probability that an individual given say X units of infected blood would become infected, and that is something that we realize is highly uncertain. We would never be able to really put any bounds on that value but we could potentially look at scenarios in which we vary this infectious dose right up to the value of one so that anybody given an infected unit of blood becomes infected which is a plausible value but also not just the infectious dose but also the numbers of donations recipients of transfusion really determine this R naught value. So, it is the magnitude of that blood supply and this just gives some figures for the UK and for the similar figures available in the US from the national blood service figures for 1996-97. We had 1.9 million donors donating just 2.2 million units of blood. We also have some good data on red cell transfusions so where the blood is actually going to and that gives estimates of the units received per 100,000 population per year. It,also, gives good estimates of the age distributions and this is a final point I would like to stop on.

This is the age distribution of the recipients and the donors. So,you can see that blood donors are typically in the 30-to-50 age range but as we all know transfusion recipients are very much older individuals and this age distribution is also very, very important for this

concept of a self-sustaining epidemic because if these were the primary infections and we do see infections in that age group they might go on to donate blood that is used and infects individuals in this age group but it is then fairly unlikely that we would get infections going back into this population simply because of the age distribution but those receiving red cell transfusions are unlike to then themselves donate blood. They are in a much smaller probability.

So, these age distributions are very important both for blood transfusion and also for surgical instruments in determining the potential scale of an epidemic by these routes and this is work that is ongoing.

So, in summary then the variant CJD clinical cases remain low and the current predictions are also low based on either fitting into clinical cases or including a subclinical or carrier state.

The prevalence estimated from the appendix survey is higher than would have been expected from the epidemic observed so far if we didn't include any sort of form of subclinical infection and then this inclusion of this subclinical infection or carrier state to explain this discrepancy between the two data sets gives rise to an estimate that approximately 20 percent of those infected will become clinical cases.

There is of course still uncertainty in the genotypes and Richard already covered some of this. Worst case scenario is where the non-MM genotypes have similar susceptibility but much, much longer incubation periods and this could result in a five-fold higher estimate of future epidemic and the big remaining uncertainties are blood transmission and potentials for secondary epidemics.

Okay, I would like to acknowledge my people who have helped with work and finally I have put a few of the key model references down for people to look at.

Thank you.

DR. PRIOLA: Thank you very much, Ghani. Will you and Dr. Knight be here for the rest of the day?

DR. GHANI: Yes.

DR. PRIOLA: Okay, so, you will be available for questions.

I think we will take a break now for about 15 minutes and reconvene at ten-fifty-five.

(Brief recess.)

DR. PRIOLA: Once again I would like to remind the Committee because I know this is tough to sit through these talks without asking questions but to keep in mind the questions that we are supposed to address as we listen to these talks so that when we get to the discussion we can get through the 10 questions we have to discuss early this

afternoon.

So, our first speaker for this next session is going to be Alan Williams and he is going to talk to us about modeling the risk of variant CJD in US donors.

Agenda Item: Modeling Risk of vCJD in US Donors - Residual Risk and Efficiency of donor Deferral - Alan Williams, PhD, OBRR, CBER

DR. WILLIAMS: Thank you. Combined with laboratory testing the screening of blood donors by medical history and other screening questions is a powerful adjunct to helping to maintain the safety of the blood supply but there are a handful of situations when safety of the blood supply is wholly dependent on the screening of donors because there simply isn't an available laboratory test and variant CJD is one of those instances.

Most of you have seen a pie chart similar to this in the past but this is a representation of the overall risk burden in the donor population prior to the initiation of any interventions, any donor screening for dietary exposure.

One can see that the major risk component is dietary exposure within the UK, components related to travel residence in Europe, a portion of the donor population that was imported from Europe at the New York Blood Center and something relating to the second set of

deferrals was the exposure to UK beef on military bases.

The first set of recommendations was issued in November 1999. I am not going to go through the details because Steve covered those in this talk and you had those in great detail last October but basically the primary deferral was related to time spent in the United Kingdom for 6 months or greater and a major consideration during that policy determination was the impact on the blood supply.

If one deferred everyone who had a contribution to that original pie chart one would lose more than 35 percent of the blood supply. Obviously that would not be tolerable. So, with the first recommendation there was an estimated loss of 2 percent which was tolerated and left this as the fractional component of risk proportionally a larger component from the base exposure. So, it was a sizeable component 32 percent from UK travel and then the Euro blood and Europe exposure.

Then in January 2002 the second set of recommendations issued which tightened the deferral for UK travel added base exposure and this is the representation or the impact on that second pie chart. The total risk burden reduction was estimated to be about 91 percent from that original pie chart and one can see here the representation of the DOD exposure removed by the deferral.

the DOD exposure left in because of time that was lower than the time period of the recommendation.

UK exposure cut not quite in half with a little bit of UK exposure left primarily due to individuals who traveled less than 3 months and similarly for European exposure.

Now, this gulf really I think shows the two elements that are incorporated into the model. The white areas were risk is removed what we are going to be looking at in a major component of my talk is what is the efficiency of those donor screenings; has everyone in fact with that risk been taken out of the blood supply or is there a false-negative rate for the donor screening questions? The segments of the pie that are left there represent the shorter term deferrals, those who have been to Europe for just a couple of days or a week and are not subject to the deferral but may well have had dietary exposure throughout this period and represents quite a large number of donors.

So, just to reiterate factors related to the current donor screening procedures are considered in the proposed FDA model that Dr. Anderson described. The first is periods of dietary BSE/vCJD risk among donors that are less than the current deferral criteria. These are estimated from the original donor travel survey data and

estimated as about 9 percent of the total risk burden prior to any implementation of donor screening.

The second factor included in the model is the consideration of the sensitivity of current donor screening procedures to exclude those donors with deferrable risk when they appear for donation.

FDA is proposing that in the absence of empirical measures the proposed FDA risk model should incorporate an estimate range of 90 to 90 (sic) percent sensitivity to occur in donor screening procedures to exclude that deferrable risk.

The second point, due to the donor population size, the limited other risk-reduction measures and the fact that the donor population dietary risk really is the risk contribution to the model the impact of this factor of sensitivity on the model is quite large.

So, the balance of this presentation will concern the rationale behind the 90 to 90 percent sensitivity estimate for the questions.

I think one thing to understand is what are the different components of donor screening. A policy is developed which is a combination of regulatory policy and industry standards and local blood establishment policy and this is generally made known to potential donors through educational materials, web sites, donor calls with

questions. Often they get a little prescreening over the phone.

So, the elements that contribute to donor screening are the reduction of entire population subsets such as occurred in the past. Paid donors are eligible for donation but in the whole blood segment those units need to be labeled as being from a paid donor. Prisoners for some time have been ineligible for blood donation.

Then through education there is a large component of self-deferral before a blood drive. This is the group that Dr. Anderson mentioned that are aware that they are not eligible and simply don't appear at the blood center.

A second self-deferral is folks who appear at the blood center. They may not have been aware of it beforehand that they are not eligible but they see the materials while they are sitting waiting to be interviewed and determined that they are not eligible and leave.

There are also those where it is very hard to get any sort of empirical measures of how many donors actually do that because they are not available for study. The highly visible area of donor screening is a deferral by staff during the medical history interview process and I will say more about that in a moment and then finally if the donor proceeds with donation and that risk factor is not appropriately elucidated sometimes additional

information comes back to the blood center and we find out about that risk after donation and in instances when that unit has been issued for transfusion that would constitute a biologic deviation and be reportable to FDA.

So, there are limited data available but that tends to be somewhat a passive reporting system. So, again it is hard to get rigorous data.

I mentioned the deferral on site that I would say more about. The 1999 recommendations there was an estimate of 2.4 percent of deferral among the blood donor population and 2002 about 5 percent, a little bit over 7 percent overall.

You can see that the on-site deferral experience and these have been presented through the years by Red Cross and other blood establishments, the current deferral is 3 to 4 per 1000 overall, most of this representing not first- time donors because the definition of first-time donors gets very complex but Red Cross has considered this as donors who have no previous onset exposure to the variant CJ question. So, although they may have donated previously it was in a time before the deferral was put into place.

So, you can see that the bulk of those deferrals are those who had no previous administration of the question and about 7 per 10,000, those who had a previous

experience of the question may have traveled since that time but may have been missed in the earlier question administration.

A small proportion but when looking at about 14 million donations per year it can constitute a sizeable number of individuals and then similar data among the source plasma population, about 4 per 1000 deferral among candidate donors. These are donors whose plasma has not become part of the plasma pool because they are not yet qualified donors and if they a positive question response their donation is removed and the ongoing rate about 4 per 10,000,not incompatible with the whole blood donor population but there are probably other factors such as level of education, materials that are encountered and demographics that in fact probably account for some of those numbers in the underlying rationale.

So, how does one assess the sensitivity of donor screening? The things that we would really like to get at but we can't for variant CJD are changes in donor seroprevalence, reduction in adverse events to recipients or comparisons with risk levels in the general population.

Now, we can't get at any of this for variant CJD. So, the approach that we took was looking at some non-agents and some extrapolations from analogous situations with other transfusion transmitted disease risk factors,

and then I also wanted to be sure to mention that there has been a lot of recent work in the questionnaire process itself. The Blood Products Advisory Committee has worked closely with FDA and the blood collection community so that the questionnaires currently being used for donors now have been cognitively assessed for understanding by donors, a lot of this work by the National Center for Health Statistics. So, really for the first time we have some confidence that the questions have been through a rigorous qualification process.

So, to look at some of the comparisons, first looking at marker prevalence and although I am not showing data for incidence presumably data should be available to make some similar comparisons using incidence of infectious disease markers.

So, here we are looking at comparing the general population versus first-time donors. First-time donors have not donated. They have not been prescreened. It is the best population to try to correlate with general population data.

So, looking at HIV seroprevalence, a report by Jerry McQuillan which is the Dallas County Household Survey found a little less than 1/2 percent HIV-positive in donor age general population subjects in Dallas County. That can be compared with about the same time frame HIV

seropositivity of .03 percent in first-time donors. So, the difference between those two should be the impact of the education, screening on the donors and results in a 93.6 percent reduction in HIV seroprevalence.

Similarly one can make that comparison by looking over time and this I would say is the classic graph developed by Dr. Mike Gershon and his colleagues in the early 1990s.

This was a combination of looking at Irwin(?) Memorial Blood Center seroprevalence data together with some of the prevalence data for targeted studies within the San Francisco area and the NHLBI transfusion safety study, and this graph was produced to show the risk of HIV transmission per unit of blood starting with the earliest days of the epidemic through 1985 which was the development of specific screening.

It shows that the epidemic was under way for several years before initially recognized, then recognized by clusters of Pneumocystis carinii and other clinical syndromes and then the first post-transfusion AIDS case report and the recognition of high risk donor subpopulations which were then subject to deferral and self-deferral, and a lot of self-deferral took place so that by the time the test actually became available the risk in the transfused blood had been reduced about 90

percent solely on the donor screening aspect.

Similar comparisons, we started looking at seroprevalence, and here we are looking at risk from accepted blood donors and there was a study published by the University of Chicago showing that in the general population of the country there is about a 4.1 percent prevalence of males who have had sexual contact with other males in the past 5 years.

Compare that with survey data and I think the publication was shared with you a little more than 1/2 percent of that risk, males who have had sex with males since 1977 in accepted male donors, so, again, general population versus the male donor population about an 86 percent reduction and then one last example comparing intravenous drug use risk. Again, the Dallas Household Survey documented a little under 4 percent IDU since 1978 in the general population versus 1/2 percent intravenous drug use ever among accepted donors, again about an 86, 87 percent reduction.

Now, those show the positive impact of screening but I think there are also data which show quite convincingly that there is a false-negative aspect of screening and this comes from several different types of observational studies but basically data collected from donors after they are accepted for donation may identify

behavioral risks that should have prevented their donation and that is what is being called deferrable risks.

I think again some of the classic data come from interviews with HIV seropositive donors, many of these studies sponsored by the Centers for Disease Control. For the period of the late 1980s and then another study in 1997 for both males and females when a donor is found HIV seropositive and subject to one-on-one interview one clearly sees risks that should have resulted in the deferral of that donor including MSM risk in males, heterosexual contact in a small component of injecting drug use and then similarly for women a much larger group with no reported risk but again others with non-heterosexual contact and one can see those types of data whether it is interviews with donors who have been identified with hepatitis infection or HTLV. One commonly sees risks that should have resulted in deferral and then similarly the Red(?) study did a post-donation anonymous survey of risks among accepted donors. This was published in JAMA in 1997 and then repeated in 1998 and also published with very similar results but a wider range of risks assessed and this shows that really for all the risks that are being screened for there is some false negative that gets through into the accepted donor population.

Just one anecdote that I happened to look at and

didn't make it on the slide but males who trade drugs or sex for sexual contact there is a general population figure for that, I think, again, the Dallas Household Survey reported 11.6 percent in the general population versus 1/2 percent in blood donors. So, here we are seeing about a 20-fold risk reduction there as well.

So, you can see we are looking at general ballpark of risk reduction ranges.

From a behavioral science perspective one can understand why there are difficulties both in screening individuals for histories as well as trying to get rigorous data to look at efficacy.

Information about personal behaviors is inherently difficult to collect. One big thing is the social acceptability of information and clearly for injecting drug use and MSM that would probably be a larger factor than for travel history.

Response rates on behavioral surveys tend to be low. There tend to be missing data when someone completes a questionnaire and inconsistencies are frequent.

Now, keep in mind that blood establishments are regulated and they simply need to have all the blanks filled in. So, that is less of an issue within a regulated blood collection environment but it is a background problem with history taking.

People tend to avoid careful reading. I think for the donor setting there are those who are convinced that a video presentation or a one-on-one interview is better than simply giving somebody two pages of educational material to read but still the community is very dependent on reading material.

It is known that there is an educational effect of donor screening that even if a donor has missed the first time they are in there is a likelihood that they will be caught the second, third or fourth time that they are in.

So, there is a reduction in deferrable risk with subsequent donations and the Red study has shown some of that information for some of the major screening factors.

What happens when a donor determines that they are in fact, the individual that is being talked about in that screening questionnaire? There can be an aspect of denial and there can be quite a proactive lack of respect for policy if you have an individual who is knowledgeable and feels that the donor screening is out of line that in fact out of lack of respect they simply will not identify themselves as the subject of that policy and fail to self-defer.

There can also be external factors such as secondary gain for donation be it peer pressure coming to

the donation site with a group of friends and not wanting to appear to stick out by being deferred. Plasma donors in the country largely are paid for their donations. So, peer pressure, other secondary gains and the environment, what is the privacy of the donor screening procedure; can one in fact give a socially less acceptable answer and be assured that it will remain confidential? And then finally, the aspect that has been looked at recently with respect to the questionnaire is the issue of comprehension of the donors and question complexity. Both of these are an acknowledged problem for the travel histories where one has to think of the cumulative travel history and determine whether or not that exceeds a 3-month period for the UK. I think there are probably those, a few of those in this room who would have some difficulty doing that if they are not current blood donors.

So, in conclusion based upon limited data from analogous donor screening situations we believe that a 90 to 99 percent estimate of screening sensitivity is bound, is realistic. The 90 percent lower bound supported by screening experience with other transfusion transmitted infections, the 99 percent upper bound supported by behavioral factors, the lower likelihood of travel among plasma donors and the high proportion of repeat donors, I mentioned that qualified donor aspect for source plasma

donors and in fact all donors now it is an industry standard, are prequalified so that de facto all donors for source plasma are repeat donors.

There may be other ways to get at the predictive value and sensitivity of the questions but the work hasn't been done. There could be targeted follow up of the reasons for the post-donation information reports. There could be on-site attempts at validation and there could be comparison of results from different donor screening modes such as post-donation interviews or surveys to help continue to study this aspect.

So, I remind you that the TSE Advisory Committee in fact gave a mandate for the initial collection of survey data which you have heard about now many times so that if there is a key area of data collection I urge you to identify that and make it known most likely to the National Heart, Lung and Blood Institute which funds these types of studies and would be capable of carrying that out.

Thank you.

DR. PRIOLA: Thank you, Dr. Williams.

We will move on to the talk by Dr. David Asher who is going to tell us about estimates of variant CJD infectivity in plasma.

Agenda Item: VCJD Infectivity of Plasma - Estimates from Experimental Models - David Asher, MD, OBRR, CBER

DR. ASHER: Thanks. First, I want to say that to comment on the loss of Al Jenny so soon after Beth Williams, they were two of the people that I have relied on for years for expert advice besides being two of the nicest people that I can think of and I, personally, feel a tremendous sense of loss at their deaths.

We are asking the Committee to comment on several assumptions used in FDA's provisional variant CJD risk assessment for plasma derivatives. We have attempted to use very conservative assumptions about infectivity in plasma. We have assumed the infectivity to be present in blood throughout incubation period although we certainly that that won't prove to be true.

The maximum and minimum incubation periods of variant CJD are not known. Depending on how you estimate the minimum incubation period somewhere between 5 and 12 years after oral exposure seems reasonable and the one case of transfusion transmitted vCJD 6 years.

About infectivity how much infectivity might be present in human blood during various stages of the incubation period, the shorter answer is we don't know. All we can say with any confidence is that two units of non-

leuko reduced packed red blood cells each contained at least one human intravenous infecting dose which translates into something like .005 doses per milliliter minimum.

However, it seems likely that there is more infectivity than that and we have taken provisionally 0.1 dose per milliliter as a reasonable minimum.

The rest of the model is based on what we know from experimental studies in rodents and 10 infectious doses per milliliter has been taken as an approximation of a common result.

We took 310 as the maximum dose because that is the maximum reported anywhere in the literature for animals although as you will learn that number is not really well supported.

In the 8 minutes or so that remains in this talk I can't review much of what we know about TSE agents in blood but I do want to remind you that for sporadic CJD attempts to transmit disease by inoculation of patients' blood into non-human primates even whole units into chimpanzees have failed. Claims of transmission of CJD from patients into rodents have not been confirmed.

Those observations are consistent with the epidemiological studies that failed to show blood transfusion or exposure to blood products as a risk factor for sporadic CJD and especially the surveillance of more

than 100 recipients of labile blood components from donors who later got sporadic CJD presented here found that no recipient has ever been recognized with sporadic CJD, quite a different situation from that that we see with variant CJD as you know.

Studies of animal TSEs revealed similar difficulties in detecting agent in blood but when those difficulties were overcome a troubling consistency in detection of small amounts of infectivity in blood of animals during the incubation periods of TSEs was seen.

For many years William Hadlow and Carl Eklund hypothesized that there might be a blood-borne phase of infection in scrapie. They tried and failed to transmit the disease from sheep and goat and mouse blood into mice.

Several years ago Hunter Houston and colleagues succeeded as reviewed by Richard Knight earlier today, succeeded in transmitting natural scrapie to sheep by transfusion demonstrating the previous failures had probably been limited both by the species barrier of the assay and by the small amount of blood that it was possible to assay in experimental animals by intracerebral inoculation.

Shortly before the scrapie transmission by transfusion was demonstrated by Hunter and colleagues the same investigator succeeded in transmitting sheep adapted

BSE by transfusion to scrapie-free sheep.

Those experiments did not permit estimates of the amount of infectivity in blood but experiments with the BSE agents adapted to mice suggested that the amount of infectivity in mouse blood must be very small; a published incubation time assay and I will comment about that in a minute was about 5 intracerebral infectious units per ml of mouse blood.

Most work in estimating the amounts of infectivity that might be present in blood has been performed using other models of TSE adapted to rodents which was first demonstrated by Elias and Laura Manulites who demonstrated convincingly in 1978 in blood of guinea pigs infected with a strain derived for a CJD patient. Soon after that Koroda and Gibbs in 1983, reported similar findings in mice infected with a strain adapted from the brain of a patient with a familiar TSE later identified as Gershner-Streisler-Shankar(?) syndrome.

A particularly popular model has been the 263K strain of scrapie agent adapted to hamsters and I will present some of the work of Bob Rohwer who is here to participate in the next session but who kindly lent me several of his slides. That model was first reported by Heino Diringer shortly after that by Petricio Casachia and Mauricio Pochiari after hamsters were inoculated

intraperitoneally with scrapie. The results of that study were reworked recently by Phil Colmer and his colleagues at Detnar Scarveratosh(?) to estimate the average of 310 50 percent infectious doses per ml of blood during the first part of the scrapie incubation period and I want to note here that those results have at least two serious problems. First the pattern of blood infectivity which in their studies was present only in the first part of the incubation period has not been confirmed in later work and does not appear to be predictive of what we have seen for variant CJD.

In this panel prepared by Bob Rohwer I will show you what I mean if the cursor comes on. Okay, the cursor didn't come on. Okay, and I don't know where the pointer is. Okay, Heino Diringer demonstrated infectivity. The red stars are successful isolation of transmission attempts and the open circles are negative attempts, failures. In the first part of the incubation period they stopped looking at 40 days. Casachios showed infectivity on through 90 days but failed to demonstrate it after that and found no infectivity at 120 days when the animals were sick with scrapie.

If you look at other studies this is Laura Manuilitis's study in guinea pigs and you can see that after a little infectivity during the first couple of weeks

potentially coming from the initial inoculum a number of weeks went by with no infectivity and then periodic detection of infectivity and infectivity detected in some animals on into clinical disease and the work of Karoda and later Paul Brown and Delores Achevanukova no infectivity early. Infectivity appears later in the incubation period and on into clinical disease. So, the Casachio Prochiari work on which that number of 310 is based suffers from not being predictive for other models of TSE.

Another problem is that they used an incubation period assay that is highly inaccurate in estimating small amounts of infectivity.

The classical method for estimating infectivity is titration testing serial dilutions of samples looking for that dilution at which easy assay unit has a 50 percent chance of being infected. Another way of looking at it is that it estimates the volume of inoculum that has a 50 percent chance of containing infectious agent.

As the amounts of infectivity get smaller the incubation periods get longer and so during most of the range of infectivity incubation period can be used as a, or the time to death can be used as a rough estimate of how much infectivity is present.

The problem is that it at the very smallest amounts of infectivity the dose-response curve becomes non-

linear so that in this panel also prepared by Bob Roy you will see that at the end point there is a very wide spread of infectivity and animals come down anywhere from oh, I don't know, 130 days or out to 450 days and if only a small number of animals are being used those numbers cannot be used to predict accurately what the end point dilution would have been.

Paul Brown and Lois Achovanukova performed more informative estimates of infectivity using mice infected with the Fu-1 strain of GSS, the same one that Kuroda and Gibbs have developed and they did something approaching a classical titration. They found that buffy coat contained 44 in one experiment intracerebral infectivity units and 106 in another. Since in their study an ml of blood contained about a 1/20 ml of buffy coat that means that anywhere from 4 to 10 infectious units per ml plus the infectivity in the plasma must have been present and that varied from 10 to 22 infectious doses per ml in the same experiment. So, adding together the buffy coat and plasma associated infectivity it might be reasonable to conclude that whole blood probably contains somewhere between 9 and 22 infectious units per ml. Both of them are here today and would be far better than I to answer any questions. An even more precise, if very expensive assay method for infectivity has been used by Bob Rohwer called the limiting

dilution titration and it represents an expansion of the classical titration by increasing the number of assay units near the end point.

For blood that means it assaying an entire volume, large volume of material and dividing it into aliquots and injecting the whole thing intracerebrally into hamsters. The readout is therefore not an ID50 but a direct measurements of the number of lethal doses present in the whole volume corrected using the Poisson distribution for the possibility that some of the animals might have been exposed to more than a single dose of infectivity.

When they did that on multiple assays Bob and his colleagues have titrated the blood of a large number of hamsters inoculated both intracerebrally and orally at intervals after infection, the maximum amount of infectivity they found in terminally ill hamsters varying from about 2 infectious units per ml to as much as 25 infectious units per ml with both median and mean about 10 infectious units per ml.

The infectivity was first detected in this series of experiments just before about day 50 representing something less than 50 percent of the total incubation period rising gradually until the onset of illness which was of course quite different from the results that

Patricio Casachia had obtained.

At least 30 percent of the infectivity was associated with plasma in these experiments, 45 percent with buffy coat and 25 percent with red blood cells although some of Bob's other work suggest that red cells and platelets may not be intrinsically infected. I am sure we will hear more about that in the next session.

So, to conclude the provisional risk assessment for plasma derivatives is proposing as an assumption using a triangular distribution for the amount of infectivity that might be present in blood of donors incubating variant CJD a minimum of .1 ID50 per milliliter of blood mostly likely 10 ID50 and a maximum of 310 ID50 acknowledging the uncertainty regarding the assumption.

As I noted the experimental basis for the 310 ID50 per ml is questionable. However, it does represent the highest published value for rodent blood. The value is only about a log and a half higher than the mean value estimated for hamsters and that difference could be considered as a safety margin.

Perhaps members of the Committee think that we should even use a higher margin of safety or perhaps you know about information that we are not aware of.

Until last week we had a preliminary sensitivity analysis that had suggested that differences of this

magnitude were not likely to be major drivers of overall risk. However, when the values were recalculated changing some of the other assumptions it appears that the level of infectivity in blood may not be an inconsequential element in risk although it doesn't appear to be as important as the prevalence of infection in the donor population or the ability of the manufacturing process to reduce infectivity.

Thanks very much.

DR. PRIOLA: We will move on to Dr. Scott for her presentation.

Agenda Item: Review of TSE Clearance in FVIII Product Manufacturing - Dorothy Scott, MD, OBRR, CBER

DR. SCOTT: Thanks. As Dr. Asher just mentioned the amount of clearance in steps used to manufacture any product really is important for the risk assessment, that is it is a variable that is found to have a lot of impact. So, right now I am going to review the publicly available information on TSE clearance by steps used to manufacture just Factor 8 products.

These are the questions to you. Do you agree with our proposed approach for estimating clearance of TSEs from Factor 8 products by manufacturing for use in the risk assessment model and what experimental data would enable refinement of these estimates and allow comparisons of clearance affected by various steps in Factor 8

manufacture?

Just to very briefly remind everybody this is how a typical clearance step is done. You take a TSE infected material. Usually this is brain because it has a very high titer, but this can also be plasma from an infected animal and you add that to the starting plasma which would be like a plasma pool or intermediate material. Obviously this is all done at the lab scale. Then you take a scale-downed process or a series of processes that you want to study to see if they result in any clearance and you measure at the end of this process the leftover infectivity and this measurement as has been mentioned is typically in logs of reduction.

There are two main kinds of studies that are done but the most common form manufacturing processes is the spiking studies.

The reason for that is because if you use infected brain you can demonstrated significant clearance levels because the spike might be 6 to 9 logs of infectivity. Therefore if you end up with three or two you can show a substantial amount of clearance if it exists.

However, this has been criticized because the physical similarity to the blood-borne form of TSE agents of brain material is uncertain. There has been similar behavior demonstrated in some situations, that is

convergence of in general of fairly high clearance for alcohol precipitations with spiking experiments and endogenous infectivity experiments but this has particularly been questioned for some other steps such as filtrations that are size dependent because there may be some forms of TSE infectivity that are quite small.

At least when the characteristics of blood-borne infectivity are defined the relevance of spiking preparations can then really be studied and understood. Endogenous infectivity studies using starting plasma of an infected animal are certainly more relevant it can be argued but they cannot demonstrate high levels of clearance because the starting infectivity is usually on the order of 1 to 2 logs per ml.

Those are very difficult experiments to titrate. So, there are two ways that we thought of to estimate the TSE clearance in Factor 8 product manufacturing. One is to use the published literature to identify clearance values from similar steps for Factor 8 or other products and we have seen this done in other risk assessments but I would point out there is a probable major flaw in this which is the fact that different clearance levels are often demonstrated for what appear to be similar steps, but these differences are likely due to product and process specifics. You don't need to read all of this. This is just

an example of TSE clearance studies. Here is your reduction factor and these all use depth filtration with some kind of upstream process that allows material to be filtered.

This is a starting material and you can see this comes from published information including a package insert but basically the reduction factors that you get with depth filtration are highly dependent obviously potentially on the type of depth filter that is used but even not entirely that and on the starting material and its characteristics which would include different protein concentrations, pHs, ionic strengths and levels of alcohol or other things that are used to precipitate.

So, we didn't choose to use this more general method. Rather we thought it would be better to use product specific studies to identify clearance values. These are obviously more relevant to the specific products but they are not available for all Factor 8 products in the US and even when they are peer reviewed and published many of them have not been evaluated in detail by CBER.

There are lots of variations in the study methods including different spiking preparations. Even the brain preparations have different methodologies and they might be variably clarified, solubilized, sonicated or filtered and then of course there are microsomal and fibril preparations.

Furthermore the assays for TSE at the beginning and at the end may be surrogates, that is PRP, scrapie measures or bioassays and these results can sometimes differ.

I would just point out that the labeling claim that we offer for TSE clearance is based on demonstration of infectivity reduction at this time.

Now, what about the Factor 8 products that we look at? I just wanted to mention overall the Factor 8 products that we have and the purity has typically been defined by their Factor 8 activity and these have been called intermediate purity and you can see that that has a lower amount of Factor 8 per milligram of protein than a higher purity preparation or what is called a very high purity preparation. However, there are lots of methods used even to produce these intermediate purity products and overall for all of these products we see cryoprecipitation as a very common feature but there are also PEG precipitations in some cases, size exclusion chromatography, ion exchange, monoclonal antibody affinity chromatography and heparin affinity chromatography.

So, it is more than just cryoprecipitation. All of these products have a number of other subsequent steps that further purify the Factor 8.

I would like to mention, also, that many of the

intermediate purity products contain von Wiilebrand's factor, and this is very important for people with von Willebrand's disease obviously.

The potential clearance of variant CJD or any TSE may not correlate with the classic definitions of purity. It really is process dependent. So, if you think of studies of TSE clearance and Factor 8 products one of these is not published. What we did do though is we took six of these reports and looked at the amount of clearance that we got and basically this is a summary and actually it is very similar to what PPTA has presented to this Committee in the past that cryoprecipitations typically do not result in a lot of clearance, that PEG or glycine precipitation just each step by itself may result in some level of clearance, maybe slightly higher with ion exchange chromatography and maybe slightly higher with affinity purification.

Now, how are our current plasma-derived Factor 8 products made? There is not a lot of detail here and the reason is because this came primarily from package inserts and a lot of the processes that are used in the manufacture are proprietary.

So, I just listed some of these, the heparin affinity for alphanate, PEG precipitation for Koate and immunoaffinity for these three products as well as ion exchange for both of these.

So, in other words what I am telling you here is this is not complete and understandably not because of the proprietary nature of manufacturing.

Now, this is our proposal for TSE clearance values to be used in the risk assessment. There is a range of clearance values that is suggested by the available studies for different manufacturing steps and the ranges that we would like to select are consistent with additional data that is available to us which has not been published.

What we propose to do is to run the risk assessment three times with three different clearance ranges, a likely minimum of 2 to 3 logs and this would more or less reflect a single step with an intermediate level of clearance in that 2 to 3 range, a mid-range clearance level of 4 to 6 logs which would usually involved a single step with a higher clearance level or multiple additive steps, that is throughput experiments sometimes demonstrate that if you start and do a number of steps in sequence that you get a higher amount of removal than you would if you studied just one of those steps.

In other words, they can be additive, and then a likely maximum of 7 to 9 logs which typically would involve two higher clearance steps, that is if they are additive.

So, I just put the questions back up again. Do you agree with this approach for estimating clearance? I

think that I hope I have helped you understand that we do not have a comprehensive data set for these products and what data would help us refine these estimates because this is an important risk parameter.

Thank you.

DR. PRIOLA: We will move on to the last talk by Dr. Weinstein.

Agenda Item: FVIII Product Usage In Clinical Settings - Mark Weinstein, PhD, OBRR, CBER

DR. WEINSTEIN: As Dr. Anderson mentioned I will talk about the utilization of Factor 8 products in clinical settings. Utilization factors being considered for the model include the severity of the disease and treatment regimens.

I will also talk about our proposal to model cumulative variant CJD exposure per year assuming a linear ID50 dose response.

The first question that we are presenting to the Committee regarding this topic is what data should be used to estimate how much Factor 8 is used by typical patients. For this estimation we need to know what the definition of a typical patient is; how much product is used per treatment; what is the frequency of dosage and what should be the time period to be evaluated?

To answer these questions I will briefly review

some of the characteristics of the patient populations we are considering and available data sources for estimates of dosage and dosage frequency.

I will also mention some of the limitations that we have in our data collection. Regarding the patient populations we are considering hemophilia A is an inherited X-linked recessive trait. It is caused by a deficiency of the coagulation Factor 8 related to mutations of the cloning of the clotting factor gene.

The age-adjusted prevalence of hemophilia in the United States is approximately 1 in 10,000 males. Factor 8 normally circulates in the plasma bound to a second very large protein, von Willebrand's factor. I will just point it out in the model. There is a Factor 8 protein bound to the von Willebrand's factor.

The von Willebrand's factor protects Factor 8 from proteolysis, enhances Factor 8 synthesis and concentrates Factor 8 at the site of active hemostasis. Von Willebrand's factor is also needed for binding of platelets to wound sites. Von Willebrand's disease is caused by reduced levels of Factor 8 activity and there are several types of von Willebrand's and subtypes of von Willebrand's disease but we will be considering in our model type 3 which is the most severe and requires treatment with plasma-derived products.

Von Willebrand's factor protein occurs in higher concentrations than Factor 8. In hemophilia A one can have no circulating Factor 8 but normal levels of von Willebrand's factor but in severe forms of von Willebrand's disease with little or no von Willebrand's factor present there will be little circulating Factor 8 and I will discuss that in the next slide.

To treat hemophilia A one needs products that contain Factor 8 but may or may not contain von Willebrand's factor.

To treat type 3 von Willebrand's disease you need concentrates that contain both von Willebrand's factor and Factor 8.

This chart outlines some of the characteristics of the hemophilia A population and von Willebrand's disease population that we are considering. Each of the populations is treated on average with different total doses of product and at different frequencies.

Hemophilia A patients with severe disease have less than 1 percent Factor 8 and have spontaneous bleeding predominantly in joints and muscles. They constitute the largest proportion of the hemophilia A population and there were roughly 6200 patients in the United States in 2002, our base year for our calculations for our model that had severe hemophilia A.

Those with moderate disease with Factor 8 levels from 1 to 5 percent have occasional spontaneous bleeding with severe bleeding accompanying trauma or surgery. We estimate there are about 3600 individuals in this category or 25 percent of the total hemophilia A population.

Those with mild hemophilia characterized by severe bleeding with major trauma or surgery are about 30 percent of the total population or about 3600 individuals.

Type 3 von Willebrand's disease is quite rare. These folks have less than 1 percent von Willebrand's factor and 2 to 3 percent Factor 8. They often have mucosal bleeding and severe bleeding with trauma or surgery. We estimate that there are approximately 250 of these individuals in the United States.

Regarding product usage the picture is extremely complex. First most hemophilia A patients we estimate on the order of 70 to 80 percent use recombinant Factor 8 and this is particularly true in the case of children.

As I mentioned previously von Willebrand's disease patients have to use products containing von Willebrand's factor.

The frequency of product usage and dosage are highly variable and depend on the patient's weight, type of bleed and clinical severity of the disease.

Analyzing data about product usage from different

data sources is complicated because of the variation in how investigators define terms such as prophylaxis, intermittent or secondary prophylaxis and episodic or on demand treatment.

For example in some studies prophylaxis has been defined as receiving a product every other day or twice per week for 45 weeks or more per year.

However, on the form used by CDC in their uniform data collection program prophylaxis is defined as receipt of treatment products to prevent bleeding or to prevent rebleeding. Prophylaxis is further divided into a category of continuous if products are to be administered indefinitely or on a regular schedule to prevent any and all bleeding.

Intermittent prophylaxis is defined as the patient receiving treatment products on a regular schedule for a period of at least 28 days and at least one occasion since the last annual visit but therapy was not expected to last indefinitely.

Episodic is defined as receiving product only in response to bleeding complications. You will notice that in this data collection form that there is no specified or amount of product to be used.

Now, the best quantitative data that we currently have access to is from a CDC study carried out from 1993 to

1998 on all hemophilia A patients in six states. These states included Massachusetts, New York, Colorado, Georgia, Louisiana and Oklahoma.

Data was obtained from patient reports obtained from physicians, hospitals, clinical labs and hemophilia treatment centers. The list of information obtained in this study is quite extensive and will be very helpful to us. It includes the severity of the disease based on the activity range of Factor 8, the total number of bleeding episodes per year, and very importantly an estimate of the amount of product used per year, the pattern of usage whether it is prophylaxis or episodic, the number of weeks scheduled for prophylaxis and the brand of product being used.

Possible limitations of this data include that it might not reflect current usage. Changes in the average weight and activity level of patients using plasma-derived products may have changed which will affect the average amount of product used. Extrapolations to other states in the United States might not be accurate although the diversity of states in the original study was planned to be representative of the entire country but unfortunately for our purposes no data was collected specifically on type 3 of von Willebrand's disease patients.

The second source of information comes from the current program that was initiated by the CDC in 1998

called the universal data collection program. Patients voluntarily give information to the survey and we can obtain information regarding the numbers of hemophilia treatment center patients from the start of the program, the disease type, whether it is hemophilia A, severe, moderate, mild and type 3 von Willebrand's disease, the treatment prescription, again, unfortunately not quantitative but whether it is episodic, continuous or intermittent and the product brand used by the patients.

No information has been collected about the amount of product used. We, therefore have to extrapolate the amount of product used from the survey study. About 85 percent of patients who go to hemophilia treatment centers are enrolled in the UDC program and from the 1993 to 1998 survey data about 70 percent of the total hemophilia A population visit hemophilia treatment centers.

The patient population that doesn't visit hemophilia treatment centers may be different from those who do. For example, they may have milder forms of the disease.

Also, we know that some patients may use more than one product brand or type of product. Nevertheless using a combination of data from the survey and from the UDC data we have calculated the following information.

Most of the patients who use plasma-derived

products are in the episodic category. Most use monoclonal affinity purified Factor 8.

Of the total 6200 hemophilia patient population in the severe category about 29 percent use plasma-derived products. Twelve percent of the 3600 patients in the moderate category use plasma-derived Factor 8 and 6 percent of the 4600 in the mild category use plasma-derived Factor 8.

Of the 189 type 3 patients who receive plasma-derived clotting factors all were on episodic treatment. Now, as to the amount of product used we can make some educated guesses based on current practice. For example, regarding prophylactic use some clinicians have defined prophylaxis as using 25 to 50 units of Factor 8 per kilogram 2 to 3.5 doses per week and for a 70-kilogram man using 25 units per kilogram for 52 weeks per year we calculate that that would amount to about 182,000 units per year.

At 50 units per kilogram, 3-1/2 times per week he would use about 637,000 units.

Again, the term "episodic" is ill defined for our purposes but just to cite one study in the literature a product was termed episodic when it was used at doses from 12.5 to 53 units per kilogram and it was infused 4 to 72 times per year.

In this study if we use that frequency wit h our 70-kilogram individual this would amount to receiving anywhere from 3500 to 270,000 units per year and he would receive a median dose of about 45,500 units per year.

Now, we can get some sense from the literature that we are at least in the ballpark about the amounts of product used per year from a study by Linden. She used the information obtained in the 1993 to 1998 survey study and extracted only the information pertaining to New York State. Dr. Linden reported that patients under prophylaxis in the severe, moderate and mild category used about 200,000, 100,000 and 25,000 units per year on average respectively.

Those on episodic treatment who were in the severe category used 80,000 units, moderates 21,000 units and milds around 3600 units.

Now, unfortunately these data are confounded because the estimates were combined from both hemophilia A and B patients. However, a very important point is that we can go back to the original survey data from all six states and with the very generous help of Mike Souci at the CDC who is in charge of the database and does much of our statistical analysis we can separate our data out about the use of product in hemophilia A patients to get detailed information on product use for each patient.

So, in conclusion regarding clinical use the existing data are limited and have not been analyzed for estimates of clinical use of specific brands of Factor 8 products in patient groups. We plan to analyze data from the ongoing UDC survey to estimate the numbers of patients using specific brands and the distribution of disease types. We, also, plan to extrapolate data from the 1993 to 1998 survey in the six states to estimate the total number of US patients and product consumption per patient with stratification according to the clinical setting.

If there is inconsistent information from these two analyses it would be reconciled using patient-based medical records data.

Now, we also know that in the future we may be able to get more accurate data about product usage from a survey study of inhibitor formation in hemophilia A patients.

This study is part of a larger data collection effort called the National Bleeding Disorders Coalition. However, this project is still very much in the planning stage and it might be a number of years before we are actually able to get data from this source.

We are, of course, interested in whether the Committee has further ideas about how we should collect data.

I would like next to turn to the question of whether repeated exposures to low doses of variant CJD infectivity lead to clinical disease. The data about risk of cumulative exposure is limited to a few studies in animals and I will describe one such study by Diringer.

Hamsters were fed one dose of scrapie-infected hamster brain for 1 day, one dose each day for 10 days or one dose every 4 days for 10 exposures.

There were about 60 animals in each of these studies. Approximately 1 percent of the animals fed a single dose died while 8 percent receiving a dose every day for 10 days died and 4 percent died of those receiving a single dose once every 4 days for 10 exposures. The authors concluded that hamsters receiving a repeated standard infectious dose several times have a higher risk of developing scrapie than those receiving a single infectious dose.

In another part of the study the authors fed the hamsters one infectious dose once. They, also, divided the dose into 10 tenths and gave one tenth eery day for 10 days to one group of animals and one tenth every fourth day for 10 exposures.

The animals who received the full dose all at once had 11 percent risk of infection while 8 percent had a risk of infection when the dose was spread out over 10 days

and 4 percent had a risk when treatment was spread out over 40 days.

The study suggested that there was a smaller risk of infection associated with longer intervals between feeding.

These findings suggested exposure to repeated low doses of variant CJD infectious material by the oral route increases the potential for infection but that increase in the time between doses may decrease the risk.

So, in conclusion the risk of variant CJD infection may not be linearly related to cumulative exposure. Nevertheless despite possible low prevalence of variant CJD in plasma donors and limitations to pool size repeated dosing substantially increases potential risk of variant CJD exposure in Factor 8 product recipients.

We propose in our model based on these considerations to estimate the risk per annum in plasma derived or von Willebrand's factor product users rather than the risk per dose and we are asking whether the Committee agrees with this proposal.

DR. PRIOLA: Thank you very much, Dr. Weinstein. We will move on to the open public hearing portion of the meeting.

Agenda Item: Open Public Hearing

DR. FREAS: As part of the FDA Advisory Committee

procedure we hold open public hearings to give members of the public an opportunity to make a statement concerning matters pending before the Committee. As Chairperson at this time I have received two written submissions for the meeting record, an e-mail from Ms.Sachau and an e-mail from Terry Singeltary. These e-mails are currently in the Committee members' folders, the public viewing notebook and copies are available at the reception desk upon request.

We, also, have received three requests for oral presentations for this morning's open public hearing sessions. The first requester is Dr. Peter Ostrow, professor and former dean of the University of Buffalo Medical School on behalf of the CJD Foundation Medical Education Program.

Dr. Ostrow?

I am sorry, the most important thing before you begin the Chair must read a statement regarding all open public hearing speakers.

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

public hearing speaker at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise FDA encourages you at the beginning of your statement to advise the Committee if you do not have any 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.

Now, you can go ahead.

DR. OSTROW: Thank you. Thanks for the opportunity to present at this meeting, and there are no financial relationships to report. I am going to show you a brief preview of a continuing medical education program about CJD that addresses some issues that are not well understood by health care workers including physicians and even neurologists. The CJD Foundation became aware of this information gap through their many contacts with patients' families and the questions that these people had about the disease, questions that physicians were often unable to

answer.

In some cases the families also complained that the diagnosis seemed to take longer than it should have, that they felt like they were in the dark during the workup and that once a diagnosis of CJD had been made health care workers at various levels were not well prepared to deal with it and to some extent this is quite understandable. CJD is a very rare disease and few physicians have had much experience with it and certainly it can be very hard to diagnose especially in the early stages, and there is also a lot of misinformation freely available in the popular press.

Our program is intended to provide information to physicians that will make them more familiar with these diseases, that will help them in the workup, that will facilitate more useful and supportive interaction with patients' families and that will help physicians counter some of the widespread misconceptions about CJD.

I would like to acknowledge three people who are here today who have starring roles in this production, Dr. Dick Johnson, Dr. Richard Knight and Florence Kranitz, President of the CJD Foundation.

Our producer, Cathy Nelson is also here to make sure that this thing works and that I don't speak too long and now I would like you to see our preview.

(A DVD was shown.)

DR. OSTROW: This DVD which is aimed at physicians and residents will be available at the end of this year through the CJD Foundation. We hope to distribute it widely. I should mention that it will also include a review of the Red Cross Look Back study that the CJD Foundation is collaborating in to look at blood transmissibility. It is our hope that we will obtain support to produce a series of these things aimed not just at physicians but also at other health care workers, at the funeral industry, at patients and their families and also at the general public and thanks again for the opportunity to present today.

DR. FREAS: Thank you, Dr. Ostrow. Based on that preview I will look forward to seeing the full feature film.

We have two additional presenters this morning. They are Mr. Mark Skinner, President of the World Federation of the Hemophilia Foundation from Montreal, Canada and Andy Wertzel from the National Hemophilia Foundation. They have agreed since we are behind schedule to pool their time and Mr. Mark Skinner, President of the World Federation of Hemophilia Foundation will be making the presentation.

MR.SKINNER: Good afternoon. Thank you for having us and I have no financial disclosures. In fact both the

WFH and NHF adopt strict ethical guidelines and would preclude us from having an investment in any of the companies or products we are talking about here today.

The issue that we are talking about and the reason that I am speaking today on behalf of both organizations, the National Hemophilia Foundation located here in the US and the World Federation which represents 107 member nations around the world is in fact that the actions of the FDA on this issue are of vital importance to the global patient population and the actions of the leading regulatory bodies including the FDA will certainly be heard around the world and will resonate and have the potential for impact on the use and the treatment of patients globally.

The World Federation of Hemophilia in fact last October in October 2004 published our first guidance document or complete guidance document. We published several before that discussing the assessment of risk as it relates to TSEs and hemophilia products.

We do believe that it is feasible to counter this emerging threat in our patient population but we also recognize that it is important that we balance the issues of safety and supply and we think of risk in this total context which includes access to treatment and also includes the impact on the supply of products and certainly

actions of the Committee, the TSE Committee and the FDA in considering this important issue are a clear sign that the regulators are not complacent.

As a patient population we certainly adopt; we adhere; and we encourage regulators to advance the precautionary principle when there is incomplete scientific information which is certainly what we are faced here with today.

We acknowledge as a patient population that we are dealing in an area of uncertainty and we don't expect precise and exact answers. We do appreciate the effort to communicate in an open and transparent manner. That doesn't always occur. It is in fact occurring here today but there are certainly steps beyond and before this that are important for us as a patient population to be involved in and perhaps most significantly the FDA is not the only regulatory agency around the world which in fact is talking about this subject and so as regulatory authorities in France, Spain, the UK, Australia have all opined on similar subjects we are certainly seeing a divergence among the risk assessments and so the confusion among the patient population globally or the risk for confusion is certainly growing every day.

As I mentioned before we published our risk assessment back in last October and the parameters which we

identified as they would relate to TSE risk for patients using plasma derivatives are listed out here. These are certainly very similar to the ones that the Committee has been addressing.

What I would say as an aside is that this risk assessment from the World Federation has actually now been accepted by Vox Sanguine(?) and it will be published in an article authored by Albert Ferugia, James Ironside and Paul Giangrande and we expect that to be published electronically in December and in the January issue of Vox Sanguine.

I am going to start first with the sixth issue because it is the most important and in the interests of time I can certainly skip over some of the others but the area in question of risk communication with the patient population, the clear and unequivocal answer on the part of the patients is that risk communication is important and the actions of publishing and developing a risk assessment are very helpful with a couple of caveats, that there is in fact advance consultation, that the patients do have a right to be informed, that the patients do have a right to be consulted and that it is vitally important that the leading patient organizations have an opportunity to be consulted in the development of the risk assessments as well as our leading clinicians and this doesn't mean simply

a consultation in the context such as this but throughout the development process we need to have an opportunity for the patients to interact, to understand the kinds of issues t hat are going forward because certainly as we move forward and a risk assessment is published it is vital that the patient population's knowledge and understanding of the issues of certainty and uncertainty are acknowledged and understood.

If a risk assessment is dropped into laps of the patient population without adequate information we will see significant harm done to the patient population and this notion is certainly reinforced from the experience of the eighties.

One of the conclusions and recommendations of the IOM study relating to the HIV decision-making process was that it is shared responsibility and groups such as the National Hemophilia Foundation and other patient organizations representing the hemophilia community have a right and should be involved and should share the responsibility of decision making as it relates to infections such as HIV.

So, we believe the guidance from the eighties is applicable today and we should continue to monitor and learn from the lessons of the eighties.

The consequences on the public health for the

5100 odd patients in the UK that have hemophilia were in fact quite severe. We saw rapid access denials for patients for dental procedures. We saw denials for basic procedures including endoscopies in major hospitals around the UK and in fact those procedures continue today, some out of fear and some out of just simply the cost on the public health system.

If you are left with little choice but to destroy the medical instruments afterwards who is going to bear that cost, and so the hemophilia patient population was rapidly stigmatized because of the notification process that was not optional but was mandatory in the UK in which letters were sent not only to their general practitioners but also to their dentists and it was put in all of their files that in fact they were at risk for variant CJD.

Now, granted there are several approaches and the approach that the UK took was one of a general health precaution. So, the patient population as a group was generalized and they did not adopt the approach of individual risk assessments for individual patients which of course for the many reasons we have heard here this morning would be extremely difficult but we think precisely because of the adverse outcomes that occurred in the UK and because the patient population for hemophilia and not those with immune deficiency or alpha 1 anti-trypsin deficiency

or in fact for the general blood transfusion recipient where there is an absolute risk known for transmission of vCJD, they did not receive the same universal precautions and as a result they weren't stigmatized but in fact some of those patients may in fact have a greater risk.

So, we as a patient population were actually singled out and have suffered great harm to our health care as a result of that. So, we are hoping that the Federal Government here in the US and other regulatory authorities have learned from this lesson and understand the importance not only of advanced consultation which did occur to some degree in the UK but of thinking through this process and allowing the patient population and our health care providers, our physicians to work with you to develop the appropriate response.

So, in summary as it relates to risk communication we as a patient population do think that we have the right to be informed and consulted. We strongly support the precautionary approach as it relates to patient groups. We do think it is important that we need to balance over reaction and patient stigmatization with the under reaction and the lack of information and lack of transparency. It is an extremely difficult balance. It is sensitive and we think through working with the patient groups that we can achieve the appropriate balance.

Certainly in risk assessment or any guidance that is offered has to come with counseling, competent explanation and clear information and you have to acknowledge uncertainty. I mentioned before the lack of consensus and the confusion between the global risk assessments certainly is one that will not only confound here in the US because patients do read the Internet. They do hear about the information happening around the world but will certainly make it difficult to manage treatment and care around the world and perhaps have an impact on product supply ultimately around the world and certainly the patients locally and nationally all need to be treated the same, that we need to think of this as a global problem and certainly given that the treatment products on which we rely are in fact global.

I would use just by way of illustration to emphasize the point of the importance of risk communication just this past weekend we had the National Hemophilia Foundation Annual Meeting and I had an opportunity to present on risk communication as it relates to variant CJD.

Following the meeting a young mother with a son of the age of 12 came up to me and in tears. I mean she is truly worried. She doesn't know what to do in terms of treating her patient. He has a high titer inhibitor and he is looking at immune tolerance using the plasma derivative

with von Willebrand's factor to treat his condition but the one thing that she did tell me clearly and I think this goes right to the answer to question No. 6 is she said, "I appreciate very much knowing what we do know and what we don't know. The absence of information is more fearful than knowing what we don't know and as a mother I appreciate the openness and having a chance to hear it early and to make decisions with my health care provider."

Just quickly I want to run through a couple of the other questions and I don't know that these require a great deal of response. I will point out just one or two instances where our position differs and most of our answers here in fact come from the risk guidance we published last October.

Similar to the FDA when there is a doubt and when there is a variety of estimates in terms of what prevalence should be we adopt a conservative approach as has the FDA and suggested that we would encourage the Committee to adopt that as well. Obviously most of the risk assessment will hinge from this and this is the critical issue which is why you have it No. 1 and we did as well.

The prevalence of vCJD in the US we agree very much with the donor deferral mechanisms and until there is a clear pathogen reduction or elimination process that has been validated we have to maintain the integrity of the

donor process and we would encourage the Committee to do that of course keeping in mind that it needs to be updated as new scientific evidence is available going forward.

Perhaps this is the area of slight difference with the FDA's assessment and guidance to date is that we do believe that the larger animal models are more predictive and we have adopted a similar position of the UEO and the UK in a one-to-one equivalency between intracerebral and intravenous routes of transmission. The level of CJD infectivity in human plasma, again, the similar approach following the precautionary principle adopting between the two and the options presented of the conservative estimate.

Dorothy Scott talked about this and we agree completely that clearance values must be product and process specific and without analyzing and evaluating each product it is impossible to have a generalized approach to the Factor 8 derivatives and the other products on which our community depends and part and parcel to that and assuming that you do agree to go forward with the risk assessment and communicate it to the community we do believe that it is appropriate for the FDA to consider actually including a label warning in the plasma derivative product speaking to variant CJD and while we are not typical authors of this kind of warning that is done

through the regulatory process there is some language that we have put together and some thoughts that we believe would be useful and certainly mirrors the experience of similar warnings for HIV and HCV that have been previously communicated.

Again, we think it is important that it be indicated that it is highly precautionary,that there are no known transmissions but communicating uncertainty is an important step in informing the patient population.

A comment on the CDC data. We certainly agree that the UDC data, I had been a participant in this study since its inception, is very useful and perhaps the only available source. I would remind you as Mark pointed out that there are in fact a number of deficiencies in this data. There was a reference earlier perhaps supplementing this data with insurer data and I would suggest that is not the best option to do given the experience of working with insurer data and reimbursement and trying to understand treatment patterns. I think that you would not find that of great use. You may in fact find that some other countries which have a more centralized health care system you might be able to find data that would be more instructive as to plasma use treatment and dosage and duration of treatment that could supplement the CDC data and I would encourage you to look outside the US before looking to the insurers

and payers within the US.

That question was deleted in the final questions. We do believe that risk is communicated and certainly from our experience with other pathogens that the patient populations are dependent upon it and that is consistent with what the FDA has recommended.

So, thank you.

DR. FREAS: Thank you very much, Mr. Skinner.

Is there anyone else in the audience who at this time would like to make a short comment to the Committee?

MR. CAVANAUGH: Thank you. I am Dave Cavanaugh with the Committee of 10,000. I will be quite brief, no financial interests. We appreciate what the World Federation has already come to the conclusion of but some of what we heard this morning was quite disturbing and I just want to speak to it in the hopes that you can bookmark it in your discussions. The whole discussion of preclinical numbers in the UK was very upsetting and there was only a brief reference later on as to the infectivity of persons during that period.

We have a couple of ideas about latter half, former half of the incubation period. We know so little. It is very much a call to be cautious and advisory as much as possible.

There was a discussion of the fractionation and

reduction of infectivity as well and every time I heard the figure 90 percent I thought of 10 percent. That is all it would take and it makes us very nervous. Again, we need to understand that only in a few spiking studies has anybody been able to claim an acceptable, putatively acceptable level of reduction. It is not established. It is transmissible through factor. We have to assume that until it is absolutely wiped out as a possibility and it certainly is through whole blood. There is no national association of blood transfusion recipients. The folks in the blood products family sometimes have to represent that but please take that into account as well.

On the usage the material that Mark was presenting about calculating amount consumed it is known that 70, 80 percent of persons with hemophilia utilize in some degree hemophilia treatment centers but it is often not those that are mild that don't but those that are severely affected and have complicating factors like HIV and hepatitis that have to seek out infectious disease specialists and hepatologists. So, I wouldn't discount that population. I would at least assume that it is at the same level of risk and finally I got here at eight-thirty this morning thinking we started at nine. So, I missed the first presentation from USDA and I haven't heard that agency mentioned elsewhere this morning but you are linked to

USDA. You are our FEMA. I hate to say it that way but that means rising to the occasion.

We have a motto that we have started. I don't think it is ready to take it on Oprah yet but the motto is if you eat beef don't give blood. The item that I wanted to say that I had forgotten in a list of things that have already been discussed was the post donation information revelations about true MSN behavior, true IDU behavior. They are catching 1 in 200 donors. How many get away? I don't know what the estimate is and I would like to talk to Alan further about it but a lot of people come and they never have that "aha" 3 days later. So, we do have a risky blood supply.

Thank you very much.

DR. FREAS: Thank you, Mr. Cavanaugh. Is there anyone else in the audience at this time?

If not, we will close the open public hearing session for the morning. We will have one in the afternoon.

DR. PRIOLA: I think with that we will break for lunch and reconvene here at one-thirty.

(Thereupon, at 12:45 p.m., a recess was taken until 1:45 p.m., the same day.)

A F T E R N O O N S E S S I O N 1:45 PM

Agenda Item: Committee Discussion and Recommendations

DR. PRIOLA: Okay, most of the Committee members are back. If we could get started with the discussion we have 10 questions to discuss but only the very last one that relates to issue 6 is a voting question. So, the FDA is interested in our discussion and the recommendations.

So, Dr. Scott is going to present the first question to us.

DR. SCOTT: This is as you have in your sheet of questions and in the issue statement what estimate should be used to reflect the prevalence of variant CJD in the UK which of course is linked to the prevalence of vCJD potentially in donors in the US, and we had proposed using the surgical tissue surveillance data as the assumed prevalence of vCJD in the UK.

This would be the most conservative estimate that we think we can make at this time and then we also propose that we run the risk assessment model again using epidemiological predictions based on diagnosed clinical disease in the UK as an alternative assumption of prevalence and then there would be adjustments for possible latent infections during the incubation period.

So, wait for the Committee's comment on this

especially about using the surgical tissue surveillance data.

DR. PRIOLA: So, just to remind everyone this was one of the critical parameters that was pointed out earlier in the presentations and I think it was Dr. Ghani who mentioned that you can't use the clinical data as a substitution for prevalence unless you include the carrier state which is what you sort of added on your slide, right,with the latent; that is the same as the latent, yes.

So, comments from the Committee?

Dr. Geschwind?

DR. GESCHWIND: I guess one comment I had was my feeling is that the surgical data should in some ways be the lower estimate and the reason I say that is that it is under the assumption that the immunohistochemistry is not 100 percent sensitive and PNS papers so far myself and Stan Prusner and others in February of this year using the confirmation dependent immunoassay showed that many cases are missed by immunohistochemistry particularly many parts of the brain.

So, I think that we should be conservative with that.

DR. PRIOLA: Other comments from the Committee?

Does the Committee agree then in general with the FDA proposal that both sets of data should be used?

I see lots of nodding heads.

Any other discussion?

DR. BRACEY: Yes, I think it really is important to use the surgical data because again there are so many unknowns as far as the incubation period and clearly in terms of the precautionary principle the idea would be to avoid exposure rather than to avoid clinical disease.

DR. PRIOLA: Okay, if there is no further discussion we can move on to the second question.

DR.SCOTT: This is also an issue with a fair amount of impact on the ultimate outcome of the risk assessment because it has to do with how many donors in the pool might have vCJD that are not deferred. What is the residual risk? But the question reads how effective are current donor deferrals for geographic risk of vCJD and our proposal is that based on the currently available surveys of unreported risks for other conditions and allowing for margin of error that we estimate that the FDA recommended deferral policy has a 90 to 99 percent efficiency for deferring donors with a specified increased vCJD risk.

DR. PRIOLA: I forgot to bring up one point with the previous question and that is does anybody have any comments about the PRP genotype influencing that modeling because all the modeling or the model that was presented to us was met-met homozygous with the caveat that if you

included the met-val it would sort of be included with the latent carrier, the sort of subclinical state. Was that correct? I just want to make sure that, is that true, Ghani? I just want to make sure that point doesn't get overlooked because of this heterozygous subclinical individual who is picked up.

DR. GHANI: At the moment the only model, the MM homozygous and if you include allowance for their being other genetically susceptible groups you increase your estimates of clinical cases but at the moment the models are assuming that they are behaving very much the same way so that all genetic groups have potentially a subclinical infection as well. I just think one important point to note is that the models are fitting to this data from this tissue survey. So, they are not producing anything different if you assume that you use the tissue survey data. They are assuming at the moment that the tests are only sensitive in the last 75 percent of the incubation period and that we have varied that for the last 50 percent and that scale is the actual magnitude and that is something that has to be scaled in terms of the interpretation of the tissue survey as well. The actual published estimates say, "One hundred percent sensitivity." More realistically figures are probably around 50 percent.

DR. PRIOLA: Okay, thank you. I meant to bring up

that point, and I forgot.

All right, so, on to issue 2. So, how effective are the current donor deferrals for geographical vCJD risk and does the Committee agree, have anything to add to the FDA proposal to model that between 90 to 99 percent?

Dr. Telling?

DR. TELLING: I have a question for Dr. Anderson in this regard and that is for the input factors for module two. It seems to be exclusively with respect to travel to the UK but to the extent that this has been analyzed in other countries and in particular France and I realize that France is not the same as the US that that aspect had a relatively low rate of calculating the relative risk of exposure to BSE and a much more significant determinant was importation of BSE infected animals and foodstuffs and feed and so on and so forth, but I notice that that isn't a factor in your calculation for the risk inputs for module - -

PARTICIPANT: So, right now the relative risk rate that we are using for France is .05 or 5 percent of the prevalence or the risk in the UK. I agree actually. We were talking about that at lunch that it is probably necessary to actually go back and adjust that number a little but upward because France recently has I think gone up to about 12 cases.

PARTICIPANT: Fourteen.

PARTICIPANT: Fifteen.

PARTICIPANT: Do I hear 16? Now we are getting more towards you know, 8, 9, 10 percent rather than .05. It should be more like you know .08, .09, you know, .1. So, we may consider actually adjusting that particular relative risk rate. Does that answer your question?

But we are specifically addressing travel to the UK. We have also got the number of travelers set aside that traveled specifically to France and then those that traveled to Europe.

DR. TELLING: My question is what is the relative risk of actual exposure of the US, the North American population actually in general to BSE materials imported from the UK.

PARTICIPANT: Right, from domestic exposure to any BSE that may perhaps be here. We have gone ahead and done those calculations and we determined that risk to be pretty negligible. So, we will talk about that in the model but it is not absolutely integrated into the model because the number is so low for the estimate. So, we acknowledge that that risk is there, but it is just so low that it doesn't really --

DR. TELLING: I am sorry but that is where the vast majority of BSE cases, I mean it is three cases,

right, but the majority of those three cases are a result of importation, we presume of feed or cattle or whatever to Canada and then via Canada to the US. So, it is an important factor.

PARTICIPANT: Right, but we slaughter. We have got three cases but we slaughter 35 millions a year for food production. So, in the background of everything it really ends up being very low risk.

DR. BOLTON; I just wanted to say that I thought that the data actually supported better a range of 85 to 95 percent. It seems to me that 90 to 99 is a little overly optimistic.

DR. PRIOLA: Why do you want it dropped in that way?

DR. BOLTON: In the presentation I think several of the estimates that actually gave hard numbers were in the range of 86, 87 percent. Plus you have the 2 percent overestimation of the efficiency due to the false reporting essentially or false self-deferring.

So, it is not clear to me how the 90 percent as the lower end of the efficiency of the deferral policy came about. We are talking about issue 2, right? How effective are the current donor deferrals? I think 90 to 99 percent is too optimistic.

DR. PRIOLA: Dr. Williams, do you want to

comment on that at all?

DR. WILLIAMS: I think it is quite a reasonable observation. I think the rationale between the 85 and the 90 percent is those 85, 86 percent figures were referring to deferrals for which you know the social acceptability, the answer would produce a downward pressure on getting a response as part of the screening process. That said, you know, those are the numbers and I think it is a reasonable observation.

DR. PRIOLA: Dr. Leitman?

DR. LEITMAN: It has been pointed out that the majority of plasma donors for plasma products for fractionation are paid donors and that population for whatever reason doesn't travel as widely especially to Europe perhaps as do voluntary donors who donate whole blood. So, that makes me more comfortable with this geographic deferral.

Having said that paid donors are not always the most honest group because they are not altruistic. They are donating for self-interest. So, if a positive answer had financial implications they might not give that so readily. So, those two things tend to balance themselves.

DR. PRIOLA: So, you would agree with Dr. Bolton dropping it to 85 percent would be a reasonable thing?

DR. LEITMAN: No, I think 90 to 99 percent is

okay.

MR. BIAS: I thought 90 to 99 percent was optimistic just because I know the industry has done a lot to clean up their system about donor deferral but they are paid donors. Those centers are still in places where people are trading those dollars for sustenance or other things that they might need and I just thought that 90 to 99 percent meant we were doing it almost perfect and I don't think that is what is going on out there.

DR. PRIOLA: Dr. Bracey?

DR. BRACEY: This is really a request for Dr. Williams. What we are talking about are in essence projected numbers and we don't have a hard number and since this is an area where the safety is absolutely dependent upon the screening question I think that it really would be important for the Committee to send a message to the funding agencies that we need to acquire more hard information because right now we can try to draw parallels from other risks that we are dealing with but they are not the same.

DR. PRIOLA: That was something Dr. Williams brought up. What sort of other studies would you want funded to give you the information?

DR. BRACEY: In terms of just a general design a study that would look at simply the effectiveness of the

screening questionnaires and that is you know these are very complex sets of questions and there are a number of things that were discussed such as comprehension, things such as donor motivation. For example, you know, if you were in the work place there are many donors that we sometimes consider to be nearly pathologic because they must donate. If they aren't given the chance to donate they feel as though there is something wrong with them and that is not the majority of donors but you will find a very small number of donors that will sometimes not give you all the truth so that they can participate. They want to feel normal, and those are the sort of things that I think need to get teased out if you are using a question as your only means for screening.

DR. PRIOLA: Other comments from the Committee?

So, is there any major disagreement over dropping that range to the lower end to take into account the points that have been raised to go from like 85 and still keep the upper range 99; you just extend the range and they can do their model in that way? Is that acceptable to the Committee?

And recommendation for funding for further studies along the lines of what Dr. Bracey asked. Are there any other comments or can we all agree that, I mean it is always better to have more information. I don't think

anyone will disagree with that.

Okay, last chance for comments.

Mr. Bias?

MR. BIAS: I would add to that that I would have that study look specifically at certain economic, the placement of certain economic centers. I have been to a number of blood collection centers and one in particular comes to mind and it was very pristine in Green Bay with a child care center and everybody was a student and it was very pleasant to visit there and then I visited one in an inner city area and it was clear to me that folks needed the income and that is why they were in line and I would gear the study toward those centers where people are using it as income, needed income for themselves and not doing it for altruistic ways and the one I visited in Wisconsin certainly they used it for what they called it was football, beer money which was fine. They were all sort of you know middle income folks and stuff but I would be very interested in seeing a survey that looked particularly at the inner city sites where people are at risk.

DR. PRIOLA: Dr. Scott, you wanted to say something?

DR. SCOTT: I just wanted to point out that it is a general believe that plasmapheresis donors travel less perhaps because of their economic situation but to my

knowledge we don't have any real data on that and it would be nice to have some.

DR. ALLEN: I think my suggestion would be that to the extent further studies are designed and developed in this area that they look broadly at the issues of donor deferral and not necessarily just focus on this one risk. I mean trying to look specifically at geographic risk when we don't have a good measure of risk from food intake; you know, we have made some presumptions here in terms of time factors but we don't have good data. Just to the extent that additional studies are designed and carried out I think my recommendation to the FDA would be to look at a very broad scale design that meets the needs of multiple points not just this one specific one.

DR. BOLTON: I hate to delay these proceedings but this has been said now several times and I am just curious since this is a science-based decision-making process I have heard several times now the idea that the plasmapheresis donors travel less, but Dr. Scott just said that there are no data. So, the question is where does that come from if there aren't any data in support of that then why are we bringing it up?

DR. PRIOLA: Dr.Scott?

Okay, Dr. Leitman?

DR. LEITMAN: There are deferral rates and we know

how many persons in the volunteer collection centers are deferred for a positive answer to the various demographic deferrals. At my center I can give you exact numbers. Other centers can give you the number. So, I assume that the plasma collection centers, paid donors can also give you that data. That assumes an honest answer and you don't get quite the number of self-deferrals that don't make it into the center because they know they are not supposed to. I assume that that is much lower in the paid centers but we don't know about the honesty of the answers.

DR. BOLTON; So, it really is a question of weighing is the answer honest given the act that there may also be economic incentives to not tell the truth versus is there actually less travel.

DR. WILLIAMS: There is one other side to the answer that I think will hold up scientifically. In the blood donor studies there was a clear correlation with age and so you are covering a cumulative travel history. It is clear it is going to be an age-specific rise and it is known that the plasma donor population is younger. Now, that is corrected in part of the model but that would apply to the risk associations as well, I think.

DR. SCOTT: I would, also, point out that the amount of estimated and actual loss of donors in the plasma sector we understood was lower when we instituted the

geographic donor deferrals. I guess mu point really was that we don't have numbers.

DR. PRIOLA: Okay, I think given that this was another one of those parameters that was a high-impact parameter the call for new studies to get those sorts of numbers is something the Committee is asking for.

So, let us move on then to question 3.

DR. SCOTT: Question 3 is what is the intravenous infectivity range in ID50? What level should be selected for plasma based on animal studies and we propose that this model uses statistical distribution of infectivity with a minimum value of 0.1 ICID50 and most likely a value of 10, a maximum value of 310 as Dr. Asher explained and we also propose because the agent in primates may more closely reflect the human situation than rodent models that we model the IC to IV ratio for infectivity over a range of 1 to 5 based on recent primate study.

DR. PRIOLA: Any comments from the Committee?

DR. SALMAN: I think using the maximum value of 310 is very high, that is not justifiable if we follow on the same assumptions and being even on the very pessimistic side I think it still is very high.

DR. PRIOLA: Dr. Brown?

DR.BROWN; I would second that. The notion of a maximum based on a study that you don't believe strikes me

as inappropriate even though it is higher than anything, well, and also because it is higher than anything that you could possibly imagine. Every other study has established an absolute maximum of blood infectivity or blood component infectivity at about a log and one-half and blood consistently, whole blood consistently ranges between 10 and 25.

I would suggest that as a maximum if one must have a maximum that it be set at 100, that is 2 logs rather than 320.

DR. PRIOLA: I agree; 310 is somewhat arbitrary given you don't believe the experiments. You might as well pick 400, 500, whatever.

Any other comments?

So, the lower end of the range we can agree upon and then set that upper end at 2 logs, at 100.

DR. BOLTON: This is a range and given new information comes in it can be adjusted as the model develops.

DR. PRIOLA: Any other comments?

What about the IC to IV ratio? We heard one of the public hearing speakers say that they favored a one-to-one IC to IV ratio and this 1 to 5 is based on recent primate studies.

Does the Committee have any comments?

Dr. Brown?

DR.BROWN; One to one is a little pessimistic. Our study in mice was about 1 to 7. Earlier studies have, an earlier study at least by Kimberlin was 1 to 10. The primate study is based on very few animals and I think it is possible that it is a perfectly valid observation but it doesn't have the impact of the numbers that the earlier studies do.

So, I would think that somewhere between 5 and 10 is probably the most appropriate range.

DR. PRIOLA: So, as a lower end 1 to 5 you would say that 1 to 5 is at the lower end of that.

DR. BOLTON: I will respectfully disagree. I think that it is important to maintain that most pessimistic 1-to-1 relationship and then the plan is to study the range of 1 to 1 to 1 to 5. Is that not correct? Right. Dorothy is shaking her head. So, why not maintain that? I mean if you wanted to go more optimistic perhaps to go include the 1 to 10 relationship but I would hesitate to make it 1 to 5 to 1 to 10.

You are leaving out that possibility that IV exposure is exactly as efficient as IC exposure and I don't think we have enough information to really know that that is true or that it isn't true.

DR. PRIOLA: Dr. Allen?

DR. ALLEN: The other variable there is obviously the volume. Generally intracerebral tends to be a very, you know when it is done in animal studies tends to be a very small volume. If you are getting a whole unit of blood or packed red cells even, the volume is much,much greater proportionally. So, I don't disagree with you on the pessimistic. I would think perhaps extend the range from 1 to 1 to even to 1 to 10 to take in the range of available data from animal studies.

DR. BROWN: I don't want to inhibit pessimism.

(Laughter.)

DR. BROWN: I was really just suggesting that the most likely answer is going to turn out not to be 1 to 1 but the volume point is one that we have been hammering away at now for several years. If you really wanted an accurate comparison you would be obliged to inoculate the same volume IC as IV. Under those circumstances I have no doubt whatsoever that you are not going to get a 1 to 1.

DR. PRIOLA: So, the Committee would basically like to recommend a range in keeping with the range previously from 1 to 1 to 1 to 10 which would cover the most likely range IC/IV. Is that fair enough?

If there are no other comments we will move on to question 4 or question 3B.

This is the is there sufficient evidence to

estimate when variant CJD is present in the plasma.

DR. SCOTT: I think we can go to four. I am sorry about the numbering but that is actually the same thing and our proposal is that because of the uncertainties about the incubation periods of food-borne vCJD and the time during the incubation period at which infectivity appears in humans we propose to adopt a conservative approach and assume plasma to be potentially infectious throughout the incubation period.

DR. BROWN: That is really conservative with a capital "C." There have been actually several studies. I put them all together on the table for a book that Marc Turner is going to edit and it turns out that in about half a dozen studies infectivity turns up about half to two-thirds of the way through the incubation period in each one, very consistent. That is data from rodents and data from sheep. That is true, also in the sheep study. The only primate study is actually in humans and there we know that 5 years in advance at least 5 years in advance of the onset of symptomatic disease in one case the transmitted case that, or is it 3 years? I guess it is 3 years but at least we know that.

You know you can model and the more modeling you do, that is fine as long as we don't come to the conclusion before the story plays out. Again the likely answer is

that the incubation period from about being conservative halfway through is where infectivity begins to appear in the blood in those models where it appears.

DR. PRIOLA: Other comments from the Committee?

So, one of the things I see about that data depending upon the study you get infectivity early; then it goes away; then it is late. It starts in the middle. Then it goes away.

DR.BROWN: it is not that inconsistent, Sue.

DR. PRIOLA: It is not?

DR. BROWN: The early infectivity is almost certainly due to residual infectivity from the inoculation. If you sort of take away that first week or two then consistently infectivity doesn't begin before halfway through the incubation period and usually about two-thirds of the way.

DR. PRIOLA: So, you would recommend basing the model on the appearance of infectivity one-third to one-half of the way through the incubation period?

DR. BROWN: Yes, I would recommend the last half of the incubation period as being pretty conservative.

DR. PRIOLA: Other comments from Committee members?

Mr. Bias?

MR. BIAS: I just wonder if that is the most

conservative we can be since we are talking about plasma and people who are taking it on a regular basis. Doesn't that make us want to go toward the lower end? I am not exactly sure of the science. I will leave that to others but I am just a little concerned about that.

DR. BOLTON: I can't imagine if I were the one running the model that since it is just a model that I wouldn't include the entire incubation period just to see what the answer was. It is sort of an exercise in trying to figure out what the parameters are and which parameters given the biggest risks or uncertainties and it seems to me that it would make sense to again cover that range, the entire incubation period, half, maybe even the last third and see what that does to the model.

DR. PRIOLA: Dr. Anderson?

DR. ANDERSON: We can do it both ways and we have done that with particular models I think with Creutzfeldt-Jakob disease and the predictions at least come out. It is not a huge influence on the model. It probably predicts about twice as many cases if you go through the entire period versus the last half.

So, I think what I said before was that we are introducing a fair amount of uncertainty doing just the last half just because we have got to make some assumptions about incubation period and some other factors.

The good thing about using the entire incubation period is that you can then say that it can't be any worse than this with regard to that factor.

If you say that we are only assuming the last half then there is always the suspicion well, you didn't include the first half. So, what does that do to the outcome?

In the other case it certainly can't be any worse than that.

DR. ANDERSON: Right. It is a very conservative approach.

DR. PRIOLA: But you said that it wouldn't affect the outcome that much actually if you --

DR. ANDERSON: It is not going to affect the outcome as much as other factors in the model.

DR. BROWN: One of the bad things about using a broad range which I don't disagree with, David at all is that they tend to get through a process of inertia factored into the final risk assessment no matter what the answer turns out to be. Somebody is always going to say, "But you know you didn't include the whole incubation period. You had better do that," and when the data as it exists simply doesn't jibe with that I think you are obliged to set the limits for which you have science.

DR. PRIOLA: Dr. Salman?

DR. SALMAN; I am in agreement with what Paul is saying. If we use the model only as a game we don't need it. We have to try to as much as possible to have the model to mimic the infection status of what we know with the science we know.

I will question like any of these diseases, any of the diseases we know that the infection starts on the day one of the incubation period which diseases we know about that, I mean. So, we need some credibility for the model. Otherwise it will be a game.

DR. BOLTON: Let me say this. I think one thing that we do know is that from the day of infection the agent is present. It is present in the body somewhere. It may very well be in the blood and the plasma. It may not be in amounts that are easily detected, but given some of the studies and especially the recent paper from Rocky Mountain Lab that is published in Nature about the multiple injections over time I think that we have to now suspend our belief in the linear relationship between the LD50 and outcomes, in other words multiple inoculations of very low titer in fact below 1 ID50 dose will in fact result in a very high proportion of infection.

So, science based, yes, but we do know that once an individual is infected the agent is there somewhere and one of the problems with some of the animal studies is that

the route of inoculation is important. The type of agent, the strain of the agent is important and the host is important and I am not sure. I was going to ask Paul this question before but again I don't want to make these things go on too long, but in the table that you constructed, Paul how do those studies look in terms of the peripheral nature of the early part of the infection anyway? I mean are those studies that used agent strain combinations that have peripheral distribution that mimics variant CJD or are they like some of the other models that are primarily CNS based?

DR. BROWN: I suspect none of the studies were full autopsy studies in a time course manner but I can tell you that the studies that I am referring to were studies of hamster-adapted scrapie, GSS-adapted mice, vCJD, mouse adapted vCJD, sheep-adapted scrapie and sheep-adapted BSE. So, it is a fair range.

DR. PRIOLA: So, let me ask the Committee maybe just since we have two it seems like primary points of view, both of which I can understand, actually, does the Committee have any preference for this assuming infectivity present throughout the disease course or basing it on where we do have scientific data and that is saying from about halfway on?

Any preference for modeling based on infectivity, oh, hold on.

DR. EPSTEIN: I do have one suggestion. There is the question of what parameters to put in the model and there is the question of how to do sensitivity analysis and one pathway here would be that we use 50 percent of the incubation period to generate the estimate and then report out the results of the sensitivity analysis looking at infectivity throughout the incubation period and that I think has the virtue of getting at both sides of the argument without biasing if you will the model itself.

DR. PRIOLA: David, do you like that idea? Mr. Bias?

MR. BIAS: It works for me.

DR. PRIOLA: Okay, nice compromise. Okay, if we have no other comments let us move on to the next question.

DR. SCOTT: Does the Committee agree with our proposed approach for estimating clearance of vCJD infectivity from Factor 8 by manufacturing processes? We proposed to model three clearance ranges to represent a likely minimum, 2 to 3 logs, midrange 4 to 6, and maximum 7 to 9 logs of clearance of the vCJD agent from products manufactured in a variety of ways.

DR. PRIOLA: Comments from the Committee?

Paul?

DR. BROWN: Is there any particular reason that you had for and again here we are playing games in terms of

modeling but we already know that if you have a guaranteed 3 log per ml clearance as a concentration clearance you have done the job and 4 to 6 logs is nice; 7 to 9 logs is just insane. I am not sure why you are going to do that

DR. LEITMAN: For clarification just the 20,000 to 60,000 pool already gives you a log reduction, well, a 4-log reduction in concentration. So, this is over and above the effect of dilution in the pool. This is specific processing whatever that is, precipitation, filtration. So, is that beyond the several logs just by dilution?

DR. SCOTT: I guess that would be but I think the whole dilutional thing is another topic altogether. So, if you start out with 10 infectious doses per ml of plasma and you have 800 cc's of plasma of 8000 infectious doses that is going into a pool of 20,000 but that is still, if just one of those is enough to infect somebody you still have 8000 infections. Do you see what I mean?

So, you might want to have more than a few logs of clearance actually or that is one of the ways of thinking about it.

Now, in terms of how we selected these numbers we really used a combination of the data that is available to us to try to identify types of steps that are likely to result in greater or smaller amounts of clearance. This is a very sensitive parameter. At least it was in the Factor

11 risk assessment and we felt it was important to run this range to really see what happened and to see whether or not this made a difference in terms of the products.

DR. BROWN: We need I think to understand are you talking here about concentration or total mass? Are you talking about 9 logs of clearance in a unit or are you talking about a 9-log clearance per ml?

DR. SCOTT: Actually, Paul when I was talking to Dr. Leitman I was just making an example but usually we talk about per ml is my understanding.

DR. BROWN: Again, I don't understand the reason for the higher values in terms of are you modeling again or have I missed a beat here?

DR. PRIOLA: Dr. Epstein?

DR. EPSTEIN: Let me just clarify that the way the model works dilution doesn't affect the outcome of risk per dose or risk per vial because in the end you ask how many infective units are in the pool and then how many end up per vial or per dose.

So, the fact that you may have diluted it initially in the pool doesn't affect how many absolute infectious units would end up in a vial unless there is clearance. So, whether you describe the clearance as per ml or per total unit it doesn't matter. What you are computing is the residual number of ID50s per vial as mass, as total.

DR. BROWN: It does matter if you are talking processing reduction because that requires a knowledge of what you are aiming at. Are you aiming to get 9 logs reduction in a unit or 9 logs per ml? They are different.

DR. EPSTEIN: Okay, the goal in processing is per ml, but the point I am making is that the dilutional effect of pooling has no effect whatever.

DR. BROWN: I wasn't talking about pooling at all. I agree.

DR. EPSTEIN: But the earlier question and I forget who asked it was whether the clearance was above and beyond the effect of dilution itself because you have 3-log dilution and the answer is we are speaking about clearance above and beyond any dilutional effect, that the dilutional effect doesn't affect the risk estimate.

DR. BROWN: Right. As it is stated I agree. It is a different topic, but my question still stands particularly now if you are talking about per ml which is a concentration why would be the slightest bit interested in this 7-to-9-log clearance? I mean we love to have it but you are not going to because nobody in the history of the field has gotten a 9-log clearance per ml of anything by any method.

DR. SCOTT; I think it is pretty hard to estimate a 9-log clearance actually with the amount of infectivity

that you can put into something but it seems possible. I think that the reason we have a 7 to 9 is really that reflects more of an 8 which really reflects a combination of two high-level clearance steps and in fact that apparently has been observed in studies.

DR. PRIOLA: But that has been observed in studies using spiked brain material which is much, much, much higher than you will ever get in blood.

Dr. Epstein?

DR. EPSTEIN: First of all Dr. Scott gave you our answer which is it comes from combining so-called "orthogonal" procedures but I think there is another point that needs to come across here which is whether when you get below 1 ID50 per dose what does that mean; are you now just talking about the probability that there is a residual infectivity or are you saying that no one gets an infectious dose, and we don't know really how to resolve that. So, just to be a little bit concrete let us say that a person, let us say that the clearance is such that infectivity per dose is .01 ID50; are we then saying that no on gets an infectious dose because 1/100 of an iD50 infects no one or are we saying that the risk of exposure to 1 ID50 is 1 percent and it is the latter model that we are putting forward and why that matters then is for patients who are repeatedly dosed.

Remember we are talking about patients who may have hundreds of exposures per annum and thousands per lifetime and if the probability of receiving an ID50 is low per single exposure it may on the other hand not be low for cumulative exposure. So, it matters whether it is a probabilistic model and for that reason very high levels of clearance if demonstrated may in fact matter ultimately to patient safety.

DR. PRIOLA: David?

DR. BOLTON: I agree completely but the problem is now not so much in the model. It is when you take this to reality because to demonstrate anything more than maybe a 3 log clearance with natural prions in the natural fluid is going to be impossible and when you do the brain spiking even microsomal fractions, I am not sure that anybody here that has done those studies can really believe that they represent what would really be happening in naturally infected blood. It is just that we don't know. I mean that is one of the things that if we would ever get that information what is the natural physical state of variant CJD agent in human blood that would be a tremendous piece of knowledge to have because when you take a brain homogenate or brain microsomal fractions and you spike them into a sample of blood to get a titer of 10 to the 7th or 10 to the 8th it is just we have no idea that that is

in fact representing reality.

DR. BROWN: Well, you do if you know it is not. It is very simple, but this leads into what I think is going to be another question coming up. Both exogenous, that is spiked experiments and endogenous experiments are complementary and you get from one something and you get from the other something and they both should be done. In other words if you are going to be talking about optimizing validation studies what you want is validation using both because the spike study is going to give you maximum range of possibility and the endogenous study is going to give you absolute relevance so that even if you know you are only eliminating 2 logs in an endogenous study at least you have shown that what you have done applies to the endogenous infection.

So, there is contradiction and confusion. It would be terrible, for example, if you got a 7-log reduction in the filtration and then discovered you didn't get anything in endogenous. I mean I could imagine that happening if there were some size problem but doing both you have got all of the information that you can possibly have and you should do both. No one should ever be satisfied with a spike study for validation today.

DR. PRIOLA: So, in a way that argument applies to this question as well then as you alluded to because

you can accept that higher range as being experimentally the most that you can clear using an artificial system.

So, in that regard this range of logs would be okay. The low end is the endogenous more realistic one and the high end is the experimental spiked one and a limit of what you can do, okay.

Does everybody on the Committee agree with that? Yes, so would the Committee agree based upon what, I think that is an excellent argument, based upon that argument that we keep the ranges as proposed by the FDA?

Okay, let us move on then.

DR. SCOTT: It is actually linked to the last and I think that Dr. Brown was alluding to it. What experiments might enable refinement of the clearance estimates and allow comparison of clearance offered by various steps in the methods used to manufacture plasma-derived Factor 8?

DR. PRIOLA: Okay, so we can I think use as our basis what Dr. Brown just said that the spiking experiments are fine as long as they are accompanied by some simulation of an endogenous spike which it is not exactly clear what sort of endogenous spike you would use except for blood from a naturally infected animal model.

Dr. Brown?

DR. BROWN: It would be very nice when for example sheep because everyone is a little nervous about basing

human therapy on mice with cause but when we get another species or two possibly even primates if we are very lucky if we can get some idea of the concentration of infectivity in the blood in non-rodent species we will be much better off in terms of knowing what really are the maximum levels of infectivity in the blood in endogenous infections.

Today there is no estimate, no fact, no observation of the amount of infectivity in any species other than the mouse and the hamster to the best of my knowledge and that should change I would hope in the next year or two.

DR. PRIOLA: That is because that requires titering experiments that are very long term and expensive.

Any other comments as to this question?

I think the issue of using multiple animal models comes up later as well. If there are no other comments from the Committee we will move on to whatever the next question is. I have lost count. I am sorry.

PARTICIPANT: Seven.

DR. PRIOLA: Question 7.

DR. SCOTT: Only the numbers have been changed, but actually for this question the proposal has also changed, that is it is really just I think more fully described and fleshed out. What data should be used to estimate how much Factor 8 is used by typical patients?

This is from Dr. Weinstein's slide. We plan to analyze data from the ongoing UDC survey to estimate the numbers of patients using specific product brands and the distribution of disease types that is severe, moderate, mild hemophilia and type 3 von Willebrand's disease and we also plan to extrapolate data from the 1993 to 1998 survey in six states to estimate the total number of US patients and product consumption per patient with stratification by clinical setting and if there is inconsistent information from these two analyses it will need to be reconciled using patient-based medical record data.

DR. PRIOLA: So, basically you have three different routes to this question, right, three different proposals for this, that you can use all three of these data sets to address this?

DR.SCOTT: Yes, I think they are not exclusive. They really ought to be used --

DR. PRIOLA: Together. So, there is real data to be used which is very nice. Does the Committee have any comments? Do we all agree with the FDA proposal? It seems pretty reasonable.

There don't seem to be any more comments. So, let us move on to question 8.

Oh, hold on, sorry, Mr. Bias, excuse me.

MR. BIAS: I don't know how this might impact but

if there are patients who are on immune tolerance therapy how do you account for them in the model?

DR. ASHER; That is a topic. Actually we didn't bring that into play here but some of the information is available that is as far as the number of patients on immune tolerance, we do have information from the CDC, UDC collection for numbers of patients immune tolerance. We would also again have to make an approximation from essentially literature review I think at this point to get an estimate of the amount of material that would be used there but those of course would be patients who are using very high levels of product. There are relatively few of them compared to some of these other population groups but that is another group that we consider and we would be able to I think get data probably more of a, the quantitative data is difficult to get hold of for those patients but probably with the review of current practices from physicians and looking at various protocols for treating immune tolerance we could extrapolate that information.

MR. BIAS: That would be good. I am glad you can get that and my other question would be occasionally a patient like myself has an accident in a particular year. Does the UDC data also account for those spikes in usage? For instance this year my monthly average tripled for the 6 months I was injured. So, that is a big spike.

DR. ASHER: There is information from the UDC data. There is a category of how many times people have been under say a prophylactic treatment or use but we don't again have quantitative data about the amount of product being used in those particular situations which is somewhat of a limitation and the UDC data as it is currently constructed.

DR. PRIOLA: Can you get that quantitative data?

DR.ASHER: It simply isn't being collected right now. I had inquired in fact whether an additional question might be put on the survey form of the UDC data and the opinion was that the information would be not very accurate, that it was felt that it just may not be sufficient for our purposes. We are going to get more quantitative data from the survey information.

DR. ALLEN: I certainly think that there are probably alternate sources of data that could be used on a survey basis to estimate the extraordinary needs that sometimes arise and I assume also and I forget from the presentation, but data sources do show recombinant factor usage versus plasma-derived?

DR. ASHER: Yes, we can get that but of course we are primarily interested in the plasma-derived materials.

DR. PRIOLA: Dr. Bracey?

DR. BRACEY; No, I was just going to comment on

the possibility of using alternate sources as well. I think we have heard that there are probably some very good alternate sources available and if there are important data elements I think that we should go elsewhere.

MR. BIAS: I am wondering if the delivery industry, if you have ever tried to use them as a source but some of the larger providers. I mean there is not a unit of clotting factor that goes out that isn't tracked.

DR. ASHER: The question that I was uncertain about we had in fact discussed that element here but I was not certain about whether or not there was a per patient figure, in other words a delivery system may know in the aggregate, are you talking about a distributor or a home care company?

MR. BIAS: Yes, they will know per patient. They will know exactly per patient and they are very happy when it spikes. They produce a monthly report that indicates exactly how much each person uses and they will have very accurate figures on whether it spiked.

DR. ASHER: That is a good point.

DR. PRIOLA: Yes, excellent. Thank you. So, that is another point for data collection for you to put in the model.

Okay, let us move on to question 8.

DR. SCOTT: The next question is what is the

effect of plasma pool size, that is the number of donors per final product for Factor 8 recipients and we proposed to estimate plasma pool size as a range between 20 and 60 thousand donations with a bimodal distribution to reflect expected source and recovered plasma pool numbers but we feel that we should or do need to seek additional data from plasma fractionators to get a better sense of the amount that we have in the lower and the upper range, and I think in terms of the way the question is worded, what is the effect of plasma pool size this goes back to Steve Anderson's presentation where he showed the information or the modeling that indicates more frequent treatment sort removal overall of the effect of plasm pool size.

DR. PRIOLA: So, you are proposing this as a starting range really for your model knowing that you will, assuming that you will be able to get better data from the plasm fractionators eventually?

This is just a beginning range for you, the 20 to 60 thousand?

DR. SCOTT: The 60,000 actually represents a voluntary ceiling for number of donors contributing to a pool and 20,000 is based on an estimate of what we think for the lower end of plasma pool sizes really based on ad hoc observations.

DR. PRIOLA: Dr.Leitman, do you want to comment