSON PRIOLA: Could you identify yourself, please?

DOCTOR BIRD: Sheila Bird, from the Medical Research Council's Biostatistics Unit.

The majority of the tissues in the Hilton study were from people aged ten to 30, at the time of operation in 1995 to 1999, and so rather than use a multiplier of the total U.K. population it may be more appropriate to use a multiplier which is closer to either 12 million or 24 million, in respect of that particular age range. And, the problem with the surveillance at present is that we have very limited surveillance data for people over the age of 50. So, that might take down your estimate of five.

DOCTOR ANDERSON: Right.

DOCTOR BIRD: If you bear in mind that that surveillance was targeted at the high-risk, in terms of clinical cases, age group of 10 to 30.

DOCTOR ANDERSON: Right.

DOCTOR BIRD: There are also data from John Collinge, who tested, I think, about 2,000 tonsil specimens, and I think there were no positives in that.

So, mentally, you might roughly expand

that to three positives out of about 15,000.

DOCTOR SOLDAN: If I could just add to that, that the average age of blood donations, of blood donors in the U.K., is around 40 or over. So, the 20,000 of our donors in the pool -

DOCTOR ANDERSON: And then, for plasma donors is it less?

DOCTOR SOLDAN: No, well, it was the same donors, so we were the same donors fractioned for plasma, so I think that's a very important point.

And also, just to comment on that, that again the use of that three, that two of those samples were of an atypical pattern, which I know you are assuming to represent infection equivalent to the one that was typical.

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

DOCTOR SCOTT: Yes, and I think that Doctor Soldan is referring to the possibility of false positives, which is referred to in the Hilton paper, because it was an atypical pattern of staining in two out of three of the positives.

The other thing I wanted to point out is that, I gather from the paper that the finding of the three positives out of approximately 12,000 was after

they began only looking at appendectomy samples and maybe a few tonsil samples, of people aged 20 to 29. And so, that's really the group we are looking at, which isn't going to completely overlap or perfectly overlap the population of donors as we've just heard.

So, we do agree that that is something that potentially could be adjusted if we could get more information.

CHAIRPERSON PRIOLA: Doctor Hogan?

DOCTOR HOGAN: This issue comes up all the time when we talk about corneal donors versus infections, and you use the surveillance data and come up with the five in the donor pool, how did you come up with the number of two most likely out of five to donate? That is, you are sort of assuming that five - all or half of these patients will donate. What's the prevalence data in terms of donation in the U.K., how many individuals out of how many population donate, and could that affect this calculation?

Do you understand my question?

DOCTOR SOLDAN: Well, I'll refer whether it would affect your data to the risk assessment team, but it's about 7 percent in the U.K. population, it's roughly around 7 percent of the eligible age group population in the U.K. donate blood, but how that

would affect -

DOCTOR ANDERSON: Right, but I think the actual distribution, we just look at particular types of distributions when we do this modeling, and actually, whether it was two or whether it was five, there's a wide swath of things coming down around five, actually. So, it happens to go, because that's the average that we've plugged into the model as well, of five, so two ends up being the most likely. We had put that in because we are defining the other distributions by most likely. But, I put in that sort of qualifier of the mean as well, just to clarify that point.

DOCTOR HOGAN: My only point is that you can't assume that people with the disease will be donors. I know you have to assume that for your risk model, but there's a lot of people that wouldn't even do it for various reasons, wouldn't even be in the donor pool.

DOCTOR ANDERSON: Right, but you would assume there's not some pre-selection, you would assume it's just a random sample of the population, and it may be only 60 percent of the population is qualified to donate, let's say, but you would assume that's a random sample of the population.

CHAIRPERSON PRIOLA: Doctor Belay?

DOCTOR BELAY: Yeah, Mo raised this question, actually, but I didn't have the answer for it. You repeatedly said the ID50 was derived from animal studies, and you selected to use the icID50, and adjusted it for intravenous - the intravenous route.

DOCTOR ANDERSON: Right.

DOCTOR BELAY: Now, my question is, why did not - why didn't you use the ivID50 directly, is it because the data are -

DOCTOR ANDERSON: There aren't a lot of data - a lot of the data aren't generated for - it's generated for icID50, so we had to actually take all that data and convert it to ivID50.

DOCTOR BELAY: ivID50 is not available, it's not tested, or not published?

DOCTOR ANDERSON: I don't believe there's any data in the published literature where they did, specifically, ivID50, except they were probably trying to get at that with the Houston study that was earlier mentioned.

CHAIRPERSON PRIOLA: There are probably some old Kimberlin studies in mice or hamsters that are done, he did a lot of that.

DOCTOR ANDERSON: Okay.

CHAIRPERSON PRIOLA: There might be some data there for iv, but it would be probably 20 years ago.

Doctor Bracey?

DOCTOR BRACEY: Yeah, just a point of clarification. In terms of the comment about the ID50 and the most likely being ten, and that being based on the data from Brown, somehow I recall that that data related to animals that were symptomatic, and, in fact, that earlier when the animals were tested that were asymptomatic there, in essence, was no transmission. Could you comment on that?

DOCTOR ANDERSON: Well, our assumption for the model is that an individual or animal will be - will have agent in their bloodstream throughout the entire incubation period. So, that's a conservative assumption, but we acknowledge that the animal studies actually show, or certain animal studies show that probably for the first half of the incubation period there's probably not infective agent in the blood, but for the second half of the incubation period in animals there is infectivity in the blood. So, several experiments do show that, but again, we don't have the human data, so what our conservative

assumption is for the entire incubation period that agent is in the blood.

DOCTOR BRACEY: Right, I think it's a significantly conservative projection, in that, again, when the animals are in the asymptomatic state there hasn't been proof of that transmission.

DOCTOR ANDERSON: I think it's important also that what this risk assessment is, is more, you know, a public health tool. So, we weren't specifically targeting this towards clinical predictions, et cetera, but really as a public health tool. So, we do have a tendency to err on the side of sort of conservative estimates.

CHAIRPERSON PRIOLA: Okay.

I think we'll move on to the final speaker, and that's Doctor Sehulster, who is going to talk about recommendations for surgical instruments used on TSE patients.

DOCTOR SEHULSTER: Well, good morning, Committee Members and guests in our audience. Can you hear me now? Okay.

In the interest of time, I know we are running very, very late, I'll try to keep my comments very brief, and, basically, much of what I will review this morning is already available on the internet,

either from the WHO website or from two pages within the CDC website. Much of the material from CDC is already cleared guidance that is either available as a question/answer format in that first page of CDC, or in the guidelines for infection control in dental health care settings, and so they do cover very briefly CJD transmission issues in dentistry.

And, basically, what we do in terms of instrument management and developing a strategy for surgical and dental instrument management, basically, can be summarized into three major elements.

The first would be patient status, and now we recognize that certainly this is helpful, especially if you know the risk factor history or the medical status of the patient, certainly the decision-making process is easier for the confirmed or suspected patient with CJD. It gets a little tricky when you are dealing with a great deal of unknowns, as we'll see a bit later.

The other element to consider is potential tissue infectivity level and certainly from the WHO conference in 1999 the consensus is that we can divide tissues into either high-level infectivity or low-level infectivity, and certainly those that do not fall in those two categories are thought to be little

or no infectivity.

And finally, the other element of consideration is the instruments used in the procedures, and the potential for those instruments to make contact with tissues, particularly, of the high-level infectivity group.

Now, with respect to patients who are confirmed or suspected of having CJD, at least in the U.S. where fortunately for our purposes we are looking primarily at classic CJD, the material from Table 2 in the WHO document, basically, identifies the high-level infectivity tissues to brain, spinal cord and the eyes. Again, this is in the confirmed or suspected patient.

Low level infectivity tissues are a bit more broad. We have either spinal fluid, kidneys, liver and lungs, lymph nodes, spleen and placenta, and we do recognize that in dealing with variant CJD other tissues in the lymphoreticular system are certainly of concern.

Now, in the U.S. the primary procedure of concern is that of neurosurgery, but not all neurosurgeries are considered a high-risk procedure, and in this regard we focus our attention on persons, especially those who are suspect or confirmed cases of

CJD to the neurosurgical procedures performed on these persons.

If there are neurosurgeries that are performed for the purpose of diagnoses, or to obtain a non-lesionous biopsy, these are also procedures that may present with a high clinical suspicion that there's a potential for CJD transmission.

One thing to consider is the demographics of CJD patients, certainly in the U.S., when evaluating the potential for the neurosurgery to pose a risk to subsequent patients if nothing extraordinary is done for the instruments. And certainly, we would say in our estimation that biopsies in neurosurgery performed, for example, on a pediatric patient, say, less than ten years of age, may not really fall into the category of a procedure of concern, whereas, a diagnostic neurosurgery on a person in their 60s or 70s may raise the question, should you take precautions when managing the instruments?

This table, again, captures the essence of guidance that we have on the CDC website. It's formatted to resemble the table that is in the WHO document, and frankly, to simplify it what I did was, in trying to determine decontamination options Annex III refers back to the WHO document, where they list

the different methods and the strategies for instrument reprocessing. And, I think what is very obvious is that when you have a confirmed or suspected CJD patient when you are dealing with high infectivity tissues or low infectivity tissues it's prudent to use the procedures outlined in Annex III.

After that point, things get a little bit fuzzy, in terms of consensus of opinion, and certainly in reviewing the WHO document we note that for persons who are family relatives of inheritable forms of TSE there is a different sub-opinion, and so this is one of the reasons why I have put Annex III, but listed it as a point of debate because there really is continuing debate on this particular guidance.

And then, when you have tissue contact for those organs and tissues with no or little infectivity routine reprocessing procedures are appropriate for that group.

Now, in the WHO document, they certainly, as you recall, mention that the absolute safest approach to instrument management is to consider all instruments, particularly, those that are in contact with high-level infectivity tissues as a single use, and to dispose of them by incineration. But, that is not a very practical approach for many facilities, and

so, consequently, they list a series of methods for decontamination that can serve as alternatives.

And, what I've done in this and the next slide is to just remind the group of the operational parameters of these methods. In our estimation, the first three of the methods, and there are about five or six, we deem appropriate for use in the U.S. healthcare system, and so what you see are, basically, a combination of chemical and physical methods to effect prion inactivation.

And, this particular method, that that combines sodium hydroxide as an immersion chemical, autoclaving instruments while immerse in sodium hydroxide appears as the first of these methods, and we certainly recognize that this can be a hazardous process, not only for the sterilizer equipment, there are occupational health issues, and there have been concerns about how the instruments come from this process, and what is the effect on the instruments.

The second and third methods, again, I'm not going to reiterate the fine details, suffice it to say that method number two is still an immersion type method, the difference being, though, that the instruments are taken from the immersion chemical - excuse me, the items that are put into either sodium

hydroxide or sodium hypochlorite, they are transferred then to water, again, immersed in water following that chemical exposure, and put into gravity-displacement autoclave.

The third method, I'm a little ahead of myself, the third method is the one where after exposure to chemical the instrument is taken from that chemical, dried, and then put into the autoclave for the time and temperature described.

Those were methods that are suitable for heat-resistant instruments. Obviously, we have a large category of heat-sensitive instruments available in healthcare, and so the question becomes, how do we deal with the heat-sensitive methods?

The guidance is directed at, again, the confirmed or suspected CJD patient, and the most conservative approach is to discard the instrument. Again, if that is not a feasible option, the other method you can use is to either immerse or to at least flood the surface of the instrument with sodium hydroxide or sodium hypochlorite, let stand for an hour, and then after rinsing and cleaning the instrument use a low-temperature process that you have of choice.

One of the things that has come up

repeatedly are questions about, again, the effects of these chemical and autoclaving methods on instruments, and we are especially grateful to our colleagues in FDA who have undertaken research to examine these issues, because we get asked these questions quite a lot. The group at FDA looked at different kinds of instruments, the quality of materials involved, and then the effect on these instruments when exposed to either sodium hydroxide, sodium hypochlorite, and again, in conjunction with the physical reprocessing.

And, basically, I think in a very simple view the sodium hypochlorite will potentially have greater effect, a greater negative effect, on the instruments compared to that of sodium hydroxide. What they found with sodium hydroxide, primarily, was that you had more of a cosmetic effect, a discoloration, but the overall function of the instrument was less adversely affected compared to that effect for sodium hypochlorite. The consequence is that the combination method with sodium hydroxide and autoclaving can be an effective tool with minimal damage to the instruments.

Now, those are our methods and operations that are helpful when you know in advance the status of your patient and can devise your reprocessing

strategy accordingly. There were, however, a number of episodes that came to our attention over the past few years, where a patient was undergoing a neurosurgical procedure, it was determined after the procedure that the diagnosis was, in fact, CJD, and this dilemma is, now what do you do with the instruments, and how do you manage subsequent exposures and potentially notification to patients?

I'm going to limit my comments strictly to the instruments, because notification, as you've seen this morning, is a very, very delicate thing. But, as a result of this the Joint Commission for the Accreditation of Healthcare Organizations determined it was appropriate to issue what they call a sentinel alert, and major points of the sentinel alert were that, be aware that there atypical clinical presentations of patients, and that they don't always fit the mold for the classic symptoms.

One of the elements that worked against facilities was a lengthy time between the collection of the biopsy specimen and when the final pathology report was released. This interval is very difficult to be dealing with, and so, consequently, the advice of the Joint Commission was to take whatever measures you can do to shorten that interval to the shortest

possible time.

And then, this gets back to the process or the practice of quarantining instruments. The Joint Commission Advisory again suggested that neurosurgical instruments should not be reused while the diagnosis is pending.

In that regard, the Joint Commission recommended to healthcare facilities that they have policies and procedures in place so that they can determine a strategy ahead of time and act accordingly. And, they also made a formal recommendation that instruments be quarantined as they are waiting a diagnosis coming back.

Now, this is where we get more into the practical advice. This is not crystallized into a formal recommendation, but these were just some of the ideas that came out of discussions with healthcare facilities at the time. And, with regard to quarantine, quarantining, basically, is just setting the instruments aside until you have information to take action with. This really is a useful method, but there are some factors that need to be in place in order to make it a very practical approach.

The first is, again, this is if that time interval between the surgery and the final diagnosis

being returned is very short, the shorter the better.

Some facilities cannot do a quarantine approach because they lack the inventory, sufficient copies, sufficient duplications of instruments, to allow a set of neurosurgical instruments to be set aside without affecting the flow of the work in the surgical unit. So, if you are going to do a quarantine approach, it's beneficial to have sufficient inventory on hand to allow you that buffer, as it were.

More importantly, though, and this comes from research in Europe, particularly, using steel instruments, is if prion infected material is allowed to dry it becomes much harder, much more harder to inactivate. And so, the important factor in quarantining is that the instruments ideally should be kept moist during the entire period of quarantine, so that you can be working with a factor that facilitates and enhances the success of your prion reprocessing.

Now, what to do about exposing potential exposures to patients, in the event that the instruments somehow are returned back to central sterile supply, and you are trying to determine a strategy for management in this case. I think ideally most people take the approach, well, we will reprocess

the instruments at this point, move forward with a prion-specific form of decontamination, so that downstream from this event all the subsequent surgical patients have the benefit of a prion inactivation process on those instruments.

One of the things that, perhaps, helps in tracking which instruments were involved in the surgery of concern is to implement an instrument tracking approach, where you identify either the tray or key surgical instruments, so you can focus your risk management and risk assessment process to those patients who are directly affected, instead of all your surgical patients.

And finally, one element that appeared in a situation that happened in the past few months is the fact that if you have neurosurgery instruments, you've got your tray of neurosurgical instruments, there's going to be some instruments in that tray which you may have common to other surgeries. It's prudent to restrict those instruments, that in your neurosurgical tray, to that tray, and not spread them all over into other trays for other surgeries. So, we would advise in a practical sense to keep those instruments in the neurosurgery trays and keep them there.

Now, one of the things that we are certainly aware of is the fact that much of the information about prion inactivation comes from an area that doesn't exactly match what we do in central sterile reprocessing in healthcare. And, there are groups in the world today who are starting to take a look at this, in terms of evaluating decontamination processes, cleaning and terminal reprocessing, and the effect on prions, so that you have a closer fit to the practices we have today.

There are one or two papers that have started to look at this, as I mentioned. They are taking a look at the effects of different chemicals used as cleaners. The two most common categories would be those of enzymatic cleaners or alkaline cleaners, and the low temperature reprocessing arena has not been represented in previous studies up until now, where groups are starting to look at how prion inactivation can be effective using, say, peracetic acid systems, or hydrogen peroxide gas plasma. The evidence is slowly coming in, and it is very interesting to evaluate.

Other areas that we feel bear some interest is to look at the effect of repeated cycles of cleaning and conventional autoclaving and see what

effect that has on prion decontamination, and then there are questions that always need answers that may be very difficult to do, and that is to see if there are processes we do in central sterile reprocessing that could inadvertently spread prion contamination to other equipment, and what measures do we need to take to minimize this from happening. So, these are areas where we desperately need research and answers.

And finally, with dentistry, the guidance, or I should say, the statements that are in the CDC dental infection control guidelines is interesting, because our Division of Oral Health had looked at case control studies and the studies that tried to look for prion presence in polt and the facial nerves, and the statements are offered for consideration without recommendation, which means that they feel more information would be beneficial to evaluate before they come out with a hard and fast statement.

But, at the moment, what they are suggesting is that, again, if you have single-use items, or items that might be difficult to clean, to consider them disposable and do so accordingly.

As with surgical instruments, the idea is to keep instruments moist. Again, these are if you are working with a known or suspected CJD patient, or

in the case of Europe, a variant CJD patient, to keep instruments moist until such time as they can be cleaned and decontaminated.

Again, because of the lack of evidence that has documented transmission, they suggest the method that is listed in the WHO for autoclaving 18 minutes at 134 degrees Centigrade, and they also do not recommend, as some dental practices may do, do not flash sterilize the instruments, and as you know flash sterilization is a process whereby the temperature is higher than the conventional reprocessing, but the cycle time is shortened.

And again, this summarizes the current position of the Division of Oral Health. They feel that in dentistry today the risk of transmission for CJD in dental treatment is low, and at this point we've not had documentation of quantities of prions in human oral tissues, and also to date there have been no published reports of an association of CJD transmission with dental treatment. But again, they are continuing to evaluate the literature, and they are leaving the door open for, as what they might call a mid-course correction, as more information comes to the literature.

And just finally to close, one of the

areas that I think really does have a fair amount of debate ongoing is the management of the healthy, at-risk patient, and at this point -

EXECUTIVE SECRETARY FREAS: Doctor Sehulster, you have run considerably over, if you could just wrap it up we'd appreciate it.

DOCTOR SEHULSTER: Okay, this is my last slide.

Just to say that, at this point we have a group of interest, again, the blood relatives of familial CJD patients, the groups that have either a risk factor history, such as human growth hormone, or dura procedures, are more problematic to assess, simply because it's been our experience that the patient recall of these elements in their medical history is not as strong as we would like it, and, consequently, it's difficult for these persons in all cases to be identified previous or prior to their surgeries.

So, this is something that we are continuing to look at, and as we get a heightened awareness of prion risk factors and the epidemiology of prion transmission, this may be another area where guidance might be modified.

That's it.

CHAIRPERSON PRIOLA: Okay, thank you, Doctor Sehulster.

I think in the interest of time we are considerably over, we should take a break, we've been sitting here for over three hours, and I think we need about a ten-minute break, and we'll come back to the open public hearing, and then committee discussion on the questions posed, and, hopefully, move on to Topic 2.

So, everybody back at about 11:35.

EXECUTIVE SECRETARY FREAS: If Doctor Coker could come to the front table during the break I'd appreciate it.

(Whereupon, at 11:28 a.m., a recess until 11:40 a.m.)

EXECUTIVE SECRETARY FREAS: If I could ask everybody to take their seats, we are going to go ahead and resume the meeting.

CHAIRPERSON PRIOLA: If the Committee Members could take their seats we need to get started again, please.

EXECUTIVE SECRETARY FREAS: As part of the open public hearing, or as part of the Public Advisory Committee process, we hold open public hearings so that members of the public who are not on the agenda

will have an opportunity to make comments to the Committee.

Ms. Chairperson, at this time I've received one written submission, and that written submission is in the red folders on the Committee Members table, and also in the viewing folder on the public table outside the auditorium.

I have also received four requests for oral presentations, one request this morning and three in the afternoon. These presentations will be limited to a maximum of five minutes. The presenters are asked to state any financial involvements that they may have with any firms or products they wish to discuss.

The first presenter will be Doctor Samuel Coker, Ph.D., Principal Scientists and Technical Director of Pall Medical, and he's going to be discussing studies of the new Pall "smart" filter technology. But, before he does so, our Chair has the standard required announcement for this open public hearing.

CHAIRPERSON PRIOLA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing

session of the Advisory Committee meeting FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company's or a group's payment of your travel, lodging or other expenses in connection with you attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

So, with that, can we have Doctor Coker?

DOCTOR COKER: Thank you very much for the opportunity to address the Committee.

I am an employee of Pall Corporation, so I have a financial interest in the company.

Thank you very much. This presentation is actually in response to the concern that the Committee

has regarding the possibility of the second wave of variant CJD, and also for the encouragement for new technologies, as well as approaches they may be taking to address the - to reduce the transmission of vCJD through blood transfusion.

So, what I'm going to present to you is the exciting new technology from Pall Corporation that may have reduced the transmission of vCJD through blood.

Some of the work that we've done will address specifically the removal of variant CJD. As most of you have heard this morning, the transmission of variant CJD had already been confirmed, at least in two cases in the U.K.

There is still a serious concern about the second possibility of a second wave of this serious disease. The approach that was taken at Pall, for - filtration technology, what we had done basic is to use our core technology to develop a "smart" filter that will specifically remove, not only the white cell but also any pathogens, especially the infectious prion. This particular technology is not a ligand-based technology, it's based on the technology that we developed at Pall Corporation.

Some of the validation work that I will be

sharing some of the information with you, basically, is based on standard validation protocol that have been used in other various validation programs.

Most of the work actually will revolve mainly about the low titer, because this morning there was the concern about endogenous infectivity, and already by some of these models, in this particular model what we did, basically, was to use a scrapie infection, infected a lot of hamsters, collect blood from the hamsters that are endogenously infected with this particular scrapie.

Once they are infected, we collected the blood from the scrapies and processed them into the red cells. The red cells are then filtered with this new technology, and some of the results that we have are shown here, using the Western Blot to monitor the level of infectivity before and after filtration.

As you can see, the level of infectious prion before filtration is actually very, very low, and this is after you've concentrated the blood by about 50 fold. At the end of the filtration process itself, all of the infectious prion had been removed from blood, and this is what happens with the Western Blot.

The next part of the studies did take this

particular blood that had been processed with this filter and inject it directly intracerebrally into a series of hamsters and monitor them over a period of time, and to see whether they develop any scrapie disease at all.

And, basically, what we found was that the animals that received the unfiltered material, which is on the right-hand side here, two of them developed clinical signs of the disease.

At the end of that, when we look at the brain to see the presence of any infectious prion material, we identified a third one that did not show clinical sign of the disease, but was actually carrying the proteinase K-resistant form.

When we look at the hamsters that received the blood that had been processed with a new filter from Pall Corporation, none of them developed clinical signs of the disease, and there was no presence of infectious prion in the brain. So, this is demonstrating that most of the hamsters are adequately protected from developing scrapie.

The next part of work is to now take this observation and move straight forward to human variant CJD, to see whether the animal model of scrapie can allow us to extrapolate to what happens in human. So,

we use a mouse-adapted human vCJD material, and, essentially, what happens was, you take this transgenic mice, you inject intracerebrally with human variant CJD, and at the end of that we collect the brain material, extract the human vCJD and spike it into red cells.

We repeat the experiment again, we measure the level of infectious material in the blood before filtration and also at the end of the filtration process itself, and, basically, what we found was, before filtration that was the presence of - using the Western Blot, we could see the presence of infection prion. This is the human form, not the scrapie, and at the end of the filtration process all of the infectious prion had been removed from blood.

The next part of my study, now will demonstrate that you can remove the infectious prion, the next question is, what is the quality of the red cell at the end of the process? So, I'll be sharing with you some of the work that we have done to demonstrate that the red cell at the end of the processing still maintained all the above physical and biochemical properties, so the process that we've developed has very little on the quality of the cells.

We look at the level of white cell removal

also with this particular filter, and that's something I need to stress, is that this particular filter, not only removed the infectious prion, but also has the additional benefit of removing all of the white cells. The white cells are removed to the level of - releases, which is the most stringent requirement currently.

We look at the level of red cell hemolysis over a period of time, as you can see here, the most stringent requirement from the Council of Europe was a level of about 0.8 percent hemolysis. When we look at the red cell over the study period, the level of hemolysis is well below the required guidelines.

We also look at another form of red cell preparation, this is CPDA blood, again, the level of hemolysis at the end of the study period is still well within the required guidelines.

We look at what we call in here is about physical measurements of the ability of the cell to deform or to carry out its normal function of oxygen transportation, and again, there were physical properties very well maintained.

All of these data suggest that, not only do we remove the infectious prion, but also that the quality of the cells at the end of the processing is

very well maintained.

So, in summary, what we've demonstrated to you is to use a low titer infectivity study, using endogenous infectivity, and we've been able to demonstrate that we can remove infectious prion from blood below the level of sensitivity of the Western Blot, and when these filter materials were injected into hamsters, the ones that received the filter material did not develop any clinical signs at all of scrapie, and when we look at the brain material there was no presence of infectious prion.

We repeated the experiment using human material, and we were also able to demonstrate conclusively that the new filter removed, not only a scrapie, but also human vCJD material.

So, in conclusion, using this particular filter may help address the concern that the Committee may have in regards to the transmission of vCJD.

Thank you very much for the opportunity.

EXECUTIVE SECRETARY FREAS: Thank you for your presentation.

Is there anyone else in the audience at this time who would like to address the Committee on issues related to the discussion this morning?

Yes, Doctor Cavanaugh.

Please, give your name and state any affiliations.

MR. CAVANAUGH: Thank you for the promotion, it's Mr. Cavanaugh.

I'm Dave Cavanaugh, Government Relations Staff for the Committee of 10,000.

Our bylaws prohibit us to receive any financial backing from any fractionator organization or any other manufacturer of supplies being discussed here.

I'm trying to gather some of the earlier and later presentations we've heard this morning. Unfortunately, I'm not an expert on Factor XI, so I can't exactly speak to that.

We have one published article about presumed blood-borne transmission yielding a symptomatic case of vCJD in England, another found in the spleen from a non-CJD symptomatic person later last year.

From that, the U.K. wrote 6,000 letters to people with hemophilia, warning them that they were at risk, telling them to see their doctors, and tell them that, and their dentists, and not telling them what to do about it, not counseling them about stigma.

I don't know if in the U.K. with national

health your doctor can fire you, but in the early days of AIDS back here that's what happened, people went to their regular doctor, got a positive test, and were told don't come back. They are experiencing stigma over there, it's a very different situation, I'm not going to draw any parallels, because I'm uninformed on it, but it's a smaller country and they have a larger amount of symptomatic CJD, so it's not an easy time for them.

What I take out of that is the need to say here, with some alarm, blood donors get vCJD from eating infected meat. USDA is inspecting 1 percent of the cattle in this country per year, aiming at the most symptomatic. We learned from the U.K. hemophilia experience, if you will, that long-term infections become a factor of experience, or blood experience, that we are talking about an eight, nine, ten-year incubation period. Please, don't be complacent that non-symptomatic humans or animals are not infectious with CJD.

Thank you.

EXECUTIVE SECRETARY FREAS: Thank you very much for your comments.

Is there anyone else in the audience who would like to address the Committee at this time?

Seeing none, Doctor Priola, In turn the meeting over to you.

CHAIRPERSON PRIOLA: Okay. This is the part on the schedule where the Committee discusses and votes on the issue presented to them by FDA, and if everyone would look at the end of the Topic 1 handout, that's what FDA has asked us to comment on, and that is, please comment on the FDA variant CJD risk assessment for Factor XI manufactured from U.K. plasma with regard to, (A) the model is applied to Factor XI, and (B) any additional information that is needed to improve risk estimates for this Factor XI product, and there was already quite a bit of discussion during the question period after each of the major speakers this morning, are there any other comments, discussions, things the Committee would like the FDA to know, in regards to this risk assessment model?

Doctor DeArmond?

DOCTOR DeARMOND: In think the models are fine, and as Steve Anderson pointed out, one of the features that they do help with is identifying parameters that we should be investigating in a more direct way with more empirical type, more real type data.

And, I think the risk assessment as a

predictor of areas that we should look at is really good, and the conclusions they come to, though, are, as they say, just rough estimates at this stage, because there are numerous assumptions built into them.

And, for me, it's still the key issue is that we have to get some data, and the data should be easily obtainable. That's the thing that's so irritating, is that blood samples can be looked at, the techniques are much better, the end products of extracting each of these factors, the coagulation factors, they can all be searched out.

In fact, I didn't mention earlier, we have a paper coming out that these new CDI assays are even better than the neuropathology, that is, looking at vacuolation scores, and immunohistochemistry. They are superior to that. We can find no vacuolation in some cases, no immunohistochemical staining, but there's a strong confirmation of dependent immunoassay signal.

So, the techniques have improved dramatically in the last couple of years, and we should be able to get these answers.

So, my conclusion again is, the model is great, and it's giving us - it's telling us key points in the system where we have to get some data, and we

can get the data.

CHAIRPERSON PRIOLA: Doctor Petteway?

DOCTOR PETTEWAY: Thanks.

Yeah, I'd just like to agree with Steve and add to that. From the plasma protein companies we've evaluated, we think the model is very good, too, and it makes sense.

But, it's the issue of understanding risk based on establishing the initial load and threshold, and I would encourage the Committee to encourage the FDA to see if they can provide some support to get the data that Steve is talking about. There are more sensitive assays available today to investigate human blood, human CJD blood, or vCJD blood, whether it's asymptomatic or symptomatic. And, it seems to me the problem is actually getting the samples and getting those connections made.

And, that data, if available, would provide a great deal of clarity, as far as these models and estimating exposure and risk.

CHAIRPERSON PRIOLA: Doctor Salman?

DOCTOR SALMAN: I think the model is academically and scientifically very reliable. I have no problem with that.

I have some concern about labeling the

model as a risk assessment model. I still think it's an exposure or characteristics of the exposure, and I think as the table, and taking that table to the public and show the variability in the type of risk, that maybe it could come negative on the FDA with their wonderful work, because it will show like there are so much variability, and I think it's that by itself, because of the data collected are not appropriate for this type of risk model.

So, I'm in favor of encouraging the FDA to go and seek the more reliable data that can be associated with the model, but I also think the model is a very good prototype for evaluation of any type of risk related to this type of issues.

My concern is, to take this model only for Factor XI, I think Factor XI by itself is not a high level of risk as compared to the other things at least what we understand from the U.K. data.

CHAIRPERSON PRIOLA: Doctor Allen?

DOCTOR ALLEN: I agree with the previous speakers. One, we do need to get additional data to the extent possible, and factor that in to refine the model.

The model itself I think has been a elegantly developed as is possible, given the current

information. There are a number of assumptions, they are well stated. Some of them we don't necessarily fully agree with, the point I mentioned before about the comparability between the population that goes into the Hilton data and the actual blood donors during the decade of the '90s.

And, I think as long as the model is applied to the population that was exposed through Factor XI in the past, I agree, I think the probable risk is very, very small, and that then comes - and we are not talking, as I understand it, about ongoing exposure at the present time, so then the question becomes, I will vote to accept the model, the question is, what's going to be done with the model and how are we - you know, what are the decisions that are going to result afterwards. That's not part of our question here, but, obviously, that to me is of the greatest concern right now.

CHAIRPERSON PRIOLA: Doctor DiMichele?

DOCTOR DiMICHELE: Once again, I would echo what everyone else has said about the model. It seems very sound.

I think the only thing, and this was a little bit of a discussion that was going on at the break, the only thing that could certainly add to this

model would be some sort of an epidemiological sort of Kaplan-Meier assessment of risk, you know, to the sort of time-based risk out of the U.K., sort of and maybe applying two different models, one looking at those patients who are known to have potentially received contaminated product, and those who received plasma-derived product in the high-risk period but were not known to be contaminated by donations from those individuals who so far have come down with CJD.

And, I think if we could have some sort of an epidemiological Kaplan-Meier ongoing risk assessment to then put into this model, not only for this, but for all plasma derivatives which is going to come up, I think it would be very, very helpful.

And, I don't know whether, you know, we can have a model that's generated here, or whether maybe something could be generated out of the U.K.

CHAIRPERSON PRIOLA: Mr. Bias?

MR. BIAS: I think I agree with everyone else that the model looks very good. I'm still alarmed with the number of uncertainties that we have, in terms of what data we put in the model. And, I would encourage the FDA not to allow us to get carried away with the model, now that we have a model, that we really go after the data, that we not alarm patients.

We will not have the same reaction from a U.S. population that's exposed as the U.K. has had, I can almost guarantee you they won't be stoic in terms of their response.

In addition to that, with the way patients are served in this country, with about 70 percent of the bleeding disorder population being in organized hemophilia treatment, I wonder what happens to that 30 percent that is outside. And, since we have, virtually, no contact with their primary care physicians, how we would even communicate effectively with them as to what they might tell their patients. It seems that we might be creating a little hysteria, so I would just advise caution to the FDA as they move forward with the model.

CHAIRPERSON PRIOLA: Doctor Schonberger.

DOCTOR SCHONBERGER: Yes. I'd like to echo what others have said as well. I think Anderson did a tremendous job in putting all this together, and I also appreciate the U.K. colleagues for coming here and sharing what they've done.

But, as one who has been impressed with all the unknowns associated with the model to date, I'm very hesitant to take on the negative effects that have been mentioned, both by the speaker from the

public talking discrimination and labeling of a whole group of people based on this kind of model, and your concerns that you just expressed on the Committee, of creating alarm, potentially unnecessary alarm.

And, there are three factors that - three observations, I call them epidemiologic observations, that make me wonder whether the 50 percent risk down to zero percent risk, whether the 50 percent risk is really very likely to occur, and that we may be much closer to the zero percent risk that fits this model.

And, these are the facts that most persons with hemophilia would be receiving many fold times the exposures that the Factor XI recipients would be exposed to, perhaps, even a couple logs or a couple of orders of magnitude more. And yet, we've had no hemophilia patients with vCJD reported from the U.K., or for any other country as far as I'm aware.

Second, the risk of plasma derivatives, of their transmitting the prion disease, in my mind is still theoretical, because I don't really know of any such transmission that has been convincingly demonstrated.

And third, which relates to this business of asymptomatic to symptomatic, you know, could we really be seeing a group of asymptomatic individuals

and we're just waiting for a long incubation period?

And, for that, I agree that the data is not ideal, but we can look at all the data that are available to us, and to date there's been at least one iatrogenic prion disease from an exposure to a known source of prion disease, that has first appeared within varying times, depending on the route of transmission.

So, for a known source where the route of transmission was the central nervous system, the first case showed up about 1.3 years after that exposure. Okay?

For the other known type of transmission, which would be intramuscular, like the human growth hormone, or the other gonadotropin hormones, they showed up first in a period of between five and 12 years, the first case.

Now, their mean incubation period might be longer, but you start seeing the first case, you know, within 1.3 years in a central nervous system, maybe five to 12 years intramuscularly.

And, what we are dealing with is something we hadn't seen before, which would be intravenous. So, the question then becomes, how does intravenous transmission relate to IM versus IC, and I think most

of us would think it's somewhat intermediate.

And so, we would think then that enough time, given the relative efficiency of these routes of transmission, has past, that we should have seen a case already in the hemophilia patient if we really had to be concerned about this risk, because what are you dealing with, we are talking about treatments between 1989 and 1997, if my calculation is right that should be about seven and 16 years have past for hemophilia patients that would have been treated at that same time, and in the U.K. hypothesis they were talking about even blood between 1980 and 1987 as being "high risk" at 1 percent level, which adds even more time.

So, the other sort of reassuring thing is that I think the longer one has to wait to see that first case, it's probably true that the lower the overall impact that problem is going to have.

Another bit of data about what, you know, that would influence our preventative measure, is what's the chances of it spreading through the surgical arena to other patients if we are wrong? And, we don't have all the data we would like, but even there we do know that the normal type of procedures that are used in the United States, the

routine sterilization procedures, will have an effect on the titers on those equipment. I mean, you know, it may not be perfect, but you are going to get several logs of decline just from your normal, you know, the regular sterilization.

And, it may be sufficient for a contamination, for example, of a low-dose contaminated material like blood, if you had surgical equipment contaminated with blood, the routine may actually be sufficient to eliminate even the low risk that might occur or spread.

And, there's where we could use some more data, not just the data on the model, but the data on what is the effectiveness of the routine sterilization procedures used in the United States on lowering the infectivity of these instruments. And, my understanding is that, Dave Asher, if he's here, is that we talked about, at some point, trying to look at that issue and get some data on that, which would then affect, you know, these kinds of concerns that are being raised on the negative side of sending out 6,000 letters and alerting people, because just the very fact that you are sending out 6,000 letters may convey a higher risk to the recipients of those letters than actually we can document or feel exists. And, that

would be a concern that I would have.

But, now that the U.K. has done what they've done, I don't see how we cannot inform those 50 people, our Factor XI people, about at least what has happened in the U.K., so they are not caught totally off guard that this has happened, and then give them some additional information, more of the type that we've heard here around the table, that at least in the United States at this point stay tuned, we are not as alarmed, and we don't think it's, perhaps, as necessary to be informing all your physicians and so on about the situation, but be informed. And, if you want to, fine, but this is the danger, you can get the kind of discrimination you were talking about, or the alarm, but put it into a context that shows that we are not all that concerned.

CHAIRPERSON PRIOLA: Doctor DeArmond?

DOCTOR DeARMOND: Well, Larry, my wife was an epidemiologist, who has been angry at me since we got married because she wanted to work at the CDC in Atlanta, and I didn't want to go to Atlanta.

But, she says the same thing to me. I always talk about testing, and she says, the epidemiology shows there is nothing there. So, you can't create panic. And, she's always emphasizing,

don't create panic. That can be as dangerous as not telling the truth about a true infectious process.

And so, I don't know what the use of this model is going to be, and how far you are going to push it, and that goes to your question, are you going to really tell the public that there is a danger, when the epidemiology, which is really even more important than detecting the prion protein, because it tells you the final product, does disease actually emerge.

If the epidemiology is negative and stays negative, there's - I agree with you, you don't want to create panic, and you have to have a very soft letter to the Factor XI people.

CHAIRPERSON PRIOLA: Doctor Johnson.

DOCTOR JOHNSON: Sue, I'm not sure what the vote is on.

CHAIRPERSON PRIOLA: Well, it's not really a vote, it's more a discussion. So, I think there's a consensus coming around the Committee that the model is basically valid and solid, but that you need more data to be more comfortable with the predictions for exposure, not infection or disease.

That's all this is, a discussion, not a vote.

DOCTOR JOHNSON: Well, because there's

really two issues that have come up, and they need to be separated. I think everybody agrees the model is interesting. I think most of us would think it might be over-estimated, but that's all right. I mean, if it needs to be worked with, it needs better data.

The second issue is, what should be told to the 50, or all the 10,000 hemophiliacs in the United States, or the 50 who received the British material.

CHAIRPERSON PRIOLA: Right, and that's -

DOCTOR JOHNSON: And, I think that's a very different question that we should focus on.

CHAIRPERSON PRIOLA: - well, it is a very important question, it is very different, and it's also not the purview of this Committee to do, because this Committee advises the FDA, and I believe that's a CDC issue.

So, discussion of that issue in this Committee isn't really pertinent to what we are doing. It's an incredibly important question, but it's not one that we have to deal with.

That's correct, right, Doctor Epstein?

DOCTOR EPSTEIN: Notification?

CHAIRPERSON PRIOLA: Yes.

DOCTOR EPSTEIN: Yes, we have specifically

not brought that question to the Committee today, because we see this as a process taken in stages, and we felt that the first stage should be to do our own risk assessment.

The thinking of the Committee will feed into a dialogue among the Public Health Service agencies, where we will consider the questions that you are putting on the table, which are, should patients be notified, what spectrum of patients should be notified, and what are the public health messages?

So, all of that, you know, will follow in due course, but the place to start is to understand the assessment of risk and the limitations to our ability to make that assessment. So, we are only at that stage here today.

DOCTOR JOHNSON: Well, I assume that the 50 people who received it under IND there will be a, basically, ethical mandate that they be informed in some way.

DOCTOR EPSTEIN: Well, I think there are many individuals who might share that view, but it's still, there's a process we would have to follow and actually make a decision, you know, whereas treaters may feel, perhaps, ethically obliged, or obliged for whatever reason, they still want to know what's the

correct public health message.

So, it's really not going to happen until we make some decision about the significance of potential risk and what kind of public health strategy is appropriate in our country.

So, you know, there may be that desire, and we understand that, but things really won't move forward until, you know, some decisions are made.

CHAIRPERSON PRIOLA: Are there any other comments?

Doctor Gambetti.

DOCTOR GAMBETTI: In tend to agree with Steve and others that although the model is excellent, Steve, there are some information, or it would be highly desirable that additional information be added, so that we can reduce this gap and, therefore, be more useful to the recipients of the Factor XI about the risk, if any, of that transfusion.

However, I think - and so I tend to agree with the fact that, perhaps, we should withhold any information before we at least try to improve the risk assessment.

I think it would be very useful if we could be more precise, if on improvement, what exactly, what practically, could we do to the current

model, or information available on which the model has been built, to improve the risk assessment? Are there practical things that can be done in a reasonable amount of time to have better assessment, or is this a kind of vague wish that the system - the model is improved?

In other words, Steve, do you think, do you see practical things that could be done in a short - relatively short amount of time to improve the quality of the assessment?

DOCTOR DeARMOND: No. I just don't think so, because you have - the time frame is the order of months to a year, or less, weeks, to months, to a year, and it would be quite a bit to get the other data at this stage.

And also, a lot of it has to be through the cooperation of Great Britain, and that seems to be a complicated issue also.

DOCTOR GAMBETTI: So, I guess we have to base our judgment on the model that we have right now, and decide what to do in terms of informing the recipients about the risk, based on what we have seen to date.

CHAIRPERSON PRIOLA: Doctor Telling?

DOCTOR TELLING: Yeah, notwithstanding the

issues of timing here, but there are, I think, practical things that can be addressed in terms of the animal models that are being used to study these issues. And, I'm thinking in particular about the BSE transmissions that have been performed in the U.K. by Houston and co-workers, and also, more particularly, the similar animal models using non-human primates that Corinne Lasmezas is using to study new variant CJD.

However, I think you are right, these are not answers that we are going to get in the space of a few weeks or a few months.

CHAIRPERSON PRIOLA: Doctor Gaylor?

DOCTOR GAYLOR: The negative epidemiology does not necessarily mean zero risk, as we are all well aware, but I certainly would encourage trying to use the human data to the extent we could to at least maybe get a more realistic upper limit on what that risk might be.

CHAIRPERSON PRIOLA: Doctor Belay?

DOCTOR BELAY: I think the risk assessment is the best available data that we have now, and there are numbers in that final table that are associated with the output for the model.

So, I was wondering if this risk

assessment, if there is a way of validating the risk assessment, and I don't know if this is feasible or not, or whether or not a risk assessment could be validated. So, the real question is whether or not the numbers given at the final table the last table, whether or not they are close to the truth or they are totally off the chart.

What would happen, for example, if we take the model and apply to the hemophilia population? Would it be consistent or at least close to what we've observed in the human population, because the absence of vCJD cases in the hemophilia population, would, for example, the final output be 90 percent, which would be, for me, off the chart? Would it be 30 percent, 40 percent?

So, are there ways that FDA could use to validate the risk assessment? What would happen, for example, if you apply the model to red blood cell recipients? We've already observed at least two transmissions of vCJD in patients who have received white blood cells.

I'm not sure whether or not this is feasible, but I just wanted to suggest it.

CHAIRPERSON PRIOLA: Are there any other comments before we move on to Topic 2?

Okay, let's go ahead and move on to Topic 2.

Oh, I'm sorry.

EXECUTIVE SECRETARY FREAS: Before you go on to Topic 2, can I just check to see if there are any other FDA centers here who have any comments about earlier topics?

COMMANDER O'LONE: Hi, good afternoon. I am Commander Martha O'Lone, and I have addressed some of you before on behalf of the Center for Devices and Radiological Health. I just wanted to make one comment based on the discussion this morning.

I want to thank CDC, especially Doctor Sehulster for coming and talking about the concerns we have with decontamination of medical devices, and I just wanted to reiterate that we are encouraging manufacturers to provide us with both detection and decontamination validation for devices, because we do not have anything at this time that has been cleared or proved for medical devices. So, our hands are still tied without that data.

CHAIRPERSON PRIOLA: Okay, thank you, Commander O'Lone.

So, I should double check with CBER, FDA, do you have the discussion that you need or hoped to

get from the Committee on Topic 1? Okay. Apparently, they do, so let's move on to Topic 2, and the first speaker is Doctor Dorothy Scott.

DOCTOR SCOTT: I'm going to briefly provide an introduction to the second issue. We seek the Committee's advice on the design and input parameters of a risk assessment model for potential vCJD exposures from products made from U.S. plasma, so this is in contrast to what you initially saw, which was a risk of exposure from a U.K.-plasma manufactured product. And, you'll see when Steve makes his presentation where those differences lie in the assumptions that we try to make.

I'll briefly undertake the rationale for vCJD risk assessments for plasma derivatives made from U.S. plasma, and also provide a short overview of TSE clearance and how it is important to these models.

Then, Doctor Anderson will brief you on the risk assessment model for products made from U.S. plasma, and that will include the model itself, very similar to what you've already seen for Factor XI, the data and assumptions, the uncertainties, and it's use of ranges and distributions, and the potential for sensitivity analysis.

Why should we do a risk assessment for

U.S. products? We've already been over this many times. There's been a probable transfusion transmission of vCJD reported in the U.K. Although, as was just mentioned, there are no cases to date of variant CJD in any plasma derivative recipients, including those in the U.K.

New information on vCJD prevalence and actual transmission by blood allows a risk assessment to be undertaken, and these risk estimates that we get provide a basis for reexamining the adequacy of current measures to protect blood and plasma-derived products.

And, the model also provides a framework to update risk estimates, and it contributes to public health decisions potentially. As we saw in the U.K., they had a risk assessment for plasma derivatives in the early 2000s by Det Norske Veritas, and they were able to use that framework then when they did C transmissions to try to make - well, to actually make public health decisions. So, we think it's a good thing to have in place, in spite of its current uncertainties.

What can it do for us? Well, I think Steve Anderson will keep his job for a while. It provides that framework. It can help us rank product

classes that may have greater or lesser margins of safety. It can give us an estimation of the likely best case and worst case risk of exposure to vCJD via products. Again, this will change as we get more information.

It helps us think about how to estimate the need for additional risk reduction measures for our products, and it also helps us get at the levels of TSE clearance in manufacturing processes that are likely to be meaningful. And finally, it provides some level of risk communication to the public.

There are a lot of things it can't do, and this has a great deal to do with all of the uncertainties you've just heard, so I apologize for any repetitiveness. It won't tell us the actual prevalence of vCJD agents in blood or plasma donors. It won't tell us the timing of the presence of infectivity in blood, of people who have vCJD who are incubating it, how much infectivity is there we won't know from the risk assessment. The effectiveness of blood donor deferrals for geographic risk of exposure to BSE also cannot be provided by a risk assessment, but this is important information, potentially, as you'll see. It can't give us clearance data itself. It can't tell us if there's an effect of cumulative

low-level exposure to the vCJD agent, and it won't tell us anything about the susceptibility of recipients to infection.

However, the good news is, a lot of this can be learned, and is being studied, and we may have, if not some answers, some better ranges to work with.

I just want to mention that there are two published risk assessments from Europe. The first is the Det Norske Veritas risk assessment commissioned by the U.K., and I've provided the websites, and the second one is a French risk assessment.

So, the question for the Committee, quite similar to your first set of questions, please comment with regard to the U.S. risk assessment model that Doctor Anderson will present, and please comment about what additional information is needed to improve these risk estimates that might result from the model.

I'm going to go on to the second talk. I'm going to preface Doctor Anderson's talk with an overview of TSE-clearance studies in products, because of their importance to the risk assessment.

You've seen this morning that for the Factor XI risk assessment the second-most sensitive factor or variable was TSE clearance. This is why I wanted to provide more or less a summary of what we

know and what we don't know, and where improvements might be made.

Clearance during manufacturing is an important factor in the overall risk estimation, and it can be tested in scaled-down studies, that is, in lab experiments that recapitulate the manufacturing process.

And, the viral clearance studies paradigm is applied to these kinds of studies, even though TSEs may not be, or behave exactly the same as viruses.

The paradigm, very briefly, involves scaling down the manufacturing process steps, so they can be studied in the lab, and validating the scale down, proving that the lab process is the same, or very close, to the manufacturing process.

I'll show you the two models that are now used, but one of them, the most commonly used, is to spike at a manufacturing step with a high titer of the infectious TSE agent. Usually, this is a model agent, often a rodent brain preparation. Reduction factors are determined for each step that is studied, and these may or may not be summed from non-orthogonal processes to give a total log ten reduction value.

Typically, the sources of infectivity that are used are brain preparations from experimentally-

infected animals, with human or animal TSE agents, or blood from experimentally-infected animals, and this is what is referred to as endogenous experiment, or type of experiment. The forms of the infectious agent will be brain homogenate or subcellular fractions of that, sometimes membrane-free infectious material, which on occasion behaves differently for certain manufacturing steps, or blood and blood fractions.

It also needs to be considered that the form of the infectious agent might be altered during manufacturing, and this is known as conditioning, and this has to be taken into account when undertaking or planning these studies.

The outcome measures of these can be in vivo infectivity, that is, typically, considered the gold standard, but it is laborious. You can use up a lot of rodents this way. It's expensive, because of the time and the number of animals. It's also long term, because these have an incubation period, especially when you are looking at low titers of infectivity, it can be quite long. But, they are considered very relevant.

In vitro, various ways of measuring the abnormal prion protein, are used. These need to be linked somehow to in vivo infectivity, so that we know

this recapitulates that.

This is a spiking model that's commonly used. Here you take the TSE preparation, it will have a high titer of the infectious agent, on the order of 10^7 or 10^8 infectious doses or ID50s rather.

This is just an example to remind people have these are done. In this case, we are looking very upstream in plasma processing, where the spike may be put into plasma at a 10 percent or less concentration, and then the manufacturing step is undertaken. In this case, you end up with cryoprecipitate, which becomes Factor VIII, and the supernatant which may become other products.

This is called the exogenous model. You can use a high titer, which means you can measure large amounts of clearance here. The problem is, nobody is really certain how much this kind of infectivity, or what physical chemical similarity it has to the infectivity that is contained in blood. That is one of the major caveats with this model.

The endogenous infection or clearance model is difference, because here you use plasma or a blood fraction from a TSE-infected animal, and that's your starting material, not a spike material. It undergoes the manufacturing step. You can only study

low titers of starting material, because, of course, the titers of infectivity in blood are low. It's deemed by many to be highly relevant, because it is, actually, the form that is expected to be contained in human blood or plasma. Limited by the fact that you have such a low titer here, you can't measure all the clearance that might be occurring in any given manufacturing step.

There are many published TSE clearance studies, and many still to come. The steps that have been studied and found to show some clearance in many people's hand include certain alcohol precipitations, but it depends a lot on the pH ionic strength and the amount of alcohol, as well as the starting matrix, how much clearance you get. PEG precipitation, salt precipitation, depth filtration, nanofiltration, column chromatography, under some circumstances have all been reported to result in clearance in these kind of experimental studies.

In all of these cases, the clearance relies on partitioning, and there's always been a question, certainly in viral studies, how robust a step that is. In other words, you are not inactivating the agent, you are partitioning it out. You are getting it away from your final product.

The additiveness of different steps needs to be demonstrated. Scale down again is very important, and the relevance of the model is something that's under heated discussion.

Again, I want to point out, as I have before, that manufacturing processes for any given set of products are highly individual, and rigorous demonstrations of TSE clearance have to be based on the specific manufacturing process.

This is an example, I've shown it before, but it just demonstrates that you can do depth filtration for example, but the amount of reduction that you get, or TSE clearance that you get, differs depending on the starting material, or the matrix as we call it, as well as the type of depth filter, perhaps, and you see you get anywhere from no clearance to a very high level of clearance, so you cannot say depth filtration will give you four, it might give you one, it might give you five. It all depends on the specifics, and this is just simply the same case over here.

This Committee in February of 2003 endorsed our consideration of labeling claims for TSE clearance in plasma derivatives, based on demonstration of removal during manufacturing in

scale-down studies. And, we encourage that these submissions be made to us. We have received some such submissions, evaluations are in progress, and we have approved a labeling claim based on TSE clearance studies.

This, of course, is voluntary. We ask that the best current methods are used, but the problem is we have a lot of science and evolution, so the best current method when you start your study might not be the best method when you finished your study.

The model selection is not restricted at this point, but it has to be justified. Certainly, three logs of clearance is something that we think is probably meaningful for non-robust steps. By that I mean partitioning steps, but there is some discussion about whether a whole series of processes can be considered that results in a high level of clearance even if any one step does not.

So, in summary, TSE clearance is a critical variable that's considered in risk assessments for variant CJD, and it can be tested, at least, on a laboratory scale with the caveats, especially those concerning the relevance of the spike. And, improvements in ways of studying this

would be very useful.

We can get data for the risk assessments from this information, and that is especially if there's been a specific study of the product that's under discussion for the risk assessment.

I just want to remind people that there are a lot of studies that have been done on TSE clearance. I found 16, I apologize if I've missed any, but I think that things continue to move forward and we are very grateful for all the work that's already been done.

And so, now I'll pass on the podium to Doctor Anderson again.

DOCTOR ANDERSON: Okay.

I'm actually aware that I'm between you and lunch, so what I'm going to do is actually, I think I've taken my longer period of time to explain the basics of risk assessment, and I've indoctrinated you, now you are all experts, so I'm going to move quickly through the slides, because there are a lot of similarities in what I'm presenting with what I just previously presented for Factor XI, and I'll point out the differences and walk you through those mostly.

And, what we are doing here is, we are doing a preliminary risk assessment, and this is more

of a concept model for U.S. plasma derivatives and variant CJD risk.

You've seen this structure before. I'm going to follow it in explaining to you what our concept model and plan is for doing a risk assessment. Again, here's the question, It looks very similar. We have the sort of preliminary part of the question, but our question that we want to focus on is, what is the risk of potential exposure to variant CJD agent in the U.S. populations. So, what we've done is, we've moved over and we are talking about U.S. risk, specifically, in this talk, for individuals that have received U.S.-manufactured human plasma derivative products.

What we have underway are several risk assessments, actually. We have a risk assessment underway for Factor VIII, Factor IX, immunoglobulins and serum albumin. Now, I'm providing sort of an overview of our concept model and assumptions for the risk assessment, but I think it's important to say that we haven't really completed the risk assessments. So, please don't ask for results, because we don't have any at this point in time.

Again, the hazard identification step is really what I just presented in the previous talk. I'm going to walk through that, just sort of walk by

that very quickly. Again, the dose response issues are the same as in the previous talk as well.

Human data not available, animal data are very limited. Again, predicting the probability of illness is extremely uncertain in these models that we are going to generate.

Now, what I wanted to do was actually - we've actually divided this model up, so before for Factor XI we had a three-part model, what we've done is added an additional component, and what we are doing is, we are not only looking at variant CJD prevalence - potential prevalence in the United States, but we are also looking closer at plasma donation, and I think we were getting at that issue earlier with the U.K. risk assessment. We didn't have that information for the U.K., but we do have some of that information for the United States, and we are integrating that into our model to improve the predictive capabilities of the model.

So, let me just go back and explain, again we've added a component where we are looking at vCJD in the U.S. population, or potential vCJD in the U.S. population, and the potential for plasma donations that may contain the variant CJD agent. Again, we are looking at probability and quantity. We are looking

for plasma donations, what are the characteristics of plasma donors, individuals that have variant CJD, we want to look specifically at what we had talked about earlier, age specificity of variant CJD, age-specific characteristics of blood donors, because that has a direct bearing on risk. Again, reduction, and then the dose that people receive of these products.

All right. So, there's a model. Again, our outputs are, we are looking at annual exposure to variant CJD agent. This is very similar to the model that we've seen before.

Now, I'm going to walk through more slowly module A and module B, because those are sort of new and probably the most important components, and sort of just breeze by the last two components of the model, concept model at this point.

So, for predicting potential variant CJD cases in the United States, we are looking at variant CJD risk in the U.S. plasma donors, specifically, and we think that the sources may - I'm sorry, that there may be two potential sources of exposure to BSE agent and that may lead to variant CJD infection and illness.

The first one is dietary exposure to the BSE agent from U.S. domestic beef consumption. The

second one is dietary exposure to the BSE agent during extended travel to the U.K. and Europe.

What we've done is, essentially, we've eliminated number one, and it's nearly zero for our purposes of this model. We did a number of worst-case evaluations of the risk, so dietary exposure to the BSE agent from U.S. domestic beef consumption, we evaluated USDA BSE surveillance data in cattle, and then what we did was, we estimated that the risk, the potential number of vCJD cases coming from that particular route of exposure at this point, given the information that we have we assumed it was negligible based on our analyses. So, what we did was, we just assumed that zero cases would potentially come from this source.

Now we move on to the, perhaps, greater potential source or vCJD cases in the United States, and that would be through dietary exposure to the BSE agent during extended travel to the United Kingdom and Europe.

Our approach, first of all, was the model estimates variant CJD prevalence in the United Kingdom population, then what we go on to do is look at a concept called relative risk of exposure to the BSE agent, and what happens is, we are pegging everything,

all of our analyses, to that variant CJF prevalence for the U.K., and we're saying that that's, essentially, the maximum risk, where we assign that a value of one. And then what you do for relative risk is, the relative risk for France and Europe, I'm going to talk more about this in a minute, but are considerably less. It's estimated that France has a relative - the U.K. has a relative risk of one, France has a relative risk of .05, Europe has a relative risk even lower, of .015.

Then what we do is, we calculate variant CJD risk for the United States plasma donors, using this information on extended travel to U.K., France and Europe. I'm going to show you how that's done in a moment.

The calculation of U.S. donor variant CJD risk is based on prevalence of variant CJD in the U.K., relative risk for U.K., France, Europe for BSE and variant CJD. The percentage of donors with the travel history, so the percentage of U.S. donors that have actually traveled to the U.K. for extended periods of time, and then to France or Europe for extended periods of time.

Then, we are also interested in this component of the duration of U.S. traveler stay, how

long did they stay. Presumably, people that stayed for very long periods of time in the United Kingdom, for, you know, more than three months, a year, would presumably have more risk than somebody that spent three days there.

What we do is, we actually just add - we calculate this for each country that a percentage of the donor population in the U.S. may have visited. So, if we know that a donor visited the U.K., what we do is, we have a calculation where we calculate the prevalence of variant CJD, so whatever that prevalence is times the relative risk, which for the U.K. is one, the percentage of donors in the U.S. that actually traveled or were in the U.K., and subject to potential exposure to the BSE agent, and then the duration. And, we prorate the duration of exposure based on the amount of time they spent in the United Kingdom.

We go ahead and do this for several populations. The first line is for people that visited the United Kingdom, second line is for France, third line is for Europe. And, we've got another set of calculations for military populations that may have been posted to the U.K., France and Europe as well. So, I just wanted to give you a basic flavor for the types of things we are considering in the model with

this equation.

Again, the prevalence you've seen, this is our assumed prevalence based on the Hilton study of one in 4,225 individuals that may have variant CJD in the United Kingdom. The periods of time that we're interested in for establishing relative risk of U.K., France and Europe, are the periods of a three-month stay in the U.K. from the period 1980 to 1996, just to note in 1996 we are not as concerned after that point because food chain controls were put in place and high-risk tissues are thought to have not entered the food supply after that point.

In France and Europe, we are looking at a stay, if a person stayed in Europe or France for more than five years from the period of 1980 to present. This correlates with our blood donor deferral policy. We are linking our model to our current blood donor deferral policy.

The model, again, uses this concept of relative risk, and we evaluate all travel in relation to the U.K. U.K. again, is one or 100 percent, and everybody else's risk is calculated in relation to the relative risk for the United Kingdom.

So, I actually should have presented this slide a little bit earlier, after having gone through

all this. The relative risk for U.K., France and Europe for BSE and variant CJD is a soon to be one for U.S. citizens, specifically, anybody that stayed in the U.K. for a period of over five years, a traveler, et cetera, would have a relative risk of one. That's an assumption we made in the model so far.

And then, anybody that stayed for a period of less than five years from 1980 to 1996, we did a proration of this risk, so if they stayed in for four years it was 80 percent of this risk, three years 60 percent, et cetera, on down to three months. So, we apportioned the risk equally in the years between -- 17 years between 1980 and 1996 for the U.K.

For France and Europe, it was a little bit easier, anybody that stayed in France for a period of greater than five years had a relative risk of .05. Anybody in Europe had a risk of .05.

Now, this concept of relative risk is just based on exposure, the number of variant CJD cases that have been observed in France, and then also, I believe, France received approximately 5 percent of its beef supply from the U.K. during the times of the BSE epidemic. So, that's how we are getting this relative risk of .05 or 5 percent.

And, it's much lower because Europeans