repealed a few years later in 1998. This is a statement which is factual today, and I hope to god that this is a statement which will be factual five years from now, at a time when we may be reviewing some of the consequences of the decisions that we are making here.

This statement is based on a wealth of information related to classical CJD. We all agree that we do not benefit from the vast epidemiological perspective that we have for classical CJD with variant CJD, although there is some information, there is some data, and I will go through some of that as we move along. Next, please.

I don't need to go through all of the experimental data and epidemiological data which concluded that there is no convincing scientific evidence of prion infectivity in blood of CJD patients, nor that prions have been transmitted through blood or plasma products.

I will just focus on a few significant negatives; a study by Joe Gibbs and Paul Brown, in which blood from 13 cases of CJD sporadic were inoculated into non-human primate hosts, including chimpanzees, and there was no evidence of transmission in any of these cases.

Now, in these instances, whole units of blood were transfused. Blood from CJD patients were transfused to chimpanzees, with no evidence of disease.

A second study, which was conducted at Stan Prusiner's lab, using transgenic mouse hosts, which are highly susceptible to human prions. Again, 13 CJD cases were examined, or bloods from 13 CJD cases, and 12 of these were sporadic, and one familial, and again there was no evidence of transmission.

And as far as the epidemiological data is concerned, of course we have had in the U.K., and in the United States, and in Germany, studies of identified recipients from CJD donors, looked back at retrospective studies, and never has a case of CJD been demonstrated in any of these recipients.

And of course the studies of special increased risk populations, and we know, for instance, that there has never been a case of CJD in a hemophilia patient in the history of the world. And again this calls to mind that CJD and AIDS are very different.

Within a year of the emergence of HIV, within a year or two years, we started to see AIDS in hemophilia patients. Next, please.

Now, what about variant CJD? What is the current state of knowledge with respect to this issue of variant CJD in human blood? What we do know is that whole blood, red blood cells, and platelets, in the United Kingdom, from U.K. donors, have been and continue to be administered to U.K. recipients in the United Kingdom.

An estimated 30 to 40 million transfusions have occurred in the U.K. over the past 10 years. Not a single case of variant CJD has been linked to a transfusion. Several patients with variant CJD actually received transfusions, but none of these cases could be linked to a donor who had variant CJD, or for that matter classical CJD.

And in several cases of variant CJD where blood donors, but in no cases of either classical CJD or variant CJD, have ever been noted among identified recipients of blood or plasma products from any of these known variant CJD donors.

So to date there is no evidence in the United Kingdom, a country which represents 99 percent of all reported BSE, and 96 percent of all reported variant CJD in the world, there is no evidence that variant CJD has been transmitted through blood or plasma products. Next, please.

Here is a little bit more detail with respect to the studying of the U.K. on variant CJD and blood products, and this is publicly available information which can be obtained from the U.K. CJD surveillance unit.

Eight variant CJD patients received blood transfusions -- and again as I mentioned, no donors have been identified with CJD, classical or variant. And 14 variant CJD patients were blood donors, and eight variant CJD donors could be traced to 22 recipients, primarily from labile blood products.

And none of these recipients have had their names show up on the national CJD register in the U.K. to this time. Now, this is a list of the labile blood products which were administered.

Primarily, red blood cells, and then BC-depleted red blood cells, fresh/frozen plasma, whole blood, cryo-poor plasma, and cryoprecipitate in a few individuals.

Also, eight donations from these donors went into plasma pools for the production of therapeutic proteins, which then were administered to tens of thousands of recipients. Again, no recipient of plasma proteins to date has been identified with variant CJD. Next, please.

This is redundant, but I just want to call again to your attention the fact that of the 105 cases of variant CJD worldwide, 101, or roughly 96 percent, have occurred in the U.K.

The one case in Ireland, and the one case in Hong Kong, both have spent considerable time in the U.K. during the at-risk period, and really could be associated with the U.K. cases.

So the only country that stands out is France, with three de novo cases of variant CJD. These persons never went to the U.K., but we do know that France imported large quantities of U.K. beef and beef products.

And another important thing to note in this is that there have been cases of variant CJD since the initial onset in 1994, and every year through until the year 2001.

France, on the other hand, there has been no such -- there hasn't even been a flat line for variant CJD. There has been one case in 1994, and the two in 1999. The next slide, please.

And this just shows you that data in graphic form, and this is what Stan Prusiner was relating to earlier when he expressed that we are now in the triple digits with variant CJD, and this caused a

great deal of concern to Stan.

I would like to point out to my good friend, Stan Prusiner, that this tendency to arise is certainly far from what one would call an expediential rise, and I really don't think that with all of the best modeling in the world that we can ever predict exactly what is going to happen in the future.

But again look at France. These are deaths and not onset. But the one case in '96, and the one case who died in 2000, and then the third case died in 2001. This obviously is indicative of a significantly reduced exposure to BSE in France compared to the U.K.

We heard all of that this morning, to an order or two orders of magnitude less exposure. And of course one could assume that in the rest of Europe, which imported less U.K. beef products, and which have lower numbers of BSE, you would even have another order of magnitude less exposure. Next, please.

In contrast, the rise in variant CJD, which is a slight tendency to increase, to this tremendous increase of BSE in the U.K. over the period from 1987 until 1992, when BSE peaked, again there is no comparison to the rise in BSE and the current rise that we are seeing in variant CJD. Next, please.

Now, this slide just gives you the numbers of BSE throughout the world. Again, the rest of the world pales in comparison with the U.K. Only four countries have had a hundred or more cases of BSE.

What is of considerable concern today are some of the countries with lower numbers, such as Belgium, Germany, and Spain, which have had a considerable increase in the number of cases within the last 6 to 10 months. The next slide, please.

So in spite of the fact that this risk is purely theoretical, and I can't say it enough, we continue to approach this issue as though the risk were real. And that's why we already implement rational science-based precautionary policies to minimize the theoretical risk.

I think in view of the fact that the U.K. has 99 percent of all the BSE, and 96 percent of all the variant CJD in the world, it is a rational precautionary measure to implement individual donor deferral criteria for people who have traveled in the U.K.

And I think that rejection of U.K. source plasma is another rational precautionary measure to minimize a theoretical risk. We also withdraw and notify in case of a variant CJD donor, a situation

which has never occurred for us, or for that matter for anyone else in the world outside of the United Kingdom.

We have also been investing very heavily throughout the plasma-proteins industry in research on prions, and I think that the plasma-protein industry may have invested more money in research in this field than most groups, and governments, and who else, today.

And this research has been directed towards the development of extremely rapid and highly sensitive methods of prion detection. These methods are being used today to continue to research prion infectivity in the bloods of CJD cases, including variant CJD cases.

They are being used in the assessment of prion partitioning in manufacturing processes. They are being used to evaluate potential prion removal methods in manufacturing processes.

And perhaps in the future tests can be used for the potential screening of incoming plasma, and finally the industry at large is involved in conducting appropriate and well-designed prion clearance evaluations aimed at reducing uncertainty and providing relevant meaningful data. Next, please.

Now, the assessment of prion partitioning of the manufacturer of human plasma proteins is in itself complex. Since, as I have said before, prions have never been detected nor transmitted to a human plasma or plasma derivatives, we have no knowledge as to the physical or chemical nature of the theoretical prion contaminant, if it fact it even existed.

So therefore there is uncertainly as to what would be the appropriate relevance of a prion spiking agent for the study of prion partitioning and manufacturing processes.

Now, this is just a list of some of the things that have been used by different laboratories; brain homogenate; microsomal membrane fraction, caveolae-like domains, which is a specialized membrane compartment; prion rods; and the purified molecular spiked purified PrP scrapie.

The good news from all of this is in spite of the uncertainty, data from several laboratories, using different spiked forums, show multiple process steps in the plasma vaccination and infractionation schemes with robust prion removal capacities. The next slide, please.

And so this was the slide that I showed you earlier today when I tried to get into the public

session before the deliberation. Again, the risk of variant CJD transmissions through blood or plasma products remains purely theoretical and unsubstantiated by relevant scientific evidence.

I might add something today because one of the scientific experiments that is often used and passed out on the safety of human blood with respect to variant CJD is that experiment of transfusion in sheep.

Just three weeks ago, I was at a meeting in which Nora Hunter, one of the senior investigators in that study, gave an update on that study. And it is now nine months after the Lancet publication, and yet this one transfused sheep is the only animal in that study to have come down with the disease.

The positive controlled animal study, which had received an intravenous inoculation of U.K. beef brain homogenate, is not yet sick. So I really do not feel confident that that data could be used to in any way influence our thinking about variant CJD in blood.

But despite the fact that this remains a purely theoretical risk, and because we know that variant CJD is different from classical CJD -- and one of the differences is again what Stan Prusiner pointed out earlier, is the presence of variant CJD prions, or

the PrP scrapie for variant CJD patients in the lymphoid tissues of variant CJD patients.

And which by the way does not necessarily mean that it is in the blood, because in scrapie in sheep, it has been classically demonstrated that prion infectivity is found in lymphoid tissues, but it has never been detected in blood.

Nevertheless, we continue to implement numerous precautionary measures in order to further minimize this risk. The lack of rise of variant CJD in France, and its absence virtually everywhere else in the world, is notable, and reflects significantly reduced human exposure to BSE outside of the U.K.

And measures have been implemented in Europe since 1996 to enhance food safety, and reduce the potential for food borne transmission of BSE prions to humans, and this should add further reassurance, although in Europe, they didn't go into an official specified risk material ban until the year 2000.

And other individual European countries, including France, Italy, Spain, such measures were already implemented in 1996. And I think it is a pity that we didn't have somebody here today from the European commission who really knows all the numbers about when some of these measures were in place,

because a lot of the deliberations and discussions that you had were based on knowledge that nobody was sure of.

Finally, multiple manufacturing process steps in the production of purified PrPsc have been shown to have robust prion removal capacities, and in our opinion, and it is still our opinion, a pan-European approach to further minimize the above-mentioned theoretical risk does not seem warranted, nor should European plasma be considered unsuitable for the production of purified plasma products.

So we can not start the recount and I thank you.

CHAIRMAN BOLTON: Thank you. Any questions? Steve.

DR. DE ARMOND: Hank, I think that your comments, and Dr. Cliver's comment about being sued out of existence if one case of variant CJD would show up as a result of a transfusion, and so we are in dammed if we do and dammed if we don't situation. What would your recommendation have been regarding the European blood supply?

DR. BARON: Number 1, I don't have a crystal ball, and I can't say what is going to happen in the future. But my recommendation is right now is that this risk is truly theoretical. There is no evidence

or no relevant scientific finding to support it.

And my recommendation is that we should not defer donors who have spent time in Europe outside of the U.K. I would not even propose that we defer donors who have spent six months in France, not with three variant CJD cases.

CHAIRMAN BOLTON: Other questions?

DR. BAILAR: I think we are looking at this backwards. It is not the risk that is theoretical. It is the safety that is theoretical. The BSE epidemic has passed. The episode of the VCJD is far from past.

The numbers are still going up, indicating I think that there is a delay of years, and maybe decades, for the average case between the time of infection of the human being, and the appearance of the disease.

I am not really concerned about the continuing infection of humans from food consumption. I am very much concerned about what is going to be happening over the years to come with the people who may already be infected.

I think we may just be seeing the very beginning of what is going on there. Do you have some way to reassure me about this?

DR. BARON: My answer is that I don't have a crystal ball, and neither do you, nor does anybody else in this room. I think that we have to consider the supply issue, along with this very, very theoretical risk.

And I don't like to speculate and conjecture. I like to stick to facts. I think what you said earlier that the absence of proof is not proof of absence.

But I think over the years we have begun to accumulate evidence of that, and certainly with classical CJD, and now we have 10 or 15 years of people getting transfusions in the U.K., and we still have not seen variant CJD showing up in any of those transfusions, and I tell you that without a doubt that there will not be one one day? No, I cannot.

Can I tell you without a doubt that the City of Washington will have an asteroid fall on it? I cannot do that either, but we are not going to evacuate the city next week because of that.

CHAIRMAN BOLTON: Dr. Cliver.

DR. CLIVER: Just a thought. We don't know what the minimum incubation period is for VCJD, but it would be helpful as we see the record of VCJD blood donors and the surveillance of recipients, to have

some years of cumulative potential incubation period presented.

Because let's say it has been 10 years since somebody got a transfusion from somebody who came down with VCJD, that is a lot more persuasive than if it has been two.

DR. BARON: You are absolutely right, and unfortunately most of these products -- and not all of them, but most of these products -- have been administered within the last 5 years.

But some of them were administered as far back as 1981. So you are right. This unfortunate human experiment is not finished. Nonetheless, the fact today is that there has been no transmission.

Oh, by the way, also with respect to the incubation period. You know, I don't think we can assume what the incubation period would be in human-to-human transmission via an intravenous route or an intracerebral route or whatever; as opposed to the incubation period of BSE going into humans, causing variant CJD?

Because now if you are talking about variant CJD, you no longer have a species barrier to pass through, and theoretically the incubation period should be shorter than for bovine prions, especially

by an intravenous route.

Of course, you are infecting the blood and theoretically would also have a lower titer. So it is difficult to make an assumption on what the position is here today.

CHAIRMAN BOLTON: Other questions?

DR. NELSON: You cast some doubt on the sheep experiment. Could you elaborate on that, on the transmission? Is that still valid?

DR. BARON: Yes. That experiment, that study -- well, the study was not published. What was published was a single, isolated result from the study.

Twenty-one sheep were fed 5 grams of bovine brain. Then they were left alone and they were bled at different time points after the oral challenge. Then this blood was transfused into naive, previously normal, sheep.

Now, one of the orally challenged sheep came down with sheep BSE if you like, and a transfusion from that sheep to a naive sheep was related to disease in the transfused sheep after 600 days.

Actually, the incubation period was the same as the incubation period of the oral challenge with the BSE brain. It took 600 days for that sheep to get

sick by eating it, and then 600 days from the transfusion.

But again as I said the positive control, which received a high titer BSE brain homogenate by the intravenous route has not gotten sick yet, and it was not sick at the time of the publication, and it is not sick today. It is now 9 months later.

So it is already up close to that 600 day incubation period, and that just does not make sense. And anybody who has followed this field can tell you that there have been a lot of red herrings and false alarms due to improperly controlled studies.

And contamination or sample mix-up have to be considered a possibility. And I don't think you can say also that 1 in 20 actually got sick, because that is significant, because as David actually pointed out earlier this is a study where large volumes of blood are being transfused, 400 ml.

This is not a study where a 30 microliter sample of blood was inoculated into the brain of the animal. So, theoretically, if there is even a small quantity in the blood, it should have occurred in more than one sheep.

CHAIRMAN BOLTON: I don't think that we want to spend much time debating the specifics of that

particular experiment, because I don't think that we have the time, and I don't think it has particular value.

I think what we should say is that the results are not certain, and there are explanations on either side of the question, and additional studies on that particular animal and the material from it, and the completion of the remainder of the study needs to be done before we can really make much sense out of that. Yes, Bruce first, and then --

DR. EWENSTEIN: I was wondering, Dr. Baron, if you could comment on your point of view on the specific questions, or pieces of the specific questions that are before us on this section.

And that was that assuming that we discover as the tests become more sensitive that there is infectivity in plasma, what would be your recommendation based on your knowledge of the manufacturing process and of prion disease?

What would be your recommendations in terms of additional decontamination procedures, dedicated manufacturing lines, and that sort of thing?

DR. BARON: I would prefer to defer that question, because there is going to be a full presentation on that by another industry

representative following me.

So perhaps following that, we can get involved in that discussion. I don't want to do that now.

CHAIRMAN BOLTON: Dr. Schoenburger, and then I think we will move on.

DR. SCHOENBURGER: There was some discussion about the data that may or may not exist in the U.K. about blood transfusions, and who has --

CHAIRMAN BOLTON: Transfusions from VCJD?

DR. SCHOENBURGER: Yes. Want I am aware of -- and this comes from Dr. Robert Will, is that there are eight new variant CJD patients that have been linked to 22 recipients of blood.

DR. BARON: That's right.

DR. SCHOENBURGER: And these recipients, the year of the blood transfusion ranged between 1981 and 1999. And I wasn't planning on presenting this, because there is some key information that is missing, and that is the information of exactly what happened to these recipients, and how long they would survive.

And what he does have is that he knows who these recipients are, and he knows who the new variant CJD cases are, and he has linked them, and they do not link.

DR. BARON: That's correct.

DR. SCHOENBURGER: And so I would say that 14 of these 22 were presumably followed for at least 5 years if they had survived, and that is the key missing data.

And we are doing a similar type of study for classic CJD, and that is why we were sharing some of this information.

CHAIRMAN BOLTON: Thank you. Okay. Thank you, Dr. Baron. We will move on. Our next speaker is Dr. Jeff Davies, and he will speak on Considerations for Facility Cleaning.

DR. DAVIES: Thank you for the opportunity to speak on the topic of facility cleaning relations to TSEs. My name is Jeff Davies, and I work in Switzerland, in Bern, at ZLB Switzerland, which is in the middle of Europe.

In the year 2000, ZLB supplied approximately 3,600 kilograms of IVIG for the United States, and 22,000 kilograms of plasma, and we also supply IVIG to Europe and the rest of the world through our distribution agreement with Aventis.

And at ZLB, we processed approximately 1.8 million liters of plasma per annum derived from USA and European sources. In all cases, donors who have

resided in the U.K. for a period of six months during 1980 to 1996 are deferred.

Only products derived from USA plasma is provided to the USA. It is very important to realize that all manufacturers need to have procedures in place to ensure that there is no cross-contamination occurring between batches.

In today's presentation, I will speak on the current approach to cleaning, and an explanation of cleaning within our manufacturing facilities, and I will present a hypothetical on the worst case scenarios in order to highlight the existing processes in place in order to ensure batch-to-batch segregation, address the issue of segregation of EU from USA plasma, in relation to theoretical contamination with TSEs.

If a variant CJD contamination was determined to have been present in our manufacturing pool, all products prepared from that pool will be recalled. That is a matter of policy within the industry.

But the question that we really want to address is, is there a variant CJD list to products in the next manufacturing pool prepared in this equipment.

We need to establish the routine cleaning between batches from those prions, and that no dose of any product in the next batch contains an infectious dose of prions.

The routine approach for cleaning validation between batches from those prions includes mapping for worst case locations, and looking for the reservoirs if you like, the bells and so forth, and total -- analysis.

Cleaning consists of pre-rinsing with and water and treatment with either half bottle of sodium hydroxide, or one percent Ikalin, which is a sodium hydroxide-hypochlorite detergent mixture, and subsequent rinsing with water.

Cleaning validation is performed on product contact equipment. TSE is determined on swab samples, and also on -- on a routine basis, and swab samples are taken before and after the cleaning procedure.

The results from our cleaning validation show that we can demonstrate consistently a 1,000-fold reduction. We are limited to 1,000-fold reduction by the limited detection of TOC. We reduce the total organic carbon to the limit of detection.

I now want to talk about the manufacturing process that we use for IVIG in very simplified terms.

The manufacturing process can be divided into five modules, each one separated from the other by a process that shows significant reduction of TSE agent in model studies, and this was work done in Dr. Oh's laboratory.

We were able to demonstrate a reduction of 15.4 log, and there were two types of agents used. There was purified PrP and brain homogenate, and the results were not identical, but were similar with the two.

I now want to consider the cleaning within this particular facility in a hypothetical and simplified manner. We know that the cleaning process reduces total organic carbon by at least three logs, and the assumption that I want to make is the total organic carbon reduction is proportional to proteins, including TSE agents, and that is an assumption that we are making.

So for the hypothetical case, let's assume that a production pool was contaminated with a variant CJD donation, and we know that there has never been a case of a plasma contaminated that we have been able to identify with prions and plasma from a variant CJD patient.

The total load of the TSE agent would be

5,000 infectious units based on the estimation of Brown, et al., and that any TSE agent would be present in a diseased person that would not exceed 20 Ius per mil.

Now, this is -- we have not had a diseased person, and this is a hypothesis that we are putting forward. This has come from my studies and so this is a totally hypothetical case.

Then I want to propose that all the TSE agent adheres to the surface of Module One in the manufacturing process. So, we have 5,000 infectious units in our pool, and 3.7 logs all adhered to Module One at the completion of that batch.

We know that cleaning will reduce that by at least one-thousand fold. It may in fact totally eliminate it, but on the basis of our total organic carbon analysis, the most we can claim is a 1,000 fold reduction.

This leaves potentially 0.7 logs to carry across into the next batch, and if we assume it carries on into Module Two, and it adheres to Module Two, then I think it adheres to Module Two in the next batch.

If we continue this model, we can end up making assumptions for the remaining modules, which in

the very much worst case, and we would get a reduction associated with cleaning of minus 8.3 -- well, not a reduction, but we will get a potential contamination of minus 8.3 log that could end up in the final bulk product.

This is totally hypothetical, and it is totally ignoring the manufacturing process steps, and we will come back to this in a minute. Next slide, please.

Okay. So if we have a level or we have a manufacturing pool of 2,000 liters of plasma, we produce approximately 8,000 grams of IVIG, and we can calculate that there would be approximately 6.3 by 10 to the 3rd infection units per gram of IVIG.

If we look at the maximum batch, a maximum dosage of approximately 200 grams, which would be a 100 kilogram man getting two gram per kilogram, which is a very high dose of IVIG, we can estimate that the probability that a dose would be infectious is of the order of 1 in 100 million. Next slide, please.

On the basis of those assumptions, we can conclude that cleaning a line is effective and includes as a safety margin against TSE. The estimate does not take into account a possible activation of TSC agents used during cleaning, and assumes no

clearance by the process. Next slide.

That situation, however, is not realistic. If one assumes that theoretically present TSE agent does not or only partially adheres to the equipment surface, which is reality, the TSE agent would be reduced by the various production steps.

These showed an elimination capacity in model studies comparable or superior to reduction during cleaning, and there is a probability that one containing one infectious unit will be less than one in a hundred-million on those assumptions.

I now want to move to the cleaning and inactivation agents. We know that one molar of sodium hydroxide has the potential to inactivate TSE agents, and inactivation deficiencies are increased by elevated temperatures.

So we need to ask the question can one molar hydroxide or hot caustic agents be used in cleaning regimes. Cleaning validation is a major undertaking for the industry.

Changing the agents is not a trivial exercise, and what hot hydroxide may inactivate, it also has the potential to precipitate and fix prions on surfaces. Any changes to cleaning processes need to be properly validated prior to implementation.

The current manufacturing equipment in most plants around the world is not designed for such harsh chemical treatments, such as one molar of hydroxide at 60 degrees.

We know that the chromatographic resins and ultrafiltration membranes used in plants throughout the world generally would not use such conditions.

We also know that treatments of seals, gaskets, hosing materials, with hot caustic might contaminate the plant and products and would break down compounds from rubber and polymeric materials.

Hot caustic agents are also hazardous for employees, especially when equipment has to be cleaned manually, and we need to take that into account as well before introducing these sorts of procedures.

I now want to talk a little bit about cleaning and validation with infectious agents and many of these points have been raised in the previous talk. Cleaning validations involving infectious agents are important, but they do have limitations.

We need to limit conditions of CIP processes in sterile systems. The selection of TSE or the TSE agent itself is very important. What preparation is most appropriate was a point raised in the previous talk.

The recovery of potential residual infectivity can be challenging. For example, the recovery from a swab, or the use of aggressive reagents to recover the infectious agent may destroy infectivity, or even immunogenicities if you are using an immunogenic probe.

This is an area which warrants further investigation. So, in conclusion, I would just like to say that on the basis of this evaluation, existing cleaning processes are already in place to provide assurance against TSE carryover.

Harsher cleaning conditions, such as the use of hot hydroxide, or hot caustic agents, have to be carefully investigated, and they could be detrimental to plant product and employees.

We need to conduct more research on the ability of cleaning fluids to inactivate TSE, and this is supported by the industry. And we also need to extend research on the detection of trace amounts of TSE agents on the surfaces of stainless steel and equipment. Thank you.

CHAIRMAN BOLTON: Thank you, Dr. Davies. I think what I would like to do now is to hold questions until after the next two talks, and we will take all the questions for these talks at the completion of the

industry presentations.

So our next speaker will be Gordon Busenbark, and he will speak on the Complexities of Manufacturing.

MR. BUSENBARK: Good evening, Ladies and Gentlemen. My name is Gordon Busenbark, and I am President of Global Operations for Baxter BioScience. First of all, I would like to thank you for the opportunity to come here today to offer our perspective on the concepts to require manufacturers of plasma products to provide dedicated processing equipment and production lines based on the geographic origin of the plasma used to manufacture those products that are sold in the U.S.

Like all of us here today, Baxter is committed to the highest level of safety and quality for the plasma derived products that we manufacture. In today's presentation, I intend to show that product line segregation would contribute to the safety of U.S. plasma derived products.

As a control measure for variant CJD, segregation has no credible scientific support. What this measure would do unfortunately is lead to a reduction in plasma derivative manufacturing capacity, and as plant capacity is currently the supply limiting

factor, segregation would end up substantially reducing the production of these critical therapeutic products.

Segregation would have a devastating consequence for patients both in the U.S. and around the world who depend on these critical therapies. Next slide.

To help you appreciate the impact of segregation on the production of plasma derivatives, I would like to describe the current manufacturing logistics for plasma derivatives using our company, Baxter, as an example.

Baxter is one of the major manufacturers of plasma derivatives. We currently process over 4 million liters of plasma a year in five manufacturing plants, two in the U.S., and actually four in Europe.

The plasma that we process is collected from donors both in the U.S. and in Europe, but as required by our product licenses, all of the products that we distribute and sell in the U.S. are currently produced from U.S. plasma only.

However, it is important to understand that the products that we make for the U.S. market out of U.S. plasma are manufactured in both our U.S. plants and in our European plants. Next slide.

In each of our plants the manufacturer of these therapeutic products occurs as a complex, multi-step continuous process. The process flow for our Vienna, Austria facility, which is shown here as an example, illustrates from the initial plasma pooling step, to final product packaging.

The output of each process step serves as the input for the next process step. This complicated and meticulous manufacturing process, including the associated quality and regulatory review of every lot of product that we produce, results in a manufacturing process time from start to finish of anywhere between 6 to 9 months, depending on the product.

The collection process alone for plasma has a 60 day hold period from the time of collection to entry into the fractionation process. Next slide.

Baxter is, of course, very conscious of its responsibility to provide a safe and continuous supply of product to our patients. After all, at Baxter our philosophy is that there is a patient waiting for every vial or product that we produce.

With a very long lead time to produce plasma derivatives, it is critical for us to achieve optimal operating efficiency and reproduability of our manufacturing process.

Therefore, we have designed and operate our production facilities so that there is a high level of equipment usage and through put is maximized. The sequence of operations is carefully planned and executed so that there is always a careful balance of inputs and outputs at each step.

Furthermore, each of our facilities is designed to operate on a consistent 24-hour basis, seven days a week, at its optimum plasma through put level. Next slide.

The inherent complexity of the manufacturing process means significant deviations from the design capacity of our manufacturing facilities either could not be accommodated, or would result in a substantial loss of production output capacity.

Given the need to optimize the use of our production equipment, and to coordinate the manufacturing process carefully, it is clear that separate production lines for plasma of different geographic origin would require substantial modifications to our existing facilities and process flow.

Segregation would introduce severe constraints on equipment utilization, require extensive facility and equipment duplication where

none currently exists, and disrupt the very precise scheduling of operations.

The end result would be a significant reduction in output and availability of product for our patients. Next slide.

Again, using our Vienna facility as an example, product line segregation would result in disruptions in production of all U.S. distributed IGIV manufactured out of Vienna.

Our anti-inhibitor coagulant complex Fiba is an excellent example. All of the Fiba that is used to treat Factor VIII inhibitor patients world wide is manufactured in Vienna, both out of U.S. plasma and European plasma.

Factor IX concentrates and fibrin sealant produced at the Vienna facility would also be impacted. In the short term, there is no way that this facility could accommodate its current production with segregated equipment.

For patients in the U.S., this would be more than an inconvenience. It would be a health risk impacting the lives of thousands of American patients in an already constrained supply market.

A case in point is our fibrin sealant product. As the sole supplier product in the U.S.,

all supplies of this plasma derivative are manufactured in Vienna, and as such would be affected by this proposed line of product segregation.

And I would just highlight for those of you who aren't looking at the chart, that what this shows is that at the start of our process, we start processing both U.S. and European plasma in our Vienna facility.

We make a whole variety of products, both on the left side of the screen, as well as on the bottom of the chart. But we specifically highlighted up all the products that we manufacture in Vienna, and the ones that are circled in red are the ones that are actually sold here in North America.

So as you can see, some of the products that we manufacture in Vienna are sold exclusively outside the U.S., in Europe and in Asia, and Latin American; while a number of the products that we manufacture, those highlighted in red, are sold in both the U.S., Europe, and the rest of the world. Next slide.

Baxter's Vienna facility would not be the only site impacted by production line segregation. Now, some of you may think that this is a New York subway map, but it is actually a pictorial depiction of Baxter's manufacturing network in the various

manufacturing plants that we have.

To maximize output and efficiency, all of our manufacturing operations are highly integrated on a global basis, and what this means is that some products are only manufactured in one facility, and some products are manufactured in multiple facilities; and some products may be manufactured to a certain step in one facility, and then finished in a second facility.

As you can see, to optimize our ability to prepare these critical products requires frequent interaction and movement between plants. A case in point is our Lessines, Belgium facility, which does the manufacturing for all of Baxter's immunoglobulin product.

And which to put that in perspective, Baxter's share of the worldwide IGIV market is slightly over 20 percent, all of which is manufactured in our Lessines, Belgium facility. Next slide, please.

To delve further into the Lessines issue so that you understand the complexities, this facility receives the starting material for immunoglobulin in Fraction II from three locations.

Fraction II comes from our Los Angeles

facility, our Rochester, Michigan facility, and from our Vienna facility. A portion of the manufacturing process for both U.S. and European intravenous immunoglobulin utilizes common production equipment, common production tanks, and intravenous immunoglobulins, as I think everyone knows, are in short supply globally.

And any disruption at this single production site to accommodate segregated production lines could have the potential to have a significant impact on the patients who rely on this critical therapy of IGIV (sic).

In order not to impact product supply, the production line segregation being considered today could only be achieved by designing and constructing new production facilities.

For our company current manufacturing facilities would have to be either substantially modified to accommodate separate production lines approximately sized for each type of plasma.

This change could be extremely complex and would realistically take years to implement. Next slide.

Current plant modifications underway at our Los Angeles manufacturing facility provide some

perspective as to the effort associated with the facility modification in our industry.

At present, we are upgrading a portion of this facility in which the cold ethanol fractionation step is performed. The total cost of upgrading our Los Angeles facility is budgeted at $105 million, or at a cost of more than $1,000 per square foot.

And which will require 5 years to implement, from inception to licensure, by the FDA. Considering that this change involves just one portion of one facility, you can see that implementing completely segregate production lines at all of our facilities would involve an enormous expenditure of resources, and take many years to implement.

In the meantime, product supply would be significantly impacted while these changes were underway. Next slide.

The disruption of the supply of these valuable products, and the substantial costs associated with the provision of segregated production lines, could be justified if in the end there was a commensurate improvement in patient safety.

However, as you have heard today, and will hear from others, product line segregation is intended to address a theoretical concern. All evidence to

date is consistent with the view that plasma derivatives do not represent a variant CJD risk.

In addition, even if the threat of transmission of variant CJD by plasma derivatives was in fact real, product line segregation would not assure that products from U.S. plasma would be free from the risk.

Given the large number of American donors who potentially could have been exposed to variant CJD, segregation would not assure safety. Next slide. What measures should we consider then?

We believe that it is more useful to support continuing investigations leading to effective control of the spread of variant CJD and research into the agent's behavior. We encourage this committee to support those investigations, rather than requiring companies to implement ineffective segregation schemes.

Examples of the investigations currently under way by this industry will be described in the next presentation by Chris Healey of the PPTA. In closing, I would like to extend our gratitude to the committee for the opportunity to provide our perspective on this important issue. Thank you very much.

CHAIRMAN BOLTON: Thank you, and as I said before, we will hold questions until after Mr. Healey's presentation, and that is who is next. Mr. Christopher Healey is going to speak on the impact of VCJD measures regarding European donor deferrals.

MR. HEALEY: Good evening and thank you again. I am speaking on behalf of the Plasma Protein Therapeutics Association. The PPTA is a global association of the major producers of plasma therapeutics around the world.

My presentation tonight is really just a sum up of some of the messages that you have heard from the presentations and I will address some of the important issues on the impact of the potential for segregation on the market for plasma therapeutics.

PPTA member companies include those that you see here, and those are the previous speakers. So just to give you a sense of who we represent. Next slide, please.

In summary then, there is no evidence or no convincing evidence of prion infectivity in human blood or plasma, nor transmission through human blood or plasma products. This is a point that has been made repeatedly this evening.

In addition, fractionation processes achieve

meaningful prion clearance. Some of that evidence has also been presented. Current cleaning procedures are robust and obviate cross-contamination issues. The ZLB presentation highlighted this nicely, I believe.

And then finally, Dr. Scott raised the issue of labeling, and we believe that labeling requirements that are already in place adequately address this theoretical risk. Next slide.

In terms of segregation, and the impact of segregation on the marketplace, the data that we have collected through our monthly data reporting on product distribution, plasma product distribution in the U.S., indicates that 50 percent of the IVIG in the U.S. marketplace today is manufactured in part or in whole at facilities that also fractionate European plasma.

So a decision by this company, or excuse me, by this committee to segregate manufacturing lines for U.S. and European plasma would basically be putting all European plasma at risk and saying that 50 percent of the IVIG on the marketplace in the United States today is at risk.

This could have tremendous implications for the availability of these products, and in the perception of risk and health that the patients who

take them have.

In addition, the full range of plasma therapeutics would be implicated. As Dr. Scott indicated, Factor VIII and other factors, clotting factor concentrates would be implicated.

Inhibitors would be implicated, and immunoglobulins as I said, and albumin, and fibrinogen. Perhaps most importantly though the future of IVIG and other plasma therapeutics would be dramatically impacted.

We know that a number of companies currently are pursuing FDA licensure for IVIG to bring it to the U.S. marketplace. Many of these companies are located in Europe, and also process European plasma.

It is ironic that just a few years ago in 1998, when industry and when patients were faced with a dramatic shortage of IVIG, the FDA and consumers worked aggressively to find approximate clinical trial protocols to help speed IVIG to the marketplace.

And that the actions that you are considering there today would completely undo those efforts, and would basically eliminate the possibility of adding future IVIG to the U.S. market. Next slide.

With regard to cleaning, any recommendation must consider the impact on the manufacturing process,

and Dr. Davies went into this in detail. But some of the other issues to think about are the production cycle for IVIG and all plasma therapeutics is roughly 270 days from the day of donation to the date that the vial is distributed.

That is a long manufacturing time, and even minor disruptions in the processes can extend that significantly. So things like segregation, like additional validation, and cleaning steps, can have seemingly minor impact, but relatively major impact in terms of production cycles and getting product to market.

In addition, some of the other issues associated with cleaning include the need for facility shutdowns during validation, equipment retooling, refitting, and other issues of that nature. And I know that we will be responding to questions like that in just a few moments.

However, as an industry, we do believe that more can be done here, and we believe that collaborative efforts are going to yield the kind of information that we need to make sure that cleaning procedures in place are adequate.

So you will see from a later slide that we look forward to working with regulators, with the FDA,

with representatives from the EMEA, to make sure that we are all comfortable with the cleaning procedures that are in place, and that we can get a better understanding of what it means to validate these procedures with respect to infectious agents. Next slide.

Turning to labeling, Dr. Scott, as I had noted, mentioned this as a potential consideration for the committee. And as I said, we believe that the current labeling is adequate.

You can see from the overhead what the current labeling requirements are, and albumin is labeled as having an extremely remote risk, while IVIG and other products are labeled with the language that says may carry a risk of transmitting infectious agents, e.g., viruses and theoretically CJD.

We believe that nothing has changed here. We believe that the risk is still theoretical and that this labeling adequately captures the theoretical nature of that risk, notwithstanding segregation, and not withstanding additional cleaning procedures.

The risk remains theoretical and that is captured in the current labeling requirements. In addition, we think that additional labeling along these lines, or additional labelings with regard to

the nature of the threat, would simply cause fear and confusion among patients, and among doctors and treaters, and wouldn't add to the safety of the products.

So we do believe that because labeling is intended to ensure an informed physician and consumer that what is in place is sufficient. Next slide, please.

Risk assessment is another concept that has been discussed, and product-by-product risk assessment is something that might also yield additional information. We have heard that product manufacturing processes vary by company-to-company, and that the manufacturing steps for each process and product vary considerably as well.

So it is important to take a close look at each of those steps and get a better understanding of the risk and benefits associated with each of those steps, in terms of prion removal, and cleaning, and so forth, to come up with a concrete picture of what this risk may present on a product-by-product basis.

A uniform and global approach to this kind of risk assessment simply wouldn't do. Next slide, please.

So, PPTA considerations, as Dr. Baron said,

our member companies are leading providers of research funds totaling 10s of millions of dollars each year. We have some of the preeminent prion researchers in our member companies and here with you today.

So it is our intention to continue this level of funding and interest, and to continue to support research on prions, and get a better understanding of the nature of the disease, and the nature of its transmissibility, and continue this dialogue with you.

These other points have already been said. Current PPTA surveillance in the EU countries will minimize food borne transmissions. There is additional information about the precautionary measures that have been taken there.

We also believe that the U.K. is a unique circumstance, with a high BSE and VCJD rate, and that it stands alone. That the experience there can't be translated to other European countries.

And finally we believe that it is important that any policy that this committee considers, or any other regulatory bodies consider, should anticipate the ultimate appearance of BSE in this country and of VCJD in this country.

I think it would be negligent to not plan

for that in the event that does arise; and to set a policy that excludes all risk of VCJD, and then to find that it is here in the United States, would cause a lot of confusion, a lot of fear, and a lot of concern among patients.

Additional recommendations are that segregation of manufacturing lines is unwarranted, and will significantly impact current and future product availability, which is an important point.

That current cleaning procedures are adequate, but that we should work with agencies and regulatory bodies to get a better understanding, and to come to a common understanding of how to go about additional cleaning procedures. And that additional labeling isn't warranted.

Our next steps. The PPTA recently held a workshop in Europe to get all the evidence and all the information out on the table that we had available to us about prions and human TSEs.

We are planning on holding a similar workshop here and inviting regulators and patients to come and share in the dialogue, and try and get all the risks out on the table, and come to a better understanding, and an open and frank dialogue about the true risks.

So we look forward to conducting that workshop, and you can rest assured that the committee members here will be invited. In addition, we would like to develop a task force to further address the cleaning issues.

We think that this is very workable and that this task force could meet on a regular basis, and in fact bring information back to the committee to help them form any future policies that the FDA may put before the committee.

And then finally the point about continued research. That cannot be emphasized enough. As I said, our member companies are one of the leading funders of research, and we look forward to continuing that. Thank you.

CHAIRMAN BOLTON: Thank you. Now we will take all questions for Dr. Davies, Gordon Busenbark, and Christopher Healey. Let's see. I guess we are going to need each of them to be near a microphone somewhere.

And in the interest of efficiency, perhaps all at the podium, or pick a microphone and stand near it, I suppose. Yes?

DR. KATZ: I think probably Chris can answer my question. I am a little dense at this point in the

day. It is my understanding that there would be reluctance to further pursue licensure by those companies that are in the process now if segregation occurred. Would they attempt to not market their products in this country?

MR. HEALEY: The point is that we know that there is some companies with manufacturing facilities in Europe that are currently pursuing FDA licensure, and are pursuing FDA licensure for plasma products manufactured from U.S. plasma, but manufactured in Europe.

So if this committee were to make a recommendation for complete segregation, it could potentially put that -- could derail that process.

CHAIRMAN BOLTON: Bruce.

DR. EWENSTEIN: If we assume that it is not practical for the foreseeable future to segregate plasma, or change the overall production, and given how many different nuances there are in the production of the various products, and by different manufacturers, would it be possible for you folks to individually or by consensus sort of come up with a recommendation that we could talk about?

And then maybe the FDA would eventually adopt, and which would speak to how many log

reductions, for example, one should be able to demonstrate, and similar to the viral certifications that go on today.

So that one could say, okay, if there is a theoretical risk in the plasma, we can say that there is a 3 log or a 5 log, or I guess that is what I am asking, is an X-log reduction.

And that if the FDA could be satisfied that for a given product and a given manufacturing sweep, that that was accomplished, then it would become moot in terms of the source of the plasma going into the process.

MR. HEALEY: I am by no means a scientist, but from what I have heard from my colleagues, I understand that to even speak in terms of log reduction can be misleading, because the infectious dose, if there is one for brands, is not truly understood. I am sure that other can address that more completely.

With that said, I can tell you that the industry is very willing to work with the agency. As I have said, we want to develop some kind of working task force to address the cleaning issues, and it may be that that is an appropriate issue to take up as well.

So I think that the answer to your question is yes, that we would be more than willing to engage in a dialogue about how to define the issues, and how to come to some consensus on what appropriate steps are.

DR. NELSON: I think that the data or the ideas that you presented on segregation and cleaning, et cetera, were fairly clear and illuminated some issues.

But one of the issues that I wanted to ask, and that I still don't understand, is in the first half of the meeting we talked about deferring some European donors.

And how would that discussion, if implemented, our votes, affect this operation and preparation of IVIG or plasma products? What have we done in the first half of the meeting? Is that a fair question, or do you know it?

DR. DAVIES: I think it is a fair question. I think that a numer of people have raised the issues that we will have to deal with in relation to segregation, and the issues -- certainly there are issues that we would have to address in the notion to what kind of plasma we process. It can have a profound impact on businesses as we heard in the

previous presentation.

DR. NELSON: I was concerned about this earlier, but it really wasn't addressed. The plasma industry's problems weren't really discussed the way I think they should have been before we took the vote that we did at the first half of the meeting, or the first three-quarters, or however along we are now.

MR. HEALEY: I certainly share your concern and I agree with you. We didn't feel that they were fully vetted if you will. We were very encouraged by Dr. McCurdy's suggestion that plasma should be considered separately.

Ultimately, it might be that the same policy would be decided by this committee, but to have a full and open discussion of the plasma issues. The brief presentation that I read indicated that there would be, let's say, a 4 percent donor loss.

But the other issue is that casting a shadow over all of the European plasma skews the market dynamics. That plasma is going to have to be made up somewhere else, and it strains the entire global plasma products marketplace. That is the issue that we were trying to communicate.

CHAIRMAN BOLTON: Steve.

DR. BUSENBARK: Yes, I was just going to

make the comment that I think these issues are all interrelated, and that to the extent that all plasma products sold in the U.S. have to be made out of U.S. plasma, irregardless of where they are manufactured, to the extent that we have additional deferral criteria, which we talked about in the earlier half of the day, just like that will affect whole blood collections, and it will affect collection of source plasma through plasma phereses.

Because we will have to implement the same deferral criteria, and I think as many of you know, there is already a critical shortage of U.S. plasma right now that is hurting the availability of IGIV, and of plasma derived Factor VIII.

So the decision made earlier today will reduce the amount of source plasma available for U.S. products. Now, the second issue is that it has the potential to be compounded by the fact that if various European governments read into the decisions that were made today that there is now a higher risk associated with European plasma, then there is a very high likelihood that European governments may put forth initiatives to try to convert from using their own European plasma to U.S. plasma.

And which just like the issue with trying to

recruit more donors for whole blood, we are going to have the same issue, and we are going to have more people chasing after the same limited supply of U.S. plasma.

And then the third issue that I think is interrelated to this is that if there is a perceived risk based on the discussion that we had today associated with European plasma, then it calls into question all of the fractionators that have facilities in Europe where they process both U.S. and European plasma.

So even though in those facilities the products going back to the U.S. are made out of U.S. plasma, I think it is very important to recognize that they are being manufactured in plants using the exact same production equipment, the exact same filling equipment, the exact same critical systems like air handling that is used to manufacture U.S. versus European plasma.

So that's why I think it is really important to understand that the decisions that are made by the committee today have some pretty far-reaching implications.

CHAIRMAN BOLTON: Dr. De Armond.

DR. DE ARMOND: From what you presented,

plasma -- and what Hank Baron presented, plasma presents or is a special subset of blood, in which there is an even greater evidence that there is no infectivity theoretically.

DR. BUSENBARK: That is absolutely correctly, and a couple of people mentioned that this morning, and because of the manufacturing process itself, it actually reduces the prion level.

DR. DE ARMOND: And you also end up with fairly large volumes at the end, because you start with a full plasma, and it seems that you have a chance at least at the end of these multiple steps to actually check for prion protein.

Are you doing that and has there been any attempt to do some sort of immunoassay for it, or even bioassay? Or what is your plan for that, because that is really the ultimate test?

DR. DAVIES: Well, there are no assays for blood or in blood, and that is an issue, and that is something that is being developed.

DR. BUSENBARK: This is protein. You precipitate the protein, and you can do a variety of things. You can concentrate it.

DR. DAVIES: Well, there are people working on assays, and there are other people here who may

want to talk to that. But that is a key issue, and because of a lack of that technology, we can't assay in final product. But what we can do is scale down and do further studies.

DR. BARON: And perhaps Steve Petteway might want to address this after me, but Steve, we are all engaged in evaluating the different process steps, and that plasma fractionation interpretation involves precipitation steps, and it involves absorption steps, all of which are going to remove prions.

And using different methodologies in our laboratories, we use the CDI, the Confirmation Dependent Immunoassay, to measure and to put in different steps.

And if a buyer has a big program in which they are evaluating different manufacturing steps, and there are numerous steps which show robust removal, and there are still uncertainties about which is the appropriate spike.

But what is nice to know is that even studies using different spikes are showing robust removal, and maybe Steve wants to pick up from that.

DR. PETTEWAY: Yes. Now, just to follow up, I think an issue was made earlier that many of the studies that have been done so far have been done with

animal model systems.

And we now have data where we have looked at removal or petitioning human prions, both classical CJD, and we now have some data where we have just looked at variant CJD and done a comparison.

And the removal of classical and variant is exactly the same as the removal of the hamster or sheep. So I think we have reached the point now that we have enough research data that we can get together and look at the potential of how we would set up validation and provide some assurance of removal of prions through these processes. And that I would encourage the committee to think about that as a recommendation going forward.

DR. DE ARMOND: So the recommendation, I guess, is -- and I guess what I am hearing from you and from the others is that you are validating that there is an elimination of PrP prions.

DR. PETTEWAY: We have determined on a research scale that it is potentially feasible, and that the animal studies relate to human; and what we are suggesting is that we ought to meet with regulators and with the appropriate individuals to establish what the criteria for validation would be.

DR. DE ARMOND: On individual batches that

are made?

DR. PETTEWAY: Yes.

DR. DE ARMOND: So that you could certify that we have done all the proper tests on this batch?

DR. PETTEWAY: Just like we do with our own studies about validation.

CHAIRMAN BOLTON: Dr. McCurdy.

DR. MCCURDY: This comment and question -- actually, it is a question. There is more on the risk assessment and the repeated statement that risk is strictly theoretical.

In Europe, fibrin sealant, fibrin glue, has been used for a considerably longer time than in the United States, and it is also used in neurosurgery as I recall to control bleeding.

My question is whether there is any fibrin glue been used or that was used in Europe for neurosurgery, and made long enough ago so that perhaps some U.K. or French donor plasma might have been used in some of those pools.

And if so, is there enough active surveillance for a long enough period to know whether placing this material directly on the brain, which is the way it is assayed in animals, whether that does or does not cause any infectivity?

DR. BARON: I know that Bob Will in the U.K. does have some data, and for a limited time period -- I think it is an 8 to 10 year time period -- he does have for one hospital, one institution in Scotland, access to all of the patients who have undergone neurosurgery with fibrin sealants.

This is a question that we have also been looking at, and we have been working on putting together an epidemiology study looking at neurosurgery risks and neurosurgery, plus fibrin sealant risks.

And the data is very limited, and in the U.S., I don't believe that fibrin sealants have ever been used in neurosurgery. They have been used in some European countries. I believe in Germany and in the U.K.

And the only person who really has data, or who has put together data on that, is Bob Will, and we are currently actively trying to put together data in Japan and in Europe as well.

And the data that Bob Will has does not show any individuals who have undergone surgery with fibrin sealants who have been afflicted with CJD. But again it is another one of these situations where it is a short time frame that has been looked at.

CHAIRMAN BOLTON: Dr. Epstein.

DR. EPSTEIN: Yes. If I could be permitted to follow up with Dr. Petteway. Your statement that you have current studies with the variant CJD agent int he fractionation process is the first that I have ever heard publicly of any such result.

We, of course, have been awaiting such a result. I have been aware that there have been studies with the BSE agent in Europe, none of which have been reported to my knowledge in any public or private way.

So with regard to your own experiments, could you just clarify a couple of things? First of all, what was the maximum clearance at any process step; and second of all, what was the readout assay? Are you talking about immunoassay or Western blot, or are you talking about infectivity, and are you also doing infectivity?

DR. PETTEWAY: Well, if you will remember in the paper that we just finished in transfusion, where we correlated prion clearance and infectivity and established that. The methods that we used for --

CHAIRMAN BOLTON: Steve, could you move closer to the mike?

DR. PETTEWAY: I am right on top of it. The methods that we used for the experiments for the

classical CJD prions and the variant are the same as the methods that are in those papers.

And we have done studies with a low level clearance method, like cryoprecipitation, and also with a precipitation step that removes all animal, classical CJD, and sheep prions, and we just did that step for variant, and it, too, removed all the variant prion that we spiked.

The readout was a Western bloc assay. The quantitative Western bloc that you saw, and the method for which it was published in that paper.

DR. EPSTEIN: And the levels of clearance achieved was the maximum for any single step?

DR. PETTEWAY: For this particular step, it was greater than four logs.

DR. EPSTEIN: And were there more than one step that had at least four logs?

DR. PETTEWAY: Well, we chose three steps -- a low, an intermediate, and a high -- to assure ourselves that if we saw similar removal that it meant something, and it wasn't just an accident of the step that we chose.

And we have looked at the low, and we have looked at the high, and there was correlation with the low and the high, and we are doing the intermediate

now.

I mean, as you can appreciate doing experiments with the variant and a human are kind of difficult. We are doing them with Richard Rubenstein in New York and Paul Brown.

DR. EPSTEIN: And presumably this was a brain homogenate?

DR. PETTEWAY: It was a one percent brain homogenate, exactly like all the other studies that we were doing.

DR. EPSTEIN: Thank you very much.

DR. BARON: Could I just add that we are currently also doing a study on keys steps, and which we are comparing three different prions; hamster prions, sporadic CJD, and variant CJD, in parallel on key steps, using two different spiked forms.

There is the purified PrP scrapie, and the molecular spike, and microsomal membrane fraction. So that data that is being generated now, and we will probably have it available soon.

CHAIRMAN BOLTON: Peter.

DR. LURIE: I have two questions. One is for Dr. Davies, which is that you indicate that this data about the different modules in the purification and product development process, but can your or

somebody else who has done these kinds of studies speak to the appropriateness of adding up the number of logs the way you did?

I mention this because I noticed that Dr. Rohwer's study for tomorrow is that he makes the point that some of the different steps in the purification process in effect inactivated the same prions, the same fraction over and over again.

And so it raises the question to me that if it is really legitimate to add up the logs like that.

DR. DAVIES: Well, with regard to the petitioning, it is relevant. They are different steps, and in each of those modules there is a different step.

With regard to the cleaning, and the inactivation on cleaning, it was to provide an example as the sort of behavior that is being put forward on manufacturing processes, and it was purely done as a hypothetical case, and adhering to equipment.

And the sorts of behavior that we are talking about that it needs to continue to convey, in terms of contaminating a plant. So it was merely put forward to address that issue.

But certainly you can have the logs when you have distinct separation processes. And certainly the

cleaning procedures that we put in place at those different modules apply at each different module.

CHAIRMAN BOLTON: Peter, I respectfully disagree. I think that it depends on the individual steps, and that in fact the bridging experiments that were talked about are often necessary to prove that those affected reductions are additive or not.

Because oftentimes you are removing the same prions, and once they are removed in Step A, you can't remove them again in Step B.

DR. LURIE: There was a second point if I may, and that has to do with the mechanics if you will, Dr. Busenbark, about your six plants and so forth, and you showed these elaborate diagrams about what is produced where and so forth.

And it is clear that it is a very elaborate process, and with a certain amount of duplication, and I can't tell from the diagrams that every one of the steps occurs at more than one place.

But it did strike me that there was a fair amount of duplication, and other than insisting that it is impossible to do, have you actually sat down at a computer, if nowhere else, and rearranged the boxes to see if there is literally any way you can comply with separating and segregating?

DR. BARON: Yes, I think the answer to that is that is going to take some additional work on our part. This is something that we just looked at closely here over the last couple of weeks.

But our initial assessment is that, number one, we don't have the space in our existing facilities. And when you start to talk about segregation and the space -- first of all, there would be a requirement for space just to put in duplicate sets of equipment, and duplicate sets of tanks, duplicate sets of critical systems, like HVAC.

That, coupled with the fact that you would really need to look at it in terms of was it giving you the segregation you need, because as you saw from the process diagram that I had in Vienna, there are a multitude of steps.

And those are from the initial plasma thawing and plasma cooling, and all the way up to the pharmaceutical filling of the final product. And if you in fact wanted to have a full segregation scheme, you would need to segregate at every single step of the process, which could be a very complicated task.

DR. LURIE: I guess my point is that perhaps here is a way of organizing your assets as it were to minimize the duplication. I mean, there is a certain

amount of duplication, and certainly these steps occurred more than in one plant.

So I understand the problems of doing everything double. I mean, that is an obvious problem. But I don't think that that is the only scenario here. It is clear that you do certain things uniquely in some plants, and then ship the product down to the next place for processing.

It is equally clear that some things are done at two plants or more. I mean, have you really thought about this?

DR. BARON: Yes, we have given it some thought. Actually, the only product that we make the same product in multiple facilities is albumin, and interestingly the albumin process that we use even in those two separate plants in Vienna and Los Angeles is two different processes based on how they evolve.

Otherwise, outside of albumin, all of the products that we manufacture are not made in multiple plants.

DR. LURIE: It is the steps that matter, right?

DR. BARON: Right.

DR. LURIE: And not so much the product though?

DR. BARON: Right.

DR. LURIE: So the point with albumin is interesting, but the point is where are the steps duplicated, and they are in multiple places. I think that is what I took out of your drawing.

DR. BARON: No, I don't think so. If that was your impression that is not really the case, because what it was showing was that we make different products in different plants, and in many cases we would manufacture a product in a given plant up to a certain step, and then move it to another plant.

But there are really no instances where we are manufacturing the same product with similar production steps in different plants.

CHAIRMAN BOLTON: Dr. Belay.

DR. BELAY: Going back to the clearance studies. One of the problems that I have with the clearance studies is that it assumes that the spiking actually mimics natural infection, which may or may not be true.

We don't know where the infectivity would be. If, for example, blood contains the prion agent, or the infectious agent; and if this concern is valid, then the data that is collected or obtained from this clearance studies cannot necessarily be applied to the

natural infection in humans.

And another comment that I have is that you can also make the argument that plasma derivatives could actually be riskier than the components, and that is because as you know blood derivatives are produced by pulling tens of thousands of donors, which would increase the chance that one of the donors could have potentially been incubating the disease if the agent is found in the blood.

And not only is there the pulling of plasma derivatives in the production process, but they are also distributed to millions and millions of recipients, thereby increasing the chance if there is any risk that recipients may actually be at risk in developing the disease.

DR. BARON: Okay. You are right about the fact that since prions have never been found in human blood, we don't know what the physical chemical form of the prions in the human blood would be if it were indeed in human blood.

Therefore, I presented a slide in which I indicated that different laboratories have approached this differently. Some have used brain homogenate, and some have used microsomal membranes.

We have used a whole range of spikes. We

have actually taken it from the most crude form of infectivity, which is the crude brain homogenate, and going through a series of more purified forms, to the most purified form of infectivity, which is the purified PrP scrapie.

And what we have done is compare the clearance at different steps with these different forms of the prion agent, and what we have shown in our laboratories is that membrane brain spikes, whether it is microsones, caveolae-like membranes, or brain homogenates, kind of partition the same way.

The purified molecular spike partitions differently for certain steps. So our conclusion is that we do it on a worst case-best case scenario. I think we are covering all the possibilities.

You know, Paul Brown in a 1999 publication called Transfusion, and in this endogenous mouse model of blood infectivity. So this is a wild type mouse that you are not going to inoculate intracerebrally with -- I think there were GSS prions -- and so the mice developed prion disease.

And at a late stage, they have very low levels of prion in their blood. But again, remember, this is artificial. It is endogenous and they are being inoculated intracerebrally.

So what he found was that there was some infectivity in blood, at very low levels, primarily in the white blood cell component. But very low levels; 1 to 20 infected units per ml in the plasma.

And when he looked at that plasma under the electron microscope, he reported that there was no membrane debris associated with that. So what I am saying is that we looked at one edge of the spectrum, and the other edge of the spectrum.

And I think the best that we could do is provide a range. The answer is somewhere between these two, but I think at least at this stage you are getting into something meaningful, because you are covering all the possibilities.

DR. BELAY: Right. But what I am saying is that we have to be cautious in our interpretation of the data that we are collecting.

DR. BARON: Of course. That is why we took this multiple spike approach, but I think what encourages me is that when I look at the data from all the different laboratories that I continue to see robust clearance at lots of steps.

CHAIRMAN BOLTON: Do you have a comment on that?

DR. PETTEWAY: Yes, I would just like to a

point, and that is that the sheep studies that we have done, and the human studies, have been with prions from natural infections. So they are the agent of natural infection.

The issue is whether the agent, if it gets into the blood, is different. But clearly the removal that we see, compared to the experimental hamster model from humans and sheep is from naturally infected hosts.

CHAIRMAN BOLTON: I doubt if people want to beat this to death, but I thought about this a lot, and it is an issue that you really cannot resolve experimentally, because there are not enough natural prions in blood to do the experiments.

So if you do the experiments on natural prions in blood, you can only do part of one step and that's it, because if there is any removal at all, they are all gone.

So you are almost forced to rely on an artificial spike, and then you are forced to accept that, using various spikes. And the data that you get is at least representative of what happened, or what would happen in real life. Dr. Ewenstein.

DR. EWENSTEIN: Well, I was going to make just a couple of points. From the point of view of at

least the coagulation factors, I think it is important to emphasize -- and I think some of the public comments mentioned this -- that we are currently in a very dramatic period of shortage right now, especially with respect to Factor VIII.

And that going forward that it is not clear exactly when that is going to end. And when we talk about plasma products, if you include albumin, then you would have to even think about the recombinant Factor VIII, or at least the major recombinant Factor VIII that is available.

We might say almost the only recombinant Factor VIII that is available right now, and so we are really talking about an area that would affect the entire hemophilia A population for all intents and purposes.

That said, I think that we would also have to think about a sort of whether it is possible to truly distinguish U.S. plasma as safe, and European plasma as unsafe.

And we talked about trying to reduce risk before, and I voted for that proposition. But that is not to say that there is zero risk. So there is still a U.S. donor who is coming in with 2.8 months of exposure in the U.K., and he is not a zero risk

person.

We have to think about the fact that beyond donor screening and deferral, we can't do testing of plasma at this point, or testing of donors. So then you get to the next step in the blood safety net, which is inactivation.

I don't think it makes sense to beat on the donor deferral piece for the plasma derivatives so much as to try to pool what we have heard, and really encourage in our recommendation to the FDA that levels of validation be set at this point, imperfect as they might be.

And to say for the various plasma derivatives that the steps in a given manufacturing process, and not just a hypothetical one, but for each product that is licensed, has met a certain amount of reduction to the best of our current knowledge. I don't think you can get any more safety out of bifurcating the stream of plasma.

CHAIRMAN BOLTON: I am going to take one more question, and then I think we ought to move on.

DR. BAILAR: I would like to urge that we do what we can to get away from these log reduction models. They can be quite useful, helpful, informative, in the study of individual laboratory

experiments.

But several things can go wrong when you start applying them in sequence, step-wise, to working systems. The first thing is that some of the assumptions may fail.

For example, what I have seen has had the implicit assumption that the successive steps are statistically independent and that may not be true. There may be some questions about the data input, and what you used in the laboratory really matches what goes on in the field.

There can be equipment failures in the field, and there can be human failures. When I look at all of these together, I have some real concerns about the use of those models. So I would ask that we be very careful about how we use them.

I am not saying that we shouldn't use them, but they need to be seen with a lot of skepticism.

CHAIRMAN BOLTON: Yes, I think that is an issue that has been addressed, and is revisited frequently when these kinds of validation studies are done, and I think the FDA are well aware of that and will consider that.

I would like to move on given the lateness of the hour. I would really like to move on and

entertain the questions for the committee. Oh, that's right. I can't move on quite that quickly. That's right. We do have an open public hearing.

And we have, I believe, at least two speakers. So our first speaker will be Mr. Chris Lamb, from the American Red Cross.

MR. LAMB: Good evening. My name is Chris Lamb, and I am the Chief Operating Officer for the Plasma Services Unit of the American Red Cross. Thank you, Mr. Chairman, and Members of the Advisory Committee for giving me the opportunity to speak today on behalf of the American Red Cross.

The American Red Cross plasma derivatives meet approximately 25 percent of patient need for these therapies in the United States. At present, the American Red Cross contracts with for profit manufacturers to process approximately 1-1/2 million liters of plasma recovered from volunteer blood donations, anti-hemophilic factor, albumin, and intravenous immune globulin, IGIV.

IGIV and some albumin distributed by the American Red Cross and the United States are manufactured in European fractionation facilities. All other plasma products distributed by the Red Cross are manufactured in the United States.

The American Red Cross is committed to providing the safest possible blood and plasma products to patients and physicians treating those patients.

As we discussed with you earlier today, the Red Cross implemented an expanded donor deferral policy to reduce the theoretical risk of transmission of variant Creutzfeldt-Jakob disease through blood and plasma products.

Consistent with our policy of expanded donor deferral, the Red Cross believes that U.S. plasma should not be processed using common manufacturing lines as those used for European plasma.

Therefore, we are working with firms fractionating American Red Cross plasma to achieve segregation in the manufacturing process. Let me talk a little bit about the risk of variant CJD and plasma derivatives.

The Red Cross will continue to evaluate the presence and partitioning of prion plasma and plasma derived products. Our conclusions to date are as follows. Infectivity is present in plasma of experimentally infected animals, hamsters, and mice.

This was work that was done with Dr. Paul Brown and Dr. Robert Rohwer. Dr. Brown did the work

with the mice, and Dr. Rohwer did the work with the hamsters.

In experimentally infected animals, infectivity partitions into multiple fractions, including cryoprecipitate, and Fraction One Plus Two, Plus Three, the starting materials for Factor VIII and IVIG respectively. Again, this was work done with Dr. Brown and Dr. Rohwer.

Various degrees of removal of prion infectivity might be achieved through specific steps in the fractionation process. However, studies examining this process have used brain derived laboratory strains as a model agent.

Results from variant CJD agent and human plasma may be different. There is evidence that prions adhere to surfaces as has been shown for stainless steel surgical instruments.

Thus, there is a risk that the infectious agent can bind into equipment cross-contaminant subsequent batches of product. Pulling in multiple donations increases patient exposure to any infectious material.

Because we know very little about transmission of variant CJD through blood products, we must be mindful of the history of transmission of

pathogen through pool plasma products. Confirmed cases of BSE continue to spread throughout Europe.

The movement of BSE cases into Eastern Europe, highlights that we do not know much about the human reservoir that might be affected by this disease, with a multiple-year incubation period.

Consequently, we need to take all possible steps to protect the U.S. supply of plasma and blood products from potential contamination. The Red Cross is taking the following actions to reduce the potential risks of variant CJD in our plasma products.

Only plasma used in the manufacture of plasma derivatives and distributed under the American Red Cross label will be that collected by our regions, and from non-Red Cross blood centers that comply with our donor deferral policy.

The American Red Cross plasma is fractionated by contract manufacturers under their own FDA licenses. We aggressively seek fractionation facilities decided to processing plasma from U.S. sources.

And because FDA registration is necessary for changes to the contract manufacturing facilities, we would look to the FDA for expedited approval, if necessary.

In the transition period, we are consulting with leading experts to evaluate and determine the best cleaning and sterilization procedures for fractionation where plasma will be processed.

Implications for availability. As we work with the firms to manufacture IGIV to achieve segregation, there is the potential that the supply of Red Cross IGIV might be temporarily reduced.

Assuming that we have reasonable cooperation with the manufacturers, the Red Cross believes that we will be able to meet the needs of patients being treated with our IGIV product under FDA approved uses during the time it takes to achieve manufacturing separation.

We do not anticipate any impact on the availability of albumin or Factor VIII. Our conclusion is that given the scientific uncertainty surrounding variant CJD, and the potential for transmission through plasma products, the Red Cross believes that there should be segregation in the manufacture of U.S. plasma products from European-derived plasma.

Existing scientific studies have outlined the potential infectivity of certain plasma fractions by prions require us to take steps now to address

manufacturing issues.

This action, combined with an expanded deferral for blood donors, will help ensure that patients or recipients of U.S. blood or plasma products will have a reduced risk of exposure to potentially harmful TSE pathogens.

As with our variant CJD donor deferral policy, if we are wrong in a more cautious manufacturing approach, we have expended more resources than necessary.

If we are correct, the consequences of a less cautious manufacturing policy cannot be corrected. Thank you very much.

CHAIRMAN BOLTON: Thank you. Our next speaker will be Mr. Jason Bablak, from the Immune Deficiency Foundation.

MR. BABLAK: I am Jason Bablak, Vice President of Public Policy for the Immune Deficiency Foundation, and I have summarized my previous statement to a few bullet points to try to expedite this tonight.

IDF represents the primary immune deficient patients, and approximately 70 percent of those use IVIG to maintain their health. For our patient population, supply is a safety issue.

Recent IVIG shortages in the U.S. highlighted serious health consequences resulting from an inadequate supply. Currently, not enough is known about variant CJD. We believe that in the absence of scientific facts that it is prudent to take action to reduce theoretical risks so long as that action does not result in actual harm itself.

Supply of IVIG remains tight, and therefore any action that results in reduced availability could have significant negative impact on our community.

And finally we look forward to working with the plasma manufacturers in the industry workshop on risk assessment that they talked about earlier today. Thank you.

CHAIRMAN BOLTON: Thank you. And I guess now we will entertain any other public comments from the floor?

MR. HEALEY: I just wanted to reiterate the fact that the data that PPTA presents each month on the availability and distribution of products indicates that a 50 percent loss in the IVIG currently distributed in the U.S. today would be implicated through segregation.

I know that the Red Cross had raised a different number, but the numbers that we distribute

each month include the Red Cross IVIG. So that 50 percent is inclusive of that.

The other question we would have for the Red Cross is whether given their concerns about the risk that they are perceiving with the products, would it be their intention to pull current products off the marketplace. Thank you.

CHAIRMAN BOLTON: Thank you. Additional comments from the floor?

MR. YAMBURG (phonetic): Yes, my name is Yamburg, and I am the PPTA president, and I am European, and I live in the States, and I work on the road, and I see every day the consequences of disharmony in policies that are made, whether it is in the States or any other part.

The reason that I want to stand up is this. We are very concerned about the patients that need their products. You have heard enough this morning about the emotional statements that were made.

And when I talk about these needs, I become emotional, because I accept responsibility that we as a manufacturer have to do everything possible to manufacture safe products.

What you did today is that you created another disharmony. Let me give you one example, and

then I will stop because it is late. One of the things that we have to do as an industry is that we need to work in harmony and we need to work as a piece.

We have to use donor deferral criteria. What happened this morning is you are forcing the industry to work with two different donor deferral criteria; one in the States and one for Europe.

The one that you discussed today can never be implemented in Europe, and for reasons that you well know. The other thing -- and you can hear it in my voice that I am really angry, because you heard our experts standing up about what we do in the industry.

And I do not understand why the American Red Cross stands up and talks about things that we have to do which have a tremendous impact on the patients that need our products.

CHAIRMAN BOLTON: Thank you. Other comments from the floor? Seeing none, we will move on to the committee discussion then. Peter.

DR. LURIE: Yes. I am not sure if this committee has any obligation to follow the regulations of other countries, and I'm sorry that is the cost of doing business for you, but frankly I am sure that the donor criteria are different in other ways from

country to country.

And I am sure that it complicates things, but that doesn't make me want to retract what we did for one minute. I do have a question for the Red Cross gentleman though who spoke up earlier.

And he seems to have confidence that the segregation can be accomplished, and so I just want to invite him to perhaps share his thoughts on that in greater detail. How will it be done mechanically, as I think it is a mechanical issue, and how you think it can be done.

And how to the extent that you found places that are in a sense compliant, and how they are doing it. Could you perhaps enlighten us on that?

CHAIRMAN BOLTON: I am going to ask that you very briefly comment on this, because I really would like to move on to consider the questions at hand. So, please.

MR. LAMB: There is no way really to give a short answer to that. I think you have to look at the overall industry, and I don't know that there has been enough of a discussion of the way in which the plasma derivatives industry is organized.

There are really five main fractionation facilities that serve the United States. There is the

Baxter facility in Glendale, California; and there is the Alpha facility in California; and there is a Bayer facility in Clayton, North Carolina; and here is the ZLB facility in Switzerland; and there is one more, the Aventis facility.

I think you really need to take a look at where the products that are really coming into the United States, where they are coming from, the facilities, and which facilities. Not necessarily the -- well, many of these companies have many facilities, but those facilities may not provide the U.S. market.

So I really think you need to take a look at the industry as a whole, and what plants are where. For example, the Bayer facility in North Carolina -- and I don't mean to speak for Bayer -- processes only U.S. and Canadian plasma.

The issue is European plasma, and so I think you really need to take a thorough look at each of the plants, and what products are coming out, and what plasma is being processed here, and then from there what can be done.

In my mind, here are a relatively small number of products where there is a real issue. Mr. Busenbark talked about the fibrin product which is used to treat hemophiliacs that develop an inhibitor,

and that is correct.

And that particular Vienna facility is probably difficult to correct, but I think the committee has to look at are there other available therapies. There are two other available therapies in the United States, and is that an appropriate solution.

So I think you really should look at each of the products, and the facility, and which of those facilities has U.S. and non-U.S., and get more information to better determine what can be done and what can't be done.

I personally have been in the industry for 16 years and I don't believe it is as dramatic, but in a couple of minutes it is difficult to walk through that, and we, took, at the American Red Cross have a commitment to patients.

And I don't think this is an issue about one group or another group having a more or less interest in the patients. I think we all want to serve the patients. We just look at the data, and we believe that we should err on the side of caution, and that is all that we are saying.

DR. BUSENBARK: Can I state something?

CHAIRMAN BOLTON: One brief comment.

DR. BUSENBARK: I wold like to just talk specifically about three products in terms of the Baxter situation. We have talked a lot about IGIV and that is very important, because as I mentioned before on a global basis, Baxter produces in excess of 20 percent of the IGIV that is sold worldwide.

And of that 20 percent that we produce worldwide, about 80 percent of it goes back to the U.S. But I think it is important to recognize as I pointed out in my diagram -- and this underscores the complexity of the segregation -- is that we tear down and fractionate plasma at three manufacturing locations; two plants in the U.S. and one in Europe.

And to the intermediate States or Fraction 2, which is the intermediate that is used to produce IGIV. What then happens is that Fraction 2 immediate from those three plants is sent to one plant, in Lessines, Belgium.

And they then process that IGIV into final product. So there is no alternative. All of the IGIV that is manufactured worldwide -- and we make IGIV out of every liter of plasma that we process.

All of the intermediates, whether they come from L.A. or Rochester, or Vienna, go to Lessines for final processing, both out of U.S. plasma and European

plasma.

They are using common manufacturing equipment, common tanks, and we in essence to achieve this segregation scheme that has been outlined would have to have a dedicated separate facility in Lessines for processing European plasma and that would be independent from the facility that we have for U.S. plasma.

DR. LURIE: But your example makes the point that for the three previous steps, I think you said there are three separate plants, right?

DR. BUSENBARK: Yes, that is correct.

DR. LURIE: So for those three steps, you would not need to duplicate.

DR. BUSENBARK: That is correct. But the other point that I would bring out is that for two other critical products that we manufacture, fibra, which is used to treat inhibitors for patients with hemophilia A, and fibrin sealant, and those are only manufactured in one plant worldwide, and that is in Vienna.

And where roughly half of the product that we manufacture is made out of U.S. plasma for the U.S. market, and about half of the product we manufacture is sold in Europe out of European plasma.

And in that case the only way that we could segregate once again would be to construct a totally separate manufacturing facility, and totally separate equipment, and totally separate critical systems.

So we in essence would have to duplicate the plant that we have in Vienna to allow for segregation, and I just wanted to point that out to underscore the fact that it may seem simple and straightforward, but in fact when you get into the details, it becomes very complicated.

CHAIRMAN BOLTON: I am going to hazard a guess and go way out on a limb, and guess that we are not going to resolve that complex issue here tonight. So I don't know exactly how we can advise the FDA on that, except to begin to consider the questions at hand.

And unless there is a pressing question -- Dr. Ewenstein, you had one, but --

DR. EWENSTEIN: No, it wasn't a question. I was just going to comment that I thought at least about the product that I am most familiar. I mean, it seems that it would not be easy if at all possible to substitute products around as has been suggested.

I think that without getting into specifics of a lot of different products, but there is one VWF

factor A concentrate, and as far as I know, it is made only in Europe, for example.

This market has become totally integrated, at least for the part that I am aware of. I think we are likely to have sensitive tests for the plasma in a much shorter time period -- and I may be going out on a limb here -- than it would take to build or to rebuild the plant and get them approved based on my outside experience with these kinds of approval processes.

So we have to think of the practicality. It is not the money, but it is just the time line that it would take to redo all of this manufacturing.

CHAIRMAN BOLTON: I think the issue is far too complicated for us to do much, in terms of considering any kind of specific issues there. But let's move on to the questions that the FDA has asked us to consider.

The first one is to please comment on the significance of the VCJD risk from campaign manufacturing involving exposure to European plasma, and I would hazard a guess that we can say that the risk is essentially unknown, and probably very low.

I don't know that we can add much more detail to that unless somebody has superior knowledge

to my own. Stan.

DR. PRUSINER: I think you are right. We don't know the risk, and nobody around this table can define the risk, but I think there are pluses and minuses in this whole thing, and I think we ought to lay them out. I mean, we hear very strong arguments from one side, and then we hear very strong arguments from the other side.

And I think it is worth for just a second saying that if there are significant level of prions in new variant CJD people, in their plasma, and these prions behave in any way, shape, or form like those in brain, then they may well be accumulating in columns, in various fractionation steps in the equipment.

And depending upon the stringency of the sterilization that is used between the batches, they could pose a problem. We don't know. But I think to dismiss this as a non-issue, and to dismiss it as an issue that -- well, we can't produce or we can't segregate this for whatever reasons, I don't think is in the best interests of the health of people in the United States.

I mean, I don't think that this committee is really concerned about the health of the Europeans. I mean, we have Europeans who are angry, and we have

Europeans who are upset. We have them telling us that we are doing bad things here, but that is not the object of what is going on here to be very frank and open.

We are charged with this issue, and we are not charged with a globalization. I mean, when I hear all this stuff about globalization of the plasma products industry, it makes me shudder.

It makes me feel like when I have these arguments with airplane designers and the airlines that they want bigger and bigger airplanes, so that I can get sicker and sicker every time I get on the airplane.

I want smaller airplanes, and I am not sure that this is all going in the right direction. I mean, this is a big industry, doing it as efficiently as possible.

But I a not so sure that this is such a great thing the way it has evolved. Now, I am not saying that I know the answers, and I am not saying that I understand all this.

But with the bigger the batches, the bigger the problems sometimes, and if we look back on human pituitaries, this is why it all happened there, because with these enormous batches that were

processed.

So I just think that we need to step back from this for a moment, and I don't know the answers, and I agree with you, David, but I think that these are considerations.

CHAIRMAN BOLTON: Steve.

DR. DE ARMOND: Well, I think, Stan, that you really meant to say that you really care about the lives of individuals in Europe. As a physician, you don't want them to get sick, but we really as physicians, we really care about everybody, regardless of race --

DR. PRUSINER: Of course.

DR. DE ARMOND: Even if they are French. Being of French descent, I think I can say that. But it seems to me that we are stuck in a sense trying to make recommendations to the FDA, and it looks like plasma is relatively safe, even from what we can understand so far.

But we don't know the answer to that, but it does seem safe, and it looks like the processing process captures or somehow eliminates a lot of the prions. The only issue I have is what additional thing would you recommend.

You could leave it like that and say we

believe that the final product is clean, regardless of whether it comes from Europeans or from U.S. Citizens. But we can do more. I guess we could recommend further testing, and how would you recommend to do that, or what should be tested?

Do we test the equipment? Do we look more closely at inside the equipment to see if there is infectivity? We learned from these studies in Weissman's lab that you can't even wipe the infected particles off after multiple wipes.

Even with sodium hydroxide, they stick to it. So even a wipe test isn't going to tell you necessarily that there is PrP in the equipment. And the other is that because you do have big batches, you can test the batches.

You can precipitate the proteins and concentrate them, and perhaps look for PrP. But if you do those things and find that you are negative, and there is no PrP, are you then -- is that a test that you are assured that those batches are free of prions? Stan, do you have any comment on that? Is the negativity in a batch --

DR. PRUSINER: The problem is a volume problem. You can only test a small volume, a small aliquot of any one of these products, or otherwise you

use up the whole batch of what you made.

And you don't know that the prions are distributed homogeneously. I think that is an issue that we have not discussed at all here. I think that you don't even know that the prions are homogeneous themselves.

There is no reason for them to be and that is what David Bolton was alluding to, which I felt was a very interesting observation and a very interesting comment, that when you have such heterogeneity that if you do this batch removal kind of -- you do it once, and then you do it by another technique, and then another technique -- and let's say the prions are in groups A, B, and C.

You may each time be removing 10 to the 4th out of 10 to the 7th, but it may be Group A for each of these different processes. And you may be left with Groups B and C, and you can't tell that based upon these model studies where you do these added removals and you now say we have a removal now of 10 to the 15th.

DR. DE ARMOND: So do I understand from that that are current testing procedures, even the most sensitive ones, will not be of help?

DR. PRUSINER: Yes. I think when you think

about this, you really need to go back to the source. The source is the most important thing. If we had a blood test that was a hundred percent, and that would tell us that there were no prions in the blood, and this person was not producing prions, that would be the very best way to do it.

And, of course, that is the way that the plasma products industry operates when it can do that. That is what it does to make sure that there are no HIV particles floating around in the plasma that it is going to fractionate, and that is really the ultimate way to do it.

DR. DE ARMOND: So you would start with the fresh -- the blood that comes out, and take the buffy coat, because that would have the highest possibility of --

DR. PRUSINER: Well, yes, I guess so at this point. But this has not been worked out, and so I think --

CHAIRMAN BOLTON: Yes, I think we want to avoid trying to work out specific details of things here. We clearly do not have enough information to start proposing specific policies or recommendations in that way.

DR. PRUSINER: Exactly.

CHAIRMAN BOLTON: I think that there are a few general things that we can talk about. I would like to suggest that one thing that I see clearly out of this is that industry representatives need to get together with the FDA, probably in consultation with this committee, and begin to look at this issue going forward.

And what can be done, and how can it be done, and what studies need to be done, and what kind of validation tests are going to be acceptable, and how they can be done.

We are not going to resolve that issue tonight. There just is not enough time, and there isn't clearly enough information. So what I would like to do though is to -- if anybody has any more specific comments that they would like to give to the FDA regarding the significance of the VCJD risk from this mixed process, and/or Peter, the second question, any additional steps that you think should be taken at this time to address the issue of common manufacturing lines.

Let's focus on those things for the next few minutes, and try to get that out of the way. The third issue is the other specific recommendations that we can vote on, but if you can put in your mind things

about the risk, and what is the significance of the risk in this process, and what additional steps can be taken or should be taken.

DR. DE ARMOND: I don't think we can do that because we don't have any data. All we know is from what the industry tells us, is that it is a pretty clean process, and the final product, regardless of whether you run it in series, U.S. and European, and series, you end up with a clean product.

And we have to believe that at this stage because we haven't tested the blood up ahead, or ahead of time, and we haven't tested throughout the system. So what can we say? That it sounds like it is all right.

DR. LURIE: I guess one observation that I have is that compared to the discussion on the blood, we are talking about many more products at least, and with very much less data. We poured an incredible amount of attention and analysis on to the blood thing, and we don't have anything remotely like this.

And really each of the products merits its own separate analysis. Obviously, we can't do that here. But what I think needs to happen is the FDA needs to call in everyone of the manufacturers of the plasma derivative that wishes to market their product

in the United States, and literally go through the production sequence, every single step of it, and have them justify to them why that step is non-segregatable.

If it turns out that it is a straightforward matter to be able to segregate for that particular step, then I think that the manufacturer should be encouraged to do that. That's what I think we should be recommending.

CHAIRMAN BOLTON: Okay. There is a recommendation. Any additional recommendations, comments, suggestions at this point?

DR. NELSON: I think just like we talked about the supply issue with regard to blood, that needs to be considered here, too, because there are a critical group of patients that are going to die, or get sick, or have real problems.

And there has been a shortage of IVIG and other products that has created problems, serious problems for a subset of patients. And I think that needs to be taken into consideration.

And I agree that anything that could be done to improve the theoretical or actual safety, and that is a real issue that was brought up, that here we are dealing with not one donor, but a pool of 10s of

thousands, and we are dealing with one pituitary out of 10,000 or whatever.

But that there might be because of that, and because of the fact that batches go into all of this equipment, I can see that even though there may not be a risk, if there is any infectious material in blood, in plasma, this is where it might show up.

And I think we can be encouraged by the fact that there has never been hemophilic with Creutzfeld-Jakob, but of course the variant is not long enough.

But still I think we really need to look at the people who need this product. There could be recommendations made that would really jeopardize their health.

CHAIRMAN BOLTON: Dr. Davey.

DR. DAVEY: Yes, just a couple of comments. I agree with Dr. Nelson. I think it is important that these highly transfused populations over many years have not demonstrated any sign of the disease, and I think that is important information, because this has been going on now for several years.

And what I have heard -- and again maybe similar to this morning, but we do have some fairly distinct facts on the table. Number 1, I heard the industry say that they are robust in activation

processes.

I am not an expert here, but I was impressed by what they demonstrated and some of the comments from people around the table. Number 2, I hear that the change at this point is an immense undertaking of money and time, hundreds of millions of dollars, and many, many years.

Thirdly, I have heard that any steps along this line to segregate, or to build new facilities, more clearly have an impact on the supply. And I think we heard this morning -- and we have heard from some of the others now -- that the supply is very tight for IVIG and for Factor VIII, and patients will clearly suffer.

And also I would perhaps disagree with some of the comments around the table. When we can harmonize with our European colleagues on these issues, we should. There is no reason to think that we have a monopoly on how to do this.

And when we can harmonize with Europe, work with them on a single standard on a way to approach this, we should. We can't do it all the time, but when we can, we should.

So I would leave the situation, in terms of segregation, alone right now, work on new tests, and

have the industry consider what they can do to improve safety whenever possible, but segregating it seems to me seems to make no sense.

DR. DE ARMOND: That was very clear and lucid, and I think ideal.

DR. KATZ: Let me bring it to a clinical level. Was it in the fall of '97 that IVIG went away? Was that when it was? That's when I got a satellite beeper, because my blood center holds the inventory for our system hospitals.

And I have been approving every allocation of intravenous immunoglobulin since that time. There have been times when we had a little more and times when we had a little less.

I have had to tell people with hypogammagloblin anemia that they only get a half a dose this month on more than a few occasions. We have had to recommend alternate therapy, including invasive procedures like plasma exchange, for people because there wasn't enough IGIV to treat their polyneuropathy or whatever else it happened to me.

So I will be very, very cautious about taking a step like segregation now that will take years to bear fruit if retooling is required, and anticipating the availability of testing I hope in

that interval, I would be very, very cautious about taking that step. The supply is very tight.

CHAIRMAN BOLTON: Very good. Additional comments? The final question -- and I am assuming then that no one has any more comments from issues of the -- from questions one and two.

The FDA would like to know more or less informally -- and this is not something that we have to vote on these specific things, but they would like to know whether or not some of these other steps listed in A through D are things that should be considered at this time.

And we can just talk about these generally, or I think we can dispatch with them fairly quickly. Labeling to identify campaign manufacturing, involving potential exposure to European plasma. Should that be changed? Should the labeling be changed to indicate some additional risk.

Should additional decontamination procedures be used? Should the use of dedicated manufacturing lines -- well, I think we discussed that and it seems at least in my opinion to not be warranted at this time. And any other measures.

So I guess let me just put my comments out there. The labeling at this time to me seems to be

adequate, although it would be perhaps worthwhile for the FDA and the industry representatives to discuss that.

The use of additional decontamination procedures I think needs to be examined, but they really need to be validated in some way before they are launched into.

And the question there, I think becomes one of -- and I don't know how this works, but if that would affect the licensing situation. Is that something that has to be revisited. So those are my questions.

DR. NELSON: I may have misinterpreted it, but my interpretation of the labeling is that there is labeling already warning of the risk of theoretical CJD. But there isn't labeling that this particular product was campaigned if you will.

And I think what they are asking is should an additional label identify this batch, as opposed to another one. That there was a different sort of potential or a different mixing.

And I think that maybe there is something to be said for labeling, because these are patients who desperately need a product, and they maybe should be able to make a choice of do they want this, even

though the risk is not defined.

Maybe it is close to zero, and maybe theoretical, and maybe a long incubation period, but at least they know what they are getting into. And maybe there is an argument to add something to the label of a product that was manufactured with mixed --

CHAIRMAN BOLTON: Does anybody else agree with that? Other comments? Stan.

DR. PRUSINER: Yes, I agree. I think it is a difficult product, and there are people in the world who would choose one over another.

DR. NELSON: And they should have the right to choose.

DR. PRUSINER: I agree.

DR. NELSON: If they don't want to get sick tomorrow, and take the risk --

DR. PRUSINER: I agree.

CHAIRMAN BOLTON: That's something that could be implemented with very little cost. Additional comments?

DR. DAVEY: Well, I am not sure that is a great idea. If we are not going to feel that we need to segregate, and if we feel that the process is robust enough in their activation, then why do we need to set up a standard of labeling that is going to

scare some patients that they are getting some product that has additional risk over another product when we can't really say that. I think the labeling now is adequate, and I would leave it alone.

DR. PRUSINER: Well, I would like to respectfully disagree with you completely. I think you are wrong. I now that I would want to know. I would want to know if I had a child, and I certainly would want to know that information.

And I think for you to not tell me that information would be terrible, and for you to have prevented me from knowing that information if I had a child who was a hemophiliac would be terrible.

DR. DAVEY: Well, we have to respectfully disagree, Dr. Prusiner.

CHAIRMAN BOLTON: Bruce.

DR. EWENSTEIN: Well, I was going to say that one of the mistakes that we made in the hemophilia world years ago was not being totally forthcoming, and I would certainly come down on the side of trying to explain as best we can what we are talking about here.

And if you are talking about labeling material as having been derived from outside the U.S., I think that is a concept that could be explained on

a label to the average patient.

And for many plasma derivatives, and not for all, but for many of the derivatives that we are talking about, whether it is the Alpha One product.

And to some degree, IVIG, and certainly for the coagulation factors. These are very sophisticated patient groups. They have organizations that can help explain what we are trying to say on the label as well. So I would favor transparency, in terms of what is in a product.

CHAIRMAN BOLTON: And where it was processed or how it was --

DR. EWENSTEIN: That's what I mean, in terms of where it came from, et cetera.

CHAIRMAN BOLTON: Peter.

DR. LURIE: My general instinct is to agree with that, but I guess my question is how does this actually work? I mean, where is the label, and how is it that the patient gets to see the label? What is the mechanics of that?

DR. EWENSTEIN: Well, it certainly is very different for something like Factor VIII, where they take it at home, and they open the box and there is the label.

For some products -- you know, if you are

getting albumin in the hospital in the ICU, you don't know that. You don't see the label and I understand that that is a problem, and the only person who could explain that to you would be the ICU doctor.

CHAIRMAN BOLTON: Steve.

DR. DE ARMOND: Aren't there already FDA guidelines about labeling products, whether they are from human or animal, and the country of origin?

DR. NELSON: Yes, there are labels, but they are not with regard to this particular issue of mixing a source or two. It doesn't specify as I understand this level of detail at the moment.

CHAIRMAN BOLTON: There are specific risk aspects of the labeling currently, but they don't address this mixed process issue. But it could be written to do so. I don't think that is an insurmountable problem.

Additional comments or suggestions? If not, I hate to say, but we may be done. Is there no more? If not, then I believe that we would stand adjourned for this evening.

(Whereupon, at 8:24 p.m., the meeting was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: TSE A/C MEETING

Before: FDA-CBER

Date: JUNE 28, 2001

Place: BETHESDA, MD

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