FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Meeting of:

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

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TABLE OF CONTENTS

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P R O C E E D I N G S (8:30 a.m.)

Agenda Item: Administrative Remarks.

DR. FREAS: Mr. Chairman, members of the committee, invited guests, members of the public, I would like to welcome all of you to this, our 20th meeting, of the Transmissible Spongiform Encephalopathies Advisory Committee. I am Bill Freas. I will be the executive secretary for the meeting.

At this time, I would like to go around and introduce to the public the members who are seated at the head table. Will they please raise their hand as their name is called.

The first chair of the auditorium -- that is the audience's right -- is Dr. Susan Leitman, chief, blood services section, Department of transfusion Medicine, National Institute of Health.

Next to her is Dr. James Mastrianni, assistant professor of neurology, University of Chicago.

The next seat is empty. That will hopefully soon be occupied by our consumer representative, Ms. Florence Kranitz, president of the CJD Foundation.

Getting coffee at the coffee bar is Dr. James Sejvar, neuroepidemiologist, division of viral and rickettsial diseases, Centers for Disease Control and

Prevention.

In the next chair is Dr. Lynn Creekmore, regional epidemiologist, APHIS, Veterinary Services, U.S. Department of Agriculture.

Next is our industry representative, Dr. Taryn Rogalski-Salter, director, U.S. regulatory policy, Merck Research Laboratories.

Next is Ms. Jan Hamilton, advocacy director, Hemophilia Federation of America.

In the next chair is Dr. Frederick Siegal. Dr. Siegal is here as chairman of the Blood Products Advisory Committee, that met for a long meeting yesterday and he is doing double duty today serving as a voting member on this committee.

He is medical director, comprehensive HIV center, St. Vincent's Catholic Medical Centers.

Next is the chairman of this committee, the TSEAC committee, Dr. Glenn Telling, associate professor, department of microbiology, immunology and molecular genetics, University of Kentucky.

Next is Dr. Mark Skinner, president, World Federation of Hemophilia.

Next is Dr. James Lillard, associate professor of microbiology, Morehouse School of Medicine.

Next is Dr. Kathryn McComas, assistant professor,

department of communications, Cornell University.

Next, Mr. Val Bias, co-chairman, blood safety working group, National Hemophilia Foundation.

Next, Dr. Mark Powell, risk scientist, office of risk assessment and cost benefit analysis, U.S. Department of Agriculture.

Next, Dr. Laura Manuelidis, professor and head of neuropathology, Yale University School of Medicine.

Next, Dr. David Gaylor, president, Gaylor Associates, Eureka Springs, Arkansas.

Next, Dr. Richard Colvin, board of directors, Committee of Ten Thousand, and clinical assistant professor of medicine, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital.

At the end of the table, Dr. Nick Hogan, associate professor of Ophthalmology, University of Texas Southwestern Medical School.

Drs. Geschwind, Ghetti and Salman are standing members of this committee that could not be in attendance at today's meeting. I would like to welcome everyone for their attendance today.

I would now like to read into the public record the conflict of interest statement for this meeting. The Food and Drug Administration is convening today's meeting of the Transmissible Spongiform Encephalopathies Advisory

Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and consultants of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of advisory committees' compliance with federal ethics and conflict of interest laws including, but not limited to, 18 US Code, Section 208, 21 US Code, Section 355(n)(4) is being provided to participants in today's meeting and to the public.

FDA has determined that members of this advisory committee and consultants of the committee are in compliance with federal ethics and conflict of interest laws including, but not limited to, 18 US Code, Section 208, 21 US Code Section 355(n)(4).

Under 18 US Code Section 208, applicable to all government employees, and 21 US Code Section 355(n)(4) applicable to certain FDA committees, congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her financial

conflict of interest -- that is Section 208 -- and, where participation is necessary to afford essential expertise -- that is section 355.

Members and consultants of the committee who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential conflicts of interest of their own, as well as those imputed to them, including those of their employer, their spouse, their minor child, related to discussions of topic 1, FDA's risk assessment, potential exposure to vCJD from human plasma-derived anti-hemophilic factor products and potential responses, and topic 2, experimental clearance of transmissible spongiform encephalopathy infectivity in plasma-derived factor 8 products.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda also includes updates on various topics. In accordance with 18 US Code Section 208(b)(3), no waivers were required for today's discussion.

In addition, there may be regulated industry, outside organization speakers, making presentations. These speakers have financial interests associated with their

employer and other regulated firms.

The FDA asks, in the interests of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

These individuals were not screened by FDA for their conflicts of interest. Dr. Taryn Rogalski-Salter is serving as the industry representative acting on behalf of all related industry, and is employed by Merck Research Laboratories. Industry representatives are not special government employees and they do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remind members and consultants that if discussions involve any other products or firms not already on the agenda, for which an FDA has a financial or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted on the record.

FDA encourages all other meeting participants to advise the committee of any financial relationships that they may have with any sponsors, products or competitors and firms that could be affected by their presentations. Thank you.

If you would take just one second before I turn the podium over Dr. Telling to check your cell phone and

make sure it is in a silent mode, we would appreciate it. Dr. Telling, after you check your cell phone, I turn the meeting over to you.

Agenda Item: Opening Remarks.

DR. TELLING: Good morning, everyone, and thank you, Bill. I would like to welcome everybody to this meeting this morning.

We have a full agenda, a one day meeting, obviously. So, I would like to start as soon as possible. I would like to remind everybody that there are obviously time constraints and that we should keep to the agenda as much as possible.

So, the first item on the agenda is a committee update. We are going to hear about the status of the FDA's initiative on communication of the potential exposure to variant CJD risk from an investigational product plasma-derived factor XI that was manufacture from UK donor plasma. The presentation is going to be from Dr. Weinstein from the FDA.

Agenda Item: Committee Update. Status of FDA's Initiative on Communication of Potential Exposure to vCJD Risk from plasma-derived FVIII from UK Donor Plasma.

DR. WEINSTEIN: Thank you, Dr. Telling. Good morning. I would first like to give you a very brief overview of the background of this topic, and then I will

present our current plans for risk communication.

As you know, there has been recent concern about the potential of variant CJD to be transmitted by clotting factors made from the plasma of donors in the United Kingdom, where most of the cases of variant CJD have occurred.

Our concern has been increased since 2003. We have had three individuals, all in the United Kingdom, who probably acquired variant CJD through blood cell transfusions.

In the United States, there is a possible health risk to approximately 50 individuals who, between 1989 and 2000, received a factor XI product under IND. The factor XI product was used to prevent or treat bleeding due to a factor XI deficiency in these patients.

Now, the factor XI product was made from plasma from donors in the United Kingdom where we have a high prevalence of variant CJD.

It is important to note that the factor XI product was not made from the plasma of anyone known to have developed the disease, and no one who has received the product is known to have become infected with variant CJD.

Although the product was not made from the plasma of anyone known to have developed the disease, it is still possible that a person who is using the factor XI product

could have been exposed to the variant CJD agent, a donor who felt well was carrying the infection at the time of blood donation.

In response to this issue, FDA used a computer model risk assessment. We reported to this committee in February 2005 with a preliminary draft of that risk assessment and we have also had input from the committee in October 2005 which has led to further revisions of the risk assessment.

This committee advised FDA to consult with special government employees and particularly with patient advocates to obtain advice on the risk assessment, and in particular on communication materials or message points.

We have completed the risk assessment. We have had a version of the risk assessment that was presented in February 2005 on an FDA web site, and you see the address here.

We have now revised that, and we are in the process of finalizing communication materials with input that we have received from the patient advocates and from communication experts.

The overall plan now is to have teleconferences with the IND holders to share information with them, to answer any questions that they might have, and to suggest that they contact each of the patients who received this

IND product and give the information about the potential risk to these patients and inform them of this issue.

We will have an internet posting of the finalized materials. We will be notifying hemophilia treatment centers and patient advocacy organizations who will help us to disseminate the information to patients and other interested parties. Thank you.

DR. TELLINg: Thanks, Dr. Weinstein. Are there any questions of clarification from the committee?

If not, I would like to go directly to topic one, where we will hear about FDA's risk assessment for potential exposure to variant CJD in human plasma derived anti-hemophilia factor VIII products and communication materials.

We are going to have, first of all, introductory remarks from Dr. Scott, who will discuss FDA risk management strategy for potential exposure to vCJD exposure in plasma derivatives. Dr. Scott?

Agenda Item: Topic I: FDA's Risk Assessment for Potential Exposure to vCJD in Human Plasma-Derived FVIII Products and Communication Materials. Introduction: FDA Risk Management Strategy.

DR. SCOTT: Thank you very much and good morning. I am going to be introducing the first topic in the broader context of FDA's overall risk management strategy. So, that

is what you will be hearing about first, and then we will go on to the questions by way of introduction.

To date, as you know, there haven't been any reports of variant CJD transmission by any plasma derivatives, including clotting factors.

So, why are we concerned about risk at all? These are some of the reasons. In the Untied Kingdom, four cases of variant CJD infection have been reported in transfusion recipients who received non-leukocyte reduced red blood cell concentrates from donors who later developed variant CJD. The possibility of this happening by chance is extremely low.

In addition, plasma of experimentally infected animals contains TSE infectivity. This tends to be universally the case when it is looked for.

Also, in the United States, there have been three variant CJD cases diagnosed. However, two of these were long-term residents of the United Kingdom who happened to be living here when they were diagnosed, but lived in the United Kingdom during the period of highest risk for having consumed BSE contaminated products.

Just recently, on November 29, there was a report from CDC of a third patient who was in the United States that was diagnosed with variant CJD, but this was a person who had lived in Saudi Arabia until 2005.

It is interesting that he had no history of travel to Europe. However, he was not a blood donor or recipient. I think what this points out is that a few cases of variant CJD are found worldwide, and not all of these people have lived in or traveled to Europe.

This is the good news. The variant CJD epidemic is declining in the United Kingdom. What I am showing you is a graph from the statistics unit of the Health Protection Agency in the United Kingdom.

This takes you up to the third quarter of 2005. This was the best model fit. It is called the quadratic model. You can see the epidemic peaking here and coming down in 2005.

The prediction was for 2006 they would have about five cases. In fact, to date, they have had six deaths due to variant CJD. So, we are still on this trend.

FDA has a multi-tiered risk management approach for plasma derivatives with respect to variant CJD. I am going to go through each of these in more detail, but this gives you the overview, what plasma and blood donation we have, donor deferrals.

In the case of manufacturing, we have encouraged studies of TSE clearance. Final products are withdrawn if there was a vCJD donation that is recognized that contributed. So far, this hasn't happened yet in the United

States.

We also have risk communication through product labeling. We have recommended labeling for potential CJD risk in all of our plasma derivative products, and we also have TSE clearance labeling based on submission of experimental data, and this is voluntary. That is, members of industry can choose to do these studies or not.

In addition, we have the risk assessment which begins, in this case, with what we call upstream manufacturing processes and, in particular, plasma derived factor VIII which is a very early precipitation from plasma, and we will be going into that more later.

The risk assessment is important because, numbers aside, it can also identify, the model can identify, the most important contributors to risk.

This allows us to think about what might be the most efficient steps in risk management. The risk assessment also estimates the risk to patients under various scenarios and communicates those uncertainties that are involved in generating the risk assessment numbers.

We have also tried to anticipate future risk mitigation measures by developing paradigms for TSE, filtration device licensure, strategies for evaluation of donor tests, and standard preparations of the TSE agents to facilitate donor testing as well as clearance studies. Many

of you all have heard of these in previous advisory committee meetings in the last couple of years.

In more detail, this is the risk management strategy which involves deferral of blood and plasma donors who may be at increased risk of variant CJD.

This includes donors who visited or resided in countries where BSE exposure is higher, and that would be chiefly the United Kingdom, also France, the rest of Europe in the case of blood donations and transfusable components, and some European military bases that received British beef to Europe under the program that was there during the 1990s.

Donors are also deferred if they have used United Kingdom source bovine insulin, or if they have received transfusions in the United Kingdom or France since 1980.

We also recommend withdrawal of products that are made from plasma if the donor is identified with variant CJD, as I already mentioned, and the guidance that I am referring to, which is referenced here below, encourages reporting of donors with possible variant CJD in the United States to the CDC, and these will be people with a CJD diagnosis and aged less than 55.

This is the guidance recommended labeling for plasma derivatives. Albumen has a slightly more elaborate warning, which I won't read here, because actually we

believe the risk for albumen is likely to be quite low.

The warning section reads, because this product is made from human blood, it carries a risk of transmitting infectious agents, e.g., viruses and theoretically the CJD agent.

This is meant to more generically refer to the different CJD agents, familial, sporadic and variant CJD. This is intended to capture the uncertain, but still possible, risk.

In addition, for labeling, reduction of risk, if it is based on scientific demonstration by clearance studies, can be reflected in the description section.

We discussed this originally in 2003, and this committee agreed that we may consider granting a labeling claim for TSE clearance similar to the ones that we grant for viral clearance is a sponsor submits detailed study data of a specific manufacturing process studied and scaled down, and demonstrates the ability of that process to reduce TSE infectivity by bioassay.

To date, several plasma derivatives have been approved for TSE clearance labeling claims, and these include three immune globulins as well as thrombate three.

That doesn't mean that we are not evaluating studies of clotting factors. It just means that these are the ones that have gone forward to approval and have that

labeling.

This is the voluntary labeling which states that, additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of TSE considered as a model for the vCJD and CJD agents.

In addition, the claim may be made concerning the individual production steps in the logs of clearance. So, it reads, several of the individual production steps in the manufacturing process have been shown to decrease TSE infectivity of an experimental model agent.

The TSE reduction steps include -- and then the process is named and the logs of clearance. These are not added.

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

In addition, as I have already mentioned, we are developing licensure strategies and evaluating, as they arrive, filtration devices to remove TSE infectivity from blood components. This could also be useful for plasma, and candidate donor screening and diagnostic tests for variant CJD and other TSEs.

You have heard about some of these when they have

been presented at previous committees and these are well under development.

We also have collaborations internationally to develop the standard TSE preparations that will help to study candidate tests and may help in clearance studies.

We do our best to facilitate development, validation, and information sharing regarding the performance of manufacturing processes in the clearance of TSE agents from blood products.

As you may remember from the last meeting, this is a very complicated matter with respect to a lot of the variables that are involved in the studies.

Finally, I will introduce the first topic for you, which is the risk assessment for plasma-derived factor VIII products and the risk communication.

The risk assessment, as I mentioned, identifies the most important contributors to risk, and the risk communication should provide a risk estimate as well as its attendant uncertainties, because of the uncertainties of the inputs of the risk assessments themselves. We have discussed these inputs several times here.

A risk communication should also inform patients and physicians about the current scientific understanding regarding variant CJD risk from blood products to better inform treatment decisions.

These are the questions that you will be asked this morning. Do you have any comments on the technical aspects of FDA's risk assessment, including the risk estimates and uncertainties for plasma derived factor VIII From U.S. donors.

Do you agree that the key message points and additional information as described capture the essential points of the risk assessment and provide a suitable and understandable interpretation of the results.

We are also asking you to comment on the communication strategy regarding the risk assessment and its interpretation.

These are our speakers. Dr. Anderson will begin by talking about the risk assessment that he has performed with colleagues and I think that you will get a very good overview of the risk assessment and how it works.

Then Dr. Weinstein will discuss the overall risk communication approach. Then today we are very fortunate to have input from patient advocates regarding the risk communication. These are Mr. Val Bias, who is a board member of the National Hemophilia Foundation, Ms. Janice Hamilton, director of the Hemophilia Federation of America, Dr. Richard Colvin of the Committee of Ten Thousand, and Mark Sinner, the president of the World Federation of Hemophilia. >We appreciate their input quite a great deal

and look forward to the discussion. Thank you very much.

DR. TELLING: Thanks, Dr. Scott. Are there any questions from the committee of clarification on this presentation?

DR. MANUELIDIS: I just wanted to say that you mentioned Saudi Arabia. Just for some people who may not know, when I was in England with the MRC and looking at the problems, that actually it wasn't just the beef. At that time England had already shipped steers for breeding that were older to Saudi Arabia.

What I am going to sort of emphasize in some of the risk assessment things or try to say is that we don't know what the incidence of BSE is in many of the countries that we are talking about. That is a factor even in our own country, and I think that plays into risk assessment.

DR. TELLING : Thanks, Dr. Manuelidis. Actually, Dr. Scott, I had a question for you. About the two cases in the United States that spent some considerable amount of time in the United Kingdom, was there a window of time in which they spent time in the United Kingdom or were they born in the United Kingdom and raised in the United Kingdom and then subsequently emigrated to the United States?

DR. SCOTT: Our understanding is that they were UK residents for a very long period of time.

DR. TELLING: There is no particular window of

time.

DR. SCOTT: No, I don't have that off the top of my head, but there was a substantial window of time. We can get that, many, many years in the risk period.

DR. TELLING: Although it is only two cases, it may help inform what the incubation period is, if we could have that information. If, however, they were born in the United Kingdom and then moved here, that doesn't help us.

DR. SCOTT: That has been our understanding. If it is otherwise, I will let you know.

DR. HOGAN: Actually, clarification. The first case, which was a Florida case, was born in the United Kingdom, came to the United States in 2001 and came down with the symptoms just shortly thereafter.

The second case was a UK resident who lived in the United Kingdom up until 2001, came and lived in Texas for one year and then came down with the disease, went back to the United Kingdom for treatment, and that is where he was diagnosed.

DR. TELLING: Thank you, Dr. Hogan. If there are no further questions, I would like to ask Dr. Anderson from the FDA to discuss the risk assessment and its interpretation.

Agenda Item: Risk Assessment and Interpretation.

DR. ANDERSON: Thank you, Dr. Telling. I am

going to speak today about the draft risk assessment. The title of the document is up on the screen. It is a draft quantitative risk assessment of variant CJD risk potentially associated with the use of human plasma-derived Factor VIII manufactured under U.S. license from plasma collected in the United States.

I thought it was important to give a little bit of context and rationale for why FDA sort of engaged in this risk assessment process.

First off, beginning in December 2003, there was the first case of variant CJD transmission by a red cell transfusion identified in the United Kingdom.

At that time, there were concerns that variant CJD may potentially be transmitted through plasma-derived products including clotting factors.

That said, clotting factors such as plasma derived factor VIII, which is the center piece of this risk assessment, it is made from human plasma and then used in large quantities by many U.S. patients.

Transmission of variant CJD, therefore, was thought to be a potential hazard, but the magnitude of the potential risk at that time was unknown.

In the fall of 2004, FDA began developing this risk assessment in the process of evaluating potential variant CJD risk in plasma-derived factor VIII products.

Moving on to additional background, this really is a time line of some of the processes that this risk assessment process engaged in.

First off, I think this committee in particular had a fair amount of input and offered a fair amount of advice on this risk assessment on two particular occasions,a and those are outlined in the first two bullet points.

FDA presented a conceptual variant CJD factor VIII risk assessment model at the February 8, 2005 TSEAC. As we were developing the risk assessment, particular questions came up about several of the inputs that we used in developing the model.

So, we came back to the committee and sought committee discussion and advice about several of those risk assessment inputs at the October 31, 2005 TSEAC advisory committee meeting.

As the process moved along, we incorporated that advice into the risk assessment, and much of the discussion into the risk assessment.

We developed a draft in the summer of 2006 and had that peer reviewed by three external experts, and two of those are currently sitting on the committee, and that is Dr. Mark Powell from the Department of Agriculture, and then Dr. David Gaylor from Gaylor and Associates.

So, now we are at the point where we are presenting this draft risk assessment today at the advisory committee meeting.

Also, to follow this talk, Dr. Mark Weinstein is going to speak to you about some of the risk communication activities about this risk assessment.

I thought I would remind the committee of some of the inputs and final inputs in the model based on the discussion at the October 31, 2005 meeting.

I am not going to go through this slide in depth because it takes quite a while to actually go through. What I wanted to draw your attention to was two specific parameters where we actually had stratifications in the inputs that we used.

Those would be, as mentioned earlier, UK variant CJD prevalence, specifically. That is a very hard parameter to estimate, as discussion will show you.

So, with advice from the committee, we decided to use two different methods for estimating variant CJD prevalence in the United Kingdom.

One was an epidemiologically based method. That gave us a mean estimate of 1.8 variant CJD infections per million population in the United Kingdom.

Our second method we used was based on a tissue surveillance method by Hilton et al in 2004. That gave us a

mean of one infection per 4,225 individuals in the United Kingdom. I am going to talk about this a little bit more later when I talk about the exposure assessment component.

Then I wanted to draw your attention all the way down to number six, which is the clearance process of variant CJD agents that potentially occurs during manufacturing.

We stratified, after a considerable discussion decided to stratify, this particular input into three categories of clearance.

One of those is the high level of clearance of seven to nine logs of clearance, sort of a moderate level of four to six logs, and then a lower level of clearance of two to three logs.

Most of the tables that you are going to see, the reason that I point these out is that all the tables that you are going to see have representations for both of these particular estimates of prevalence.

Then one table in particular has a representation of all the levels of clearance, and that is table 5.3, and I am going to show you that table just briefly near the end of the presentation.

Most of the tables focus on this middle level of clearance because FDA believes that approximately 90 percent of the products achieve at least four logs of

clearance.

So, these are all of the parameters based on the discussion that were incorporated into the model. Let me move on to talk about the specifics of the risk assessment.

Before engaging in the risk assessment process, one of the initial steps is sort of the problem formulation. What is the question you want to answer with the risk assessment.

That question really boiled down to what is the potential variant CJD risk for recipients of plasma derived factor VIII products manufactured from plasma collected in the United States.

Then the second thing that we focus on is what is going to be the particular scope of the risk assessment. We want to know what populations might be covered under the risk assessment, what particular hazard -- which in this case is the variant CJD agent -- and then what particular product, which is factor VIII.

So, we estimated the potential variant CJD risk for US plasma-derived factor VIII recipients. We looked specifically at two populations, those patients with severe hemophilia A, and then those patients with severe von Willebrand's disease, also known as Type III disease.

Another important aspect of the scope of the risk assessment is that the potential variant CJD risk was

estimated for a one-year treatment period, and we pegged that to the year 2002, because most of our data was from the year 2002.

FDA generally believes that the results are applicable to the current year as well, because practices, and manufacturing processes, have changed, but not in a major fashion, that would affect the risk estimates, we believe.

All right, so moving on to our general analytic approach, this is a quantitative risk assessment. Input data was largely incorporated into the model using statistical distributions whenever possible.

Therefore, it is a probablistic computer based model that relies on Monte Carlo methods, and I am going to tell you how the Monte Carlo methods and a few of these methods were sort of operationalized in developing the model later in the presentation.

To start with, this is the risk assessment framework that we used by asking for the risk assessment. It was a framework that was developed by the National Academy of Sciences in 1983.

It breaks the risk assessment process into four parts, hazard identification, dose response, exposure assessment and risk characterization.

These three elements are integrated to form the

results that are generated in the risk characterization section.

One thing I wanted to say is, you are going to notice the talk really pegs and follows these four steps throughout the entire presentation. So, just a note of organization.

A little bit about background and how factor VIII is used in the clinical setting, factor VIII, remember, is the plasma protein necessary for normal blood clotting.

Two types of bleeding disorders are generally associated with the deficiency of factor VIII that we specifically evaluated in this risk assessment, and those are hemophilia A.

That is associated with a deficiency of factor VIII. Again, severe hemophilia patients, which were the focus of this assessment, have less than one percent factor VIII activity.

We also looked at von Willebrand disease patients in this risk assessment. That is a deficiency of the von Willebrand factor, which is a glycoprotein carrier of factor VIII.

It is also important to note that severe von Willebrand's disease patients also have reduced levels of Factor VIII.

Clinical usage, how does that fare with our risk

assessment. Well, approximately 25 percent of hemophilia A patients use plasma-derived factor VIII products. The other approximately 75 percent currently use recombinant factor VIII products that have been available since the early 1990s.

Von Willebrand disease patients specifically use plasma derived Factor VIII because there is no recombinant von Willebrands factor, and some of these plasma-derived factor VIII products do contain von Willebrands factor.

So, in the hazard identification section of the risk assessment, we sort of established the causality between the agent and adverse events.

It is important to note -- I am going to sort of jump to the bottom of this slide -- that to date there aren't any variant CJD cases identified in recipients of these plasma derived products.

So, this is the potential hazards that we are talking about, not a hazard that has actually been demonstrated.

The background that demonstrates that it is a potential hazard is that to date there are three variant CJD infections that were probably acquired through red cell transfusions that occurred in the United Kingdom since 2003.

Again, as I mentioned earlier, the potential

presence of the agent in human plasma suggests that it could be present also in plasma derived products, including plasma derived factor VIII. Again, this may be a hazard to human health.

The other factors that hemophilia A and von Willebrand's disease patients use, plasma derived factor VIII in large amounts often over long treatment periods, there is the potential that they may have been exposed to the variant CJD agent.

Again, I will draw your attention to the last bullet point as well. To date, no cases have been identified in recipients.

All right, moving on to the hazard identification, these are really two sort of major considerations when you look as a risk assessor at this particular problem, and some of the risk issues associated with plasma derived products.

First of all, the plasma is pooled from thousands of donors. So, there is an increased chance that plasma pools could contain variant CJD donations compared to single donors and single donations.

However, this particular risk is counter-balanced by a factor that helps out, which is TSE clearance during the manufacturing process.

Clearance likely decreases the potential CJD

infection risk by decreasing the quantity of agent that may be present in product if there is a donation present in a pool, and it decreases the potential exposure to the variant CJD agent in patients that use these products.

Factor VIII products, again, important to note, the plasma-derived products do vary in the level of reported clearance. It is also a challenge to evaluate and study clearance. Extensive studies are required to do that.

Moving on to the second component or element of risk assessment, to talk about dose response to variant CJD, again, a lot of challenges in determining dose response in this case.

The largest one, of course, if bullet number one, which is human data are absent. So, we don't know what particular dose is necessary to initiate variant CJD infection, and also what level of material might be required to actually cause an infection that progresses to a case of variant CJD. So, a big uncertainty there.

The quantity of agent in human blood and plasma is unknown. So, FDA in the risk assessment model used animal data to assess those quantities.

The question is, is the agent present throughout the incubation period in the blood or plasma. That remains a question.

The genetics and susceptibility of humans, again,

there is -- most cases occur in individuals that are methionine homozygous at codon 129 of the PRP gene, but then again, there are the non MM individuals that also may be susceptible, but no cases have appeared in those individuals. So, that adds to our uncertainty about dose response as well.

The question for dose response, is there a threshold or not, and then also is there an accumulation of agent in humans that could potentially lead to increased infection or probability of infection.

The other question, too, we used animal data to generate a basic dose response in this situation, but do those animal models actually approximate human variant CJD and disease progression accurately or appropriately.

The FDA risk assessment model, these are the basic assumptions in the model. We assume that variant CJD agent is present in the last half of the incubation period. There is a linear dose response below 2 ID50s, but there is no threshold. There is accumulation of infectious agent in the human body for a period of at least one year.

So, going through the -- this is an overview of a cartoon diagram, essentially, of our exposure assessment model, where we are assessing the potential variant CJD risk for plasma-derived factor VIII.

So, I orient you to this diagram and our process.

To the left we represent the inputs in the model. These are the data inputs that were actually used in the model.

The center part is the various modules in the model. For instance, we modeled variant CJD prevalence of the United Kingdom, used that estimate to estimate prevalence in U.S. donors, et cetera, and in the processing, used the utilization to estimate risk.

To the far right you will see outputs. These are actual outputs. You will see many of these outputs reflected as tables in the risk assessment document that was provided to the committee and is posted on the FDA web site.

To sort of walk you through the basis of this model, variant CJD prevalence in the United Kingdom, we have our two estimates.

One is a lower prevalence based on epidemiologic modeling. One is a higher prevalence estimate based on the surveillance estimates, surveillance studies of one in 4,225.

That information then is used as the basis to evaluate risk for donors with a travel history to the United Kingdom, France and other countries in Europe.

Again, we adjust that information for factors such as the year the donor traveled, their age and other factors. We also include the screening questionnaire

because the deferral program screens out approximately 90 percent of the variant CJD risk in plasma donors.

So, what we finally end up estimating here is the total number of variant CJD donations and donors that could potentially enter plasma pools.

In the factor A processing component, we are actually looking at the processing elements that go on during manufacturing. So, we consider plasma pool size, quantity of agent.

Then again here comes our friend, reduction of variant CJD agent during manufacturing. It is considered during processing.

What we derive from this is an estimate of the percentage of plasma pools or vials that contain variant CJD agents and the quantity that could be in vials containing variant CJD agent.

Then we want to estimate how are those products potentially used. So, we estimate utilization of factor VIII in our two patient populations.

Ultimately, what we are estimating is in yellow. Here is the annual exposure or dose of variant CJD agent for patients with severe hemophilia A or severe von Willebrand's disease, that use plasma derived factor VIII products.

Moving on, I thought I would just briefly discuss

the Monte Carlo method, since it is an important part of this risk assessment.

The Monte Carlo method is a tool for combining data as distributions rather than using and propagating the data as summary statistics.

Without Monte Carlo methods, the process of combining more than two distributions of the possible values or variables would be challenging.

So, how does the method work? What essentially is done is, we develop statistical distributions for as many of the inputs as possible.

The software that we use draws randomly from each of those defined distributions. So, it performs the program mathematical function.

So, for instance, it might multiply two different inputs together, and I will show you an example of that in a moment.

Then, it finally stores that result. So, that process is repeated thousands of times in what we call iterations, and the results are displayed as a new aggregate distribution. Let me show you an example of what I mean by all of that jargon.

This is an example, and it is similar to an example used in the model, although I simplified it a bit for the purposes of this presentation.

We are doing an example calculation of how we calculate intravenous ID50s per ml of plasma. So, we start with a distribution similar to what was used in the model, although not the same, of IC ID50s per ml of blood.

We have a minimum of two IC ID50s per ml, a most likely value of 10, and a maximum of 30 in this distribution. This is called a triangular distribution.

Our software picks a number of those. So, it might pick 10, for instance. It would then go ahead and multiply by 58 percent, which is a percentage of ID50s in plasma.

Then, going further on to do the actual adjustment from IC to convert the intracerebral units into intravenous units, it might pick a number from here, multiply that and get the result.

It would perform this function 10,000 times and what you would get is this aggregate distribution. The one thing I wanted to point out about that is, this distribution is very similar to a lot of the summary statistics that you will see later on in the table.

Basically, those summary statistics are distributions very much like this, with the fifth percentile, 95th percentile, and then a mean reflected. Actually, all of those tables that you are seeing were developed from distributions similar to what is shown here.

Moving on to module one, estimating prevalence of variant CJD in the United Kingdom, again, we used our two approaches.

One was an epidemiologic modeling approach of estimating variant CJD cases. Again, this is a lower prevalence estimate.

We used a method based on results from Paul Clark and Ezra Donning in the United Kingdom and published in 2005.

They predicted 70 future cases of variant CJD for the years from 2002, which is the base of our model, out to 2080.

With those cases, you can estimate a prevalence of variant CJD in the United Kingdom of 1.8 per million in the UK population. So, that is the summary of that method.

So, moving on to the second method that we used, we used a method from a tonsil appendix tissue surveillance study in UK patients, which was our higher prevalence estimate. That was done by Hilton et al in 2004 in the United Kingdom.

In that study, they identified three prion positive samples in 12,6074 samples tested. So, that gives you a mean positive that we used in the model of one positive or potential variant CJD infection in 4,225 individuals.

I can't sort of emphasize enough that this is really a critical input in the model. There are critical uncertainties as well, in these methods for estimation. I will talk about those in a minute.

These estimates are basically used to estimate variant CJD prevalence for France, other countries in Europe, for donors that stayed on military bases in Europe, and ultimately is used to estimate variant CJD prevalence in plasma donors in the United States. So, it is a very prevalent parameter in our model.

So, I wanted to sort of outline some of the uncertainties, because these are carried forward with all of our estimations in all of the numbers we generate in the model.

First of all, with our epidemiologic modeling method, all the cases that they evaluated and did their predictions on were variant CJD cases in methionine homozygous individuals at codon 129.

So, that only represents 40 percent of the population. The non-methionine homozygous individuals or non MM individuals, represent potentially 60 percent of the population and aren't represented in the calculation. So, this type of estimate may slightly underestimate the actual number of cases.

They also used several assumptions such as the

incubation period, time of infection, effectiveness of the British feed ban at that point, to do this type of estimate.

There are also uncertainties associated with the second method, used to estimate the higher prevalence estimate, and that is that prion protein was identified in appendix samples, but that doesn't necessarily tell us whether agent was present in the blood or whether the individuals developed disease.

The sample size for this study, although 12,000 individuals were studied, the size is relatively small for such a rare disease.

Other limitations are that it may underestimate variant CJD prevalence. In one particular case -- I believe it was the second transfusion transmitted case -- no agent was found in the appendix. So, that person would not have been captured in this type of methodology.

Finally, the tissue surveillance method lacks certain controls. For instance, a survey of non-BSE exposed populations wasn't done, and then the patient outcomes, again, as I alluded to earlier, are unknown. So, we don't know if those patients actually developed disease or not.

So, moving on to estimating variant CJD prevalence in US plasma donors, our modeling approach basically was to estimate the size of the US plasma donor

population with a history of travel to the United Kingdom, France or other countries of Europe since 1980.

Remember, we are assuming in this model that our basic tenet is that most of the risk in the US donor population for variant CJD comes from individuals with a travel history to the United Kingdom, France or other countries in Europe.

Then we go on to model donor travel risk using survey data from blood donor populations. We apply a relative risk estimate for donor travel to the United Kingdom, France or other countries in Europe.

We adjust that risk by several factors, including duration of stay, year and other factors. Then we add up the potential number of infections for U.S. plasma donor groups and then apply the effectiveness of the donor deferral policy.

Finally, what we estimate is a total number of potential variant CJD infected donors and donations in the United States that are used specifically for producing plasma derived Factor VIII in the United States.

So, how does relative risk and how did we actually operationalize what I just said. Relative risk was a measure that was used to estimate the probability of variant CJD infection in U.S. donors.

This type of method has been used previously in

estimating the risk associated with donors with a history of travel to the United Kingdom, France or other countries in Europe by the FDA, when we were developing the deferral policies in 1999 and then again in 2001.

Again, what happens is, we estimate variant CJD prevalence in donors that travel to France and other countries in Europe relative to the United Kingdom variant CJD prevalence.

As an example, for instance, if we had an individual that traveled to the United Kingdom for five years, we would assume that their relative risk would be one. That is equal to the prevalence of variant CJD in the United Kingdom.

If we had another individual that traveled to France for a period of five years or more, their relative risk would be adjusted by a value of .05, which is five percent of the United Kingdom risk. So, that .05 just becomes a multiplier against the prevalence of variant CJD in the United Kingdom.

Again, for other countries of Europe, our multiplier is .015. For individuals that stayed in military bases in Europe for a period of six months or more, that multiplier is .035.

This is how it is used. The relative risk, again, is estimated for the year 2001, and it was using country

specific information on BSE cases, so, for instance, in France, and then the quantity of imported beef and number of variant CJD cases and other factors.

So, once we have a relative risk assignment for individuals based on where they travel, we further adjust that relative risk estimate over a period.

We do that for over a 23-year period from 1980 to 2002, and we adjust those numbers for the duration of travel. It is a proportional adjustment.

If an individual spent one year, their risk would only be one fifth of that of an individual that stayed five years. So, that is the type of adjustment we are doing throughout this model.

We adjust for a specific year of travel based on the BSE epidemic. So, if they traveled in 1992 when the epidemic was at its height, they would be at higher risk than somebody that traveled in 1996 to the United Kingdom when the epidemic and control measures were implemented and the epidemic was at one of its lowest levels.

We include age of donor to apply the specific grade to a variant CJD in the donor population and then age specific donor rates are considered. We also consider specifically the type of donor, whether they are a source or a recovered plasma donor.

Again, what we are estimating in this model is a

significant portion of that risk has been removed by the donor deferral policies.

So, the model is estimating two remaining sources of what we call residual risk for U.S. donors and those are donors with deferrable criteria but, for some reason, weren't deferred because of limitations in the screening process.

Then, those individuals that weren't deferrable because of short-term travel that fell under the guidelines for the deferral policies.

The deferral policies eliminate approximately 90 percent of the risk for U.S. donors. For instance, for donors that travel to the United Kingdom during the period from 1980 to 1996, if they stayed a period of three months or longer, they would be eliminated. You can go on and do the same thing for France, other countries in France, and military bases.

Again, the model assumes that the efficiency of this entire deferral is approximately 85 to a maximum of 99 percent effective.

Moving on to estimating the prevalence in plasma donors, again, what we are estimating as outputs are the potential variant CJD -- the number of potential variant CJD infected plasma donors in the United States, and then the potential number of donations that could have variant

CJD agents.

Again, considerable uncertainty in these data and in this input for this specific module, and that would be the travel data for source plasma donors, we don't have travel data essentially for source plasma donors who may travel less than the whole blood donor individuals.

That was the group that was actually surveyed. This may be an overestimation in the model of the risk for source plasma donors, because we didn't survey those individuals.

Estimation of the deferral effectiveness is a challenge. How to consider variant CJD susceptible populations was a challenge. So, for instance, it is difficult to estimate the potential disease attack rate and incubation period, which remains largely unknown for these individuals that are non-MM individuals in the population.

Ultimately, percentage of infections that become symptomatic disease is unknown as well. So, a lot of uncertainties go into this particular component of the model.

Moving on to factor XI processing and manufacturing steps, our modeling approach was to estimate the probability of a plasma pool containing a variant CJD donation.

We then estimate the quantity of agent per ml of

plasma and plasma pool. We then convert for the efficiency of exposure, convert from IC, actually, to IV is what this should say.

Ultimately we are getting the IV ID50s that could be present in each vial that contains the agent. Ultimately each plasma pool, then, undergoes a log's reduction under the manufacturing process, and that is also considered in the model.

To move forward to processing, I thought it would be important to just discuss the clearance a little bit more in depth, infectivity clearance in product plasma pools.

Each product has different purification steps and clearance levels. So, varying the level of clearance, it is important to note that product specific data are not available for all products and process steps.

It is also important to note that there are data in the published literature that are available for only some purification steps. Again, those studies show significant variation between each study.

So, in order to sort of deal with this level of uncertainty, the FDA model stratifies, as I mentioned earlier, by the three clearance levels, seven to nine, four to six, and two to three logs of clearance.

Again, it is important to sort of highlight that

FDA believes that most factor VIII products have at least four logs of clearance, plasma-derived factor VIII products, that is, have at least four logs of clearance or more.

So, what are we predicting after we are done with model three in manufacturing and processing? We are predicting the percentage of plasma pools with variant CJD agent, the percentage of vials with variant CJD agent, and then the quantity of agent potentially per vial.

Moving on to some of the uncertainties with our processing information, specifically for quantity of infectivity in plasma and plasma pools, it is difficult to detect low levels of infectivity.

Infectivity of animal blood, which is the basis of our generating the parameter in the model for human blood is that this animal blood model may not necessarily be representative of levels of infectivity in human blood.

As far as infectivity of clearance, there is a lot of uncertainty there. There is no standard method for clearance study spiking materials, no standard method for animal study selection of donor and recipient animals.

The reductions that are observed in laboratory scales with high concentrations of spiked materials may not necessarily reflect reductions that occur in real processing systems.

Then it is not known if the reduction levels in different purification steps are additive or not. So, again, a fair amount of uncertainty in this particular portion of the model.

So, moving on, we now have an estimate of the percentage of vials, perhaps, and the percentage of plasma pools that could potentially contain agent.

We want to know, how do patients actually utilize these products and what might the dose of the potential hazard be.

The models output that we are predicting at this point is, we are predicting the potential dose of variant CJD ID50s per patient, and ultimately predicting the risk of variant CJD patients.

I think it is important to emphasize that this information is based on an animal dose response data and information, so that is less certain.

Even though we can provide a general prediction of risk, we can't provide a precise estimate of the risk, which is important to emphasize.

Again, going on to utilization, factors considered in the model were the type of disease, severe hemophilia, severe von Willebrand's disease, and the types of treatment regimens, prophylaxis or episodic, and then inhibitor or immune tolerance data for the patients.

So, we modeled several different patient categories according to these specific groups. The data sources we used were the CDC UDC data set to estimate size of the hemophilia A and von Willebrand's disease population, and then we also used the CDC sponsored six state study, a hemophilia surveillance study conducted from 1993 to 1998 to estimate actual utilization of these different patient populations.

Risk characterization, which is the last step of the model, really shows the results that we are getting for the model.

It really integrates the information from the exposure assessment and dose response to generate the estimates for exposure, which is the dose, and then ultimately the estimate for risk.

So, what we are doing is the exposure assessment provides this estimate of variant CJD, ID50 dose that a patient might be exposed to.

You multiply that times a factor of 0.5, which is one ID50 is equal to a 50 percent probability of infection, according to our linear dose response model to estimate the risk, and also the probability of variant CJD infection.

I am going to move on quickly through these tables. This is a table from the actual risk assessment document that calculates the annual percentage of plasma

pools containing variant CJD donations.

Again, just to orient people, remember I mentioned that we are going to be showing you in the table the higher prevalence estimates. So, that is shown to the right, and then the lower prevalence estimates from the model.

So, what this portion of the model predicts is the average percent of pools containing variant CJD agent. So, at the lower prevalence we have a predicted prevalence of variant CJD in the vials of 0.027 percent. At the higher prevalence it is 2.41 percent.

Again, there is a lot of precision shown in these tables but that is probably not warranted. I put a note under here to say that the results in the model are shown but, remember, there is considerable uncertainty with these estimates. So, just sort of a note of caution.

Again, looking at individual risks -- this is from Table 5.2A -- for severe hemophilia A patients, this is specifically at a four to six log level of clearance. Again, our lower prevalence estimate, our higher prevalence estimate.

We have patients on prophylaxis with inhibitor and with immune tolerance. At the lower prevalence, their risk would be one in 1.3 million. At the higher prevalence estimate, their risk would be estimated at one in 15,000.

Sorry, my time is up, so I am going to move pretty quickly through these. You have the document and can read that more closely as well.

Table 5.2B, this is a population based estimate. I wanted to go back and just say, this we are showing an individual estimate of risk for individuals. Here we are showing for the entire population.

So, for the entire population of 1,800 severe hemophilia A patients, we estimated they used a mean of 243 million units in the year 2002 of factor VIII, and that the risk there at the lower prevalence would be a risk of about one variant CJD infection in 3,000 years. At the higher prevalence, we would predict one potential variant CJD infection in 35 years.

Again, I am just going to call your attention to the results are highly uncertain, even though we have these tables that show a certain level of precision.

Again, I am just showing you this table to show the range of variant CJD risk for hemophilia A patients at the three different clearance levels, from two to three, four to six, and seven to nine, again, our lower and higher prevalence estimates.

I am going to focus on one particular portion of this table, the seven to nine log reduction and the four to six patients with severe hemophilia.

Again, patients under prophylaxis with inhibitor and immune tolerance, their risk at the higher prevalence would be one in 15 million and, at the higher prevalence for a four to six level log of reduction, would be one in 15,000.

Again, we are just comparing the range of risk for severe von Willebrands disease patient at the four to six log level of clearance.

For young patients under 15 years of age, under prophylaxis. their risk, the lower prevalence estimate would be one in 4.7 million, at the higher prevalence estimate, based on the data we had, was one in 52,000.

Okay, so moving on to the population based risk for patients with severe von Willebrand's disease at four to six logs of clearance, we have approximately 250 patients total in this population.

We estimate, at the lower prevalence, a mean variant CJD risk of one vCJD infection in 28,000 years and, at the higher prevalence, one in every 400 or so years.

All right, moving on to sensitivity importance analysis, I will sort of just quickly glide through this. A sensitivity analysis is used to identify key inputs or driver in the model.

This is conducted by varying input values by various levels and then observing the impact of those

variations on the final risk estimate.

What we did, actually, was an importance analysis which ranks inputs according to the level of influence on the final risk assessment. This is one type of analysis you can do.

The most important model inputs that were shown through doing this importance analysis was clearance by far was one of the greatest factors that influenced the risk estimate.

There were other factors, too, for instance, quantity used by patients, the prevalence of variant CJD in the United Kingdom, and then the efficiency of the IC to IV route.

This really just shows you a tornado diagram or graphical representation of what I just spoke about. So, you can see log manufacturing clearance has a large -- in this case it is to the left. So, it has a more negative effect. So, it reduces risk.

These factors to the right have a more positive risk, might slightly affect or increase the risk, depending on how you vary those.

Again, just sort of moving quickly to the uncertainties and data gap, again, a lot of uncertainties in this modeling exercise and risk assessment, more data are definitely needed on clearance of agent during

manufacturing steps, prevalence, utilization and a variety of other parameters listed.

All right, so finally, just to summarize the risk characterization in the model, it is not possible to precisely estimate potential risk for plasma-derived factor VIII recipients because of the uncertainties in data and knowledge of variant CJD.

What we can say is that the variant CJD risk from use of plasma derived factor VIII may not be zero, but it is most likely extremely small, based on results from the model.

The results from the model really are consistent with the observed absence of variant CJD cases in clotting factor recipients.

What we do know is that the current donor deferral policy greatly reduces the risk by deferring individuals with a history of extended travel to the United Kingdom, France and Europe since 1980.

Then the risk assessment shows that, again, the manufacturing processes have the greatest effect on reducing infectivity and reducing potential variant CJD risk.

The risk assessment really highlights a lot of the data gaps, again, in the level of clearance product usage, prevalence and dose response.

What I wanted to do was to show the level of people and engagement in this process. Hong Yang, who works in my group, actually did the yeoman's work in developing this model. So, she deserves a lot of the credit. I am just sort of the guy up here talking about the model, but she actually did most of the work for developing the model.

A lot of people from the office of blood research and review, from the center director's office, also were involved in this process.

Then I would also like to thank our peer reviewers. David Gaylor and Mark Powell did an excellent job of sort of keeping us on our toes with developing the model and providing some excellent sort of input into the model at that point last summer, and then Sonja Sandberg from the University of Framingham. With that, I will stop.

DR. TELLING: Thanks, Dr. Anderson. Are there any brief questions from the committee for clarification?

MS. HAMILTON: I just had one question about the variance from the low to the high prevalence in logs. How do you come up with that, and what are the bases for the large variation?

DR. ANDERSON: Those three categories were actually developed in internal discussion. So, looking at potential products and what is in the literature that tells us what types of steps are used for the products that are

currently in the market place and what levels of clearance might be associated with those.

So, we came up with sort of three categories, the two to three, the four to six, and then the seven to nine. We also discussed that with the committee in October as well and got some advice on that as well, and they seemed to be in agreement with using those three categories.

It is important to remember, though, that at the time we developed this over a year ago, we included that two to three level of clearance.

What we are finding, from looking at the data, is that it looks more like clearances above four logs is probably what is afforded for most products in the market place. Does that answer you question?

MS. HAMILTON: Yes.

DR. ANDERSON: it is a very complex issue and Dr. Scott is going to talk a little bit more about the clearance issue in the second half of the session.

DR. TELLING: There is going to be almost another hour of discussion later. Maybe we could revisit that.

DR. MANUELIDIS: I just have a question that I can't follow because I really don't know. How often does a patient take factor VIII? Do they take it once a month, number one.

What I am really going to get into is that you

get an accumulated dose that I think you have -- I am not clear from the data seen.

Let me just sort of finish the second part of it. I would really love to see something, what is the worst case scenario.

So, let's say that vCJD, which is not really that unlikely, has 10-fold the amount of infectivity in blood, which is why it transmits more easily in transfusion cases, and then let's say a patient takes that accumulated over several years. What would be the risk in terms of the number of cases per million that you might predict.

You might not give this overall possibility, oh, well, the risk is improbable. I think it is very good to take the absolute worst case scenario, too.

DR. TELLING: Dr. Manuelidis, I think it would be useful if we revisited this in the later session. I think it is a very important point, but I would like you to bring that up at a later time. In the meantime, I think Dr. Scott does have a point of clarification.

DR. SCOTT: Thanks a lot, Glenn. I just wanted to clarify that we have more recent data just in the last several months that indicates that we think all of our factor VIII products probably have a four log clearance or greater. I think that Steve might have said most, but we have more recent information that just came in.

DR. TELLING: Okay, thanks very much. Now we are going to hear back again from Dr. Weinstein, who is going to talk about the risk communication approach.

Agenda Item: Overall Risk Communication.

DR. WEINSTEIN: Dr. Scott has discussed overall risk management strategy for variant CJD and Dr. Anderson has described the risk assessment. Now I will address the issue of risk communication.

We have prepared a number of documents regarding the risk assessment that are now available on the FDA web site. These include the risk assessment itself and an issue summary that is written for a technical audience.

Most recently, we have presented risk communication in the form of key points and questions and answers. You have these documents in the folders that have been given to you this morning. I believe this was also sent to the committee before this meeting.

These key points and questions and answers are meant to present information to an informed audience, including patients and health care providers.

I will review how we developed the key points and questions and answers. I will then talk about the actual key points in some detail, and briefly review the questions and answers. Finally, I will talk about the communication strategy.

Note that in my slide presentation I have modified the key points that have been posted and that you have in your hand.

These minor revisions, I think, help to clarify the key points and, in some cases, add new information that we did not have at the time that they key points were written, in the copy that you have in front of you.

Now, with regard to the development of these key points and questions and answers, we had input from our sister agencies, the CDC and the NIH.

We also had information from special government employees and particularly from patient advocates. Finally, we had additional consultation with experts in risk communication.

Specifically, we asked our special government employees for their comments regarding whether the interpretive documents such as the key points and questions and answers adequately represented the findings of the risk assessment.

They were asked whether they felt the documents would be easily understood by the targeted audience, and whether they had suggestions on improving the clarity of these documents.

They were also asked about suggestions about how we might deliver the information, particularly to patients

and family members.

I have to say we are extremely appreciative of this input. We have incorporated their comments into these documents, and we think they have made significant improvements in the clarity and in the delivery of these risk messages.

Now, with regard to the actual key points, the first key point is meant to frame the issue, to give people a perspective of why we are doing this risk communication in the first place.

We note here that there have been concerns regarding the transmission of variant Creutzfeldt Jakob disease to hemophilia and von Willebrand's disease patients who receive U.S. licensed plasma-derived Factor VIII products.

Again, we note that this concern has been elevated because of the observation that, since 2003, we have had these three people, all in the United Kingdom, who probably acquired the variant CJD through blood cell transfusion.

Now, the principal concerns are to what extent, if any, there could have been contamination of U.S. clotting factors with variant CJD from infected donors, and whether the products made from their plasma would transmit the disease.

This concern, of course, is particularly true if the donors might have traveled to countries with a higher prevalence of CJD and BSE than occurs in the United States.

The next point is there to raise the issue, to clarify why we have addressed the issue of plasma-derived factor VIII rather than some other plasma derivative such as immune globulin sera or albumen.

The reason is that the factor VIII is made from a fraction of plasma that is most likely to have a higher concentration of the variant CJD infectious agent than other fractions from which products, such as albumen and immune globulins, are made.

At the same time, of course, it is important to note that the Factor VIII containing fraction is further processed using a variety of methods that we will hear about later on today that is likely to remove or at least very significantly eliminate or reduce the level of the infectious agent from the final factor VIII product.

The next two slides or the next two key points are more background information. Variant CJD originally came from a disease in cattle called bovine spongiform encephalopathy.

The transmission of BSE agents to humans occurs primarily through the ingestion of cattle products contaminated with the BSE agents. Both BSE and variant CJD

are invariably fatal brain diseases with very long incubation periods measured in years.

From 1995 through November 2006, there have been 200 cases of variant CJD reported worldwide, with 164 cases in the United Kingdom and three cases in the United States.

Again, we point out that two of the cases in the United States had lived in the United Kingdom during a key exposure period, and that the third case most likely acquired the disease in Saudi Arabia.

The incidence of variant CJD in the United Kingdom peaked in 1999 and has been declining thereafter. In the United Kingdom, the risk of acquiring variant CJD from eating beef and beef products at present appears to be negligible, estimated to be very roughly about one case in 10 billion servings.

Now, this is probably the most significant point here. Based on a recently completed risk assessment, the U.S. Public Health Service including FDA, CDC and NIH, believes that the risk from variant CJD to hemophilia A and von Willebrand's disease patients who receive U.S. licensed plasma derived Factor VIII products is most likely to be extremely small, although we do not know the risk of certainty.

Now, this is a -- this next point is consistent with our risk assessment. The agencies are not aware of any

cases of variant CJD having been reported any place in the world in patients with hemophilia A or other blood clotting disorders. This includes those who have received over a long period of time large amounts of blood clotting products manufactured from plasma donations from the United Kingdom, where the risk of variant CJD is highest.

Again, another major point is that none of the plasma derived products or factor VIII products have been made from the plasma of anyone known to have developed variant CJD in the United States, and no one who has received any of these products is known to have developed the disease.

However, there is no test yet available to detect variant CJD infection in healthy donors or recipient. The FDA used a computer model to assess the risk of variant CJD. However, again, there are many major uncertainties in the computer model and a precise estimate of the risk is not currently possible. There is no test available to detect the infection in healthy donors or recipients.

The last key point gives information about how interested persons can find out more information about variant CJD. We have a number of web sites from FDA, the CDC, U.S. Department of Agriculture. Important, information can also be obtained from a number of sources from patient advocate groups, including the National Hemophilia

Foundation, Hemophilia Federation of America, the Committee of Ten Thousand and the World Federation of Hemophilia.

I would like to next switch to just a brief review of the questions and answer document. I will just review the questions here. The answers are included in the document that you have. You can see that they are very substantial.

The questions were given to us, in part, or became apparent through discussions with the SGEs, and our own internal discussions about what we felt would be issues that interested parties might have regarding the risk assessment.

We asked, what is variant CJD and how is it spread. Is it known that plasma-derived factor VIII can transmit variant CJD.

What is the likelihood that a patient who received plasma-derived factor VIII could become infected with variant CJD.

Why did FDA do a risk assessment for plasma-derived factor VIII. What is the risk of variant CJD to patients who received transfusion products like red blood cells and plasma.

Why is FDA informing patients and health care providers and the public about variant CJD and factor VIII, plasma-derived factor VIII now.

Should patients inform their primary health care providers about a possible variant CJD exposure from U.S. licensed plasma-derived factor VIII?

Do patients who receive plasma-derived factor VIII need to do anything special when seeking dental or surgical care?

What can recipients of plasma-derived factor VIII do with this information? What are hemophilia treatment centers? Where can I find out more about them? Where can I find more information about variant CJD and plasma-derived factor VIII?

So, our communication strategy, again, we are going to have these key points, questions and answers, risk assessment and issue summaries posted on the FDA web site.

We have notified hemophilia treatment centers about this issue. They have provided input and have agreed to disseminate information.

Also, patient advocacy organizations have also been briefed and will help to publicize these findings through newsletters and other media.

The Public Health Service will be involved in outreach to trade and physician organizations. Finally, the key points in questions and answers list sources for further information and answers to questions. Thanks for your attention.

DR. TELLING: Thanks very much. We are on time. If there are any questions now of clarification, then we can take them.

MR. BIAS: One clarification. The information about the NHF information service, 1-800-HANDY, it is 1-800-42-HANDY.

DR. TELLIng: Okay, thanks very much. I would like to finish up this session before the break with very important perspectives from the advocacy organizations. The first perspective is going to be from the National Hemophilia Foundation and Mr. Bias.

Agenda Item: Patient Advocate Perspectives. National Hemophilia Foundation.

MR. BIAS: Good morning and thank you for having me this morning. Since it wasn't mentioned in my introduction -- well, actually, I say it in the speech, so I won't have to.

I have severe factor IX deficiency. I have been exposed to all the communications related to plasma-derived products, and continue to rely on those products to control my bleeding disorder.

Although the risk does not address my individual product or plasma-derived product, I share the concerns many in my community will have about this new and important information.

I want to thank you for the opportunity to share my views and those of the National Hemophilia Foundation on this important subject.

Thanks also to all of the agencies who have facilitated this process. We understand that improving our understanding of this health issue and its potential risk, and then communicating that understanding to the public is a challenging task.

The important thing is that people in this room and the agencies you represent have not shied away from that challenge.

I am here as a representative of the National Hemophilia Foundation. I also represent those in the bleeding disorder community who are affected not only by hemophilia but also by complications acquired from tainted plasma-derived products in the 1980s.

During that period, we learned the hard way, although information may be incomplete, that it is vitally important to communicate in a timely and accurate and open manner.

We also learned that we must not create barriers to communication between the government, the medical and scientific community, industry and patients. Rather, where we find those barriers, we must tear them down. That is why I am here, and I think that is why we are all here

today in this room.

Now, allow me to address the risk assessment for potential exposure to vCJD for plasma-derived factor VIII users.

I think we all understand going into this that the process had significant limitations simply because there are too many things that we don't know.

As a result, we knew that there would be limitations on what could be deduced from the process. That said, I think we are reassured by our understanding thus far that we intuitively understood that an extremely low risk of exposure remains just that, an extremely low risk.

NHF, in our communications to date, has emphasized this positive gleaning from the process. None of the information that has emerged so far should be the cause for panic or an exaggerated level of concern, and we believe that all communications should lead with that message.

It is particularly important in this context that we not create an atmosphere that could threaten the access to plasma-derived products for those who need them.

Many individuals with bleeding disorders and other health conditions rely on a reliable supply of safe plasma derived products, and we must ensure that supply is not threatened in any way or diminished.

In addition, we want to avoid unnecessarily creating the kind of fear that could negatively impact the quality of care our community receives from a range of health care providers.

At the same time, we acknowledge the continued understanding that the risk is not zero, and it is our responsibility to ensure that this fact is communicated as well.

By appropriately conveying all of these messages, we are also delivering an additional one, that we accept our responsibility to be actively engaged in trying to understand and communicate about this and other potential health risks.

It is very important that consumer advocacy organizations are a part of this product. We strongly encourage the FDA and other agencies to keep us engaged going forward, and to use us as a channel for communications with consumers.

For NHF's part, we will continue to employ our well trafficked web site, our award winning magazine, our electronic newsletter, e notes, and 1-800-42-HANDY, our information service, and other forums at our disposal to communicate this information to consumers.

However, those channels are only as good as the information that is available to us. Therefore, I encourage

all of the government agencies, the manufacturers and others to keep the information flowing to us in a timely manner.

This, in turn, allows us to communicate to our constituents, and to solicit their feedback as well. It is also important that organizations representing health care professionals be similarly engaged in this process, as they represent both an important audience in their own right and an important channel back to consumers.

Certainly NHF's medical and scientific advisory council will be taking a separate look at the implications of these findings, and we encourage you to engage MASAC members in furthering this process.

We must also engage counterpart agencies and organizations abroad to ensure that we are sharing the best information and the best strategies and solutions.

Finally, it is necessary to acknowledge that this represents an important but incremental increase in our knowledge base in our overall efforts to protect the community from blood borne pathogens.

Perhaps the most important result of this process has been to determine not only that which we don't know, but also some of what we need to learn more about.

One example of the coordinated effort to further define the risk and our ability to address that risk will

be the adoption of standardized or uniform log removal criteria in the manufacturing process.

The government, industry, the medical and scientific community must dedicate resources to doing research that will narrow our knowledge gaps.

They must also develop improved methods of screening, manufacturing and deactivation to identify and eliminate not only TSE, but all prions and other potentially infectious agents from all products, both plasma derived and recombinant.

The lives and health of the people in the bleeding disorders community depend on it, as well as the health and safety of all Americans.

In closing, I would like to thank the FDA and all of the agencies for this communication process. This strategy would have been extremely helpful to all of us if we had had such a strategy in the 1980s.

This is a huge step forward for all of us in the blood borne pathogens business. So, I want to thank everyone for their involvement and continue our pledge to work with everyone in terms of addressing these issues that affect America's blood supply. Thank you very much.

DR. TELLING: Thank you very much. Let's hear now from Janice Hamilton from the Hemophilia Federation of America.

Agenda Item: Hemophilia Federation of America.

MS. HAMILTON: Thank you for the opportunity to be here today. I would like to start by echoing most of the sentiment, many of the sentiments, all of the sentiments that Val Bias said as far as the progression of information and how much we wish we would have had this earlier. We really appreciate all the work that is being done in this area.

I want to just say that my comments are being made from being in consultation with our AFC leadership committee and our medical advisory panel.

The issue, as we see it, is how to communicate the risk of transmission of vCJD to the plasma user community. This is very difficult.

As much as I am familiar with the information, I am still concerned about how we get this information to the community so that they understand it.

Information must be comprehensible and delivered in a clinical setting, we feel, from physician to patient. We need to deter panic and allay fear that we had in the 1980s.

We need to discuss the stigma of social alienation as we had in the 1980s. We don't want to revisit that area. We want to provide available, factual information and respond to questions.

Along these lines, we need to be able to have this information, as Val said, to communicate to our constituents through our newsletters, through our web site, and through our symposia.

We need to determine the strategy to minimize the loss of access to medical services. We are very concerned about that.

There are still physicians and surgeons today who refuse to treat patients who have HIV and AIDS for invasive procedures and the like, and we see that this could be something that we need to address with this issue.

Moving on to considerations for risk assessment and risk communication strategy, risk assessment should be communicated to all physicians who provide services to individuals with a bleeding disorder.

Physicians down the line, such as internists, pediatricians, orthopedists, dentists and so forth, may not have the expertise that hematologists have, but they have the ear of the patient, and they need to have this information as well. I communicated that earlier in our comments to the group.

There should be an effort to accommodate those who don't visit an HTC. There are still people who don't attend visits with clinics with HTC, and there are some who don't see a hematologist and some who are geographically

isolated. So, there needs to be a way to communicate this information down the line to those people.

There are also some of those people that don't communicate with any of the national organizations. So, we have to find a way to infiltrate that group.

Considerations for risk assessment and risk communication strategy, communication of theoretical risk of vCJD must be forthright and honest, and I am looking forward this afternoon to the discussion on these variations of the logs present in the various groups, because especially those who are factor VIII severe and take factor every day or three or four or five days a week, that is of grave concern.

Never forget the HIV/AIDS contamination of the blood supply in the 1980s. Members of the bleeding disorders community were stigmatized and unduly threatened because of the fears associated with HIV/AIDS. As I mentioned previously, we don't want to revisit that.

We feel that the biggest risk of all is still out there. If the risk is considered to be as low as stated, can a strong recommendation be made that hemophilia patients not be treated any differently from other patients. This is very important to our community.

Yet another -- even the bigger risk of all is the risk of being denied access to care from physicians and

surgeons or from the reimbursement arena, and both of those are equally scary to us.

Then the incubation period seems to be something that is very vague and difficult to communicate this to our community.

How can you tell someone that, okay, incubation period may be as low as a month and it may be as long as 30 years. It is really scary to have that information and known how to deal with it, and how to explain the lack of symptoms during the incubation period.

Val mentioned factor IX. One of the questions that came up with our group is, is there another risk assessment that is going to be done for plasma derived factor IX, or is that something that we don't need to worry about for some reason. We mentioned XI and now we are on VIII and is something going to be done about IX.

Moving on in this same arena, is there a need -- we realize that it has been said -- for fractionators to disclaim risk of using a product with plasma-derived material. That is sort of like a statement on a package of cigarettes. We realize that it needs to be done and it needs to be done in a way that does allay panic and fear.

Will fractionators be able to accommodate a possible exodus to recombinant product as this information gets out into the community.

Von Willebrand patients and other patients who do not respond to recombinant products will continue to require plasma-derived products, because there is no recombinant product for the von Willebrnnd's product, and some patients do not respond to Benefix, which is the recombinant product, for factor IX. So, we need to still be very concerned about the plasma-derived product.

In conclusion, we feel that further surveillance is essential. We need to develop a data base of volunteers willing to give advanced directives for an autopsy.

There are so many of the deaths that occur both in the hemophilia population and others that could very well be CJD or vCJD deaths, but there is no autopsy provided.

So, if we had a group of volunteers who would give advanced directives for that, then there could be a data base for trying to study this further.

It is very important to maintain the support of the ongoing UDC study directed by the VDC through the hemophilia treatment centers.

There could be comorbidity studies and other things through this very valuable data base. We would like to encourage to maximize the use of leukocyte reduction technology for blood products, and then we are delighted to hear of the filtration possibilities, fast track

development of a test to identify vCJD and technology to eliminate it from blood and blood products.

Thank you for the opportunity to speak with you today and we are very delighted that all of this information is coming to the forefront and can be communicated, and we offer our services through any of our publication areas to help to get this to the patients.

DR. TELLING: Thanks very much, Jan. Let's hear now from Dr. Colvin from the Committee of Ten Thousand.

Agenda Item: Committee of Ten Thousand.

DR. COLVIN: Good morning and thank you, Dr. Telling and the committee, for giving me the opportunity to speak on such an important topic.

I come here today with a unique perspective. As an infectious disease physician, I have concerns about any new potential pathogen that threatens the blood supply.

As a person with severe hemophilia, factor VIII deficiency, in fact, I really have concerns any time a potential new pathogen threatens the blood supply.

Although in no way do I, nor the Committee of Ten Thousand, nor the infectious disease division of Mass General Hospital, feel that the risk of Creutzfeldt Jakob's disease transmission through plasma-derived Factor VIII is similar to the risk of HIV, HEP B or HEP C from factor VIII in previous years, I do feel that it remains prudent to

consider the lessons from the past when considering how to proceed in the face of a potentially fatal pathogen contaminating the blood supply.

For the past decade CBER has monitored the hemophilia population fairly closely for any indication that CJD has been transmitted through Factor VIII.

Additionally, CBER has made a good faith effort to understand the risk of CJD in persons who have used plasma-derived blood products.

The good news is that there have been no cases of CJD in our population, making it difficult to calculate a risk.

Unfortunately, much uncertainty remains, as we have heard today, including the underlying pathophysiology of the disease process, potential incubation period of this prion, minimal infectious doses of the prion, the actual removal of prions by fractionation, and even the prevalence of the prion itself in the general population, or an ability to test for its presence in healthy donors.

The FDA has worked very hard on the risk assessment we are discussing today. As you have heard, they have considered many sources of uncertainty.

With that, they have determined, either when calculating the risk using the highest assumption of prion prevalence and risk, that the risk if actually quite low

for the transmission of vCJD through plasma-derived Factor VIII. However, it may not be zero.

In 1995, the Institute of Medicine released its report on the infection of upward of 10,000 persons with hemophilia with HIV.

The IOM opened their report with the following statements: The events of the early 1980s revealed an important weakness in the system and its ability to deal with a new threat that was characterized by substantial uncertainty.

The risk assessment prepared by FDA calculates that the risk of CJD to persons using plasma-derived Factor VIII is very low. However, substantial uncertainty remains.

In light of this uncertainty, it seems to me that the best way to proceed is to follow the recommendations of the IOM report very carefully.

In order to ensure that we are not missing nay cases of CJD in our population, a surveillance system, as Jan just pointed out, as recommended by the IOM, should be implemented.

Additionally, the IOM recommended that the FDA should encourage the blood industry to implement partial solutions that will have little risk of causing harm. It is our responsibility here today to ensure that this has occurred and will continue to occur.

In distributing any information about the potential risk of CJD in the blood supply to users of plasma-derived Factor VIII, we must be mindful that our population has suffered great losses from previously unknown pathogens.

In that regard, we must be truthful, and we must also explain that there remain uncertainties in determining the risk of CJD from plasma-derived Factor VIII.

Those charged with distributing this information directly to patients, many of whom are relatively young physicians like myself and, therefore, would not have been practicing when the hemophilia population was infected with HIV or suffering devastating losses from AIDS, must be sympathetic when sharing information that could bring back difficult memories.

Finally, it is possible, perhaps even likely, that there will never be a case of CJD or variant CJD in persons who have used plasma-derived factor VIII. That would be very good news indeed.

However, even though the risk of transmission of vCJD through the blood supply may be low, we should not assume that the next threat is similar.

Therefore, we must take what we are learning from this threat and make sure that we act quickly and thoroughly any time a potentially new pathogen surfaces and

threatens our blood supply. Thank you very much.

DR. TELLING: Thank you, Dr. Colvin. Finally, we will hear from Mark Skinner from the World Federation of Hemophilia.

Agenda Item: World Federation of Hemophilia.

MR. SKINNER: Thank you. I am here on behalf of the 109 member nations of the World Federation of Hemophilia, roughly 400,000 patients with hemophilia located around the world.

I am also a patient with severe hemophilia A. While you had an opportunity to hear the U.S. perspective directly, I would like to give you a sense of the global perspective as well.

The WFH has been communicating with our national member organizations since roughly 2003. We have had an ongoing educational process through global symposia, meetings, fora, and communications with our national members.

In 2004, we published our risk assessment guide, which was presented to this committee back in October 2005. The important points that I just want to reiterate from this are: avoiding complacency, retaining a sense of proportion to this risk and others, and looking at the balance between safety and supply and its impact around the world and, of course, as we have all talked about today,

the importance of a continuous learning and communication process.

These are the core values or a summary of my longer presentation from last October. I don't know that there is a great need to go into detail, because they have been mentioned and are similar to that that the other patient groups communicated.

We do very much support the precautionary principle, and particularly when there is great uncertainty. Timely, clear, comprehensible communication is extremely important.

It is okay to tell the patients that you don't have all the answers and that there is uncertainty and more information is to come.

Lastly, certainly, picking up on the point that Jan has mentioned, it is critical that we avoid unintended health consequences.

I have also previously shared with you the significant negative impact on the patients with hemophilia in the United Kingdom following their risk assessment publication, and we don't want that to occur here in the United States or elsewhere.

To put this in perspective globally, there certainly is a significant potential for impact of the FDA assessment on the global market.

Seventy-five percent of the patients in the world receive no care but, of those that do, if you look at the highly developed countries like the United States, outside of those with a GNP of $10,000 or more, they are virtually entirely dependent on the plasma-derived products.

Being a global market, we know that a large portion of those products are products that are licensed or manufactured in the United States.

So, the actions of the FDA, the recommendations of the FDA, are certainly noticed, will be followed, and are of interest to patients around the world.

I should tell you that prior to this meeting, much like the patient organizations here, we did send a communication to all 109 of our member countries, as well as to every known hemophilia treatment center in the world, sharing with them the news of the FDA's discussions today and the preliminary good news that the risk is expected to be extremely low.

We have had very little feedback at this point or an expression of concern. I think that also indicates the level of understanding and knowledge and the progressive knowledge base that is occurring.

It also is important, and we have discussed this within our global TSE committee and our global blood safety committee, that it is important that this risk, like all

others, be placed in context.

It still is true -- this is a study that was actually just published earlier this year -- this is a Dutch study from obviously a highly developed country with a very comprehensive hemophilia care program -- bleeding is still the most significant risk of patients living with hemophilia.

When we talk about other risks, it is very important that we and the patients keep in perspective that the underlying disease still is the predominant cause of mortality and death after you exclude for the previous infections of HIV and HCV.

One of the things that is being raised by our members and, as we have had these discussions, is putting this risk in perspective, putting it into global perspective, putting it into historical perspective, that what the FDA is doing is not new news, but is adding to information and our existing knowledge base.

I am sorry, I thought I had corrected this on my slide. Under the United Kingdom it should be 1.8 to one million. The eight got into the wrong place.

The information that we are trying to put into context is that, if you look at the UK risk assessment, which now takes into account products which are no longer in the global market place and then you look at the FDA

risk assessment, which takes into account products which are widely used in the global market place, patients can take great reassurance from the fact that we are gaining more knowledge, that the risk assessment is showing that it is significantly lower than what the United Kingdom said, and provides further reassurance for physicians and clinicians to make decisions.

So, when we do our final risk communication to the patient, we will be attempting to put the FDA risk assessment in the historical context of what has happened in the United Kingdom, which certainly was the highest, along with Australia, Canada, France, Spain, and other countries that have done so.

We think it is important for patients to know that this is a continuing educational process and what we have learned thus far.

Finally, as it relates to the selection of treatment products, the FDA's risk assessment has certainly added to our understanding. It has identified those areas where we need to look further to develop more understanding.

The WHF position has been -- and I should say continues to be, since the publication of this risk assessment -- that both recombinant and plasma-derived products are important treatment options for patients

globally.

The risk assessment that is being put forward today is not cause for the WHF to change this position, and our confidence in the robust clearance of both types of products.

Although, as others have also said, there is the potential for the future risks that aren't known, so the continual communication process is extremely important, and we very much appreciate being included at the global level, because of the importance of the U.S. market to the global patients. Thank you.

DR. TELLING: Thanks very much, Mr. Skinner. Are there any questions from the panel at this point for the advocates, or comments? If not, remarkably, we are on time. So, I would like to adjourn for a moment for a break until 10:25, when we will reconvene.

[Brief recess.]

All right, I want to reopen the meeting.

Agenda Item: Open Public Hearing.

DR. FREAS: As part of our advisory committee process, we hold open public hearings to give the members of the public an opportunity to bring their comments and opinions to FDA.

At the present time, I have received one written submission from Terry Singletary. This submission was

passed out to all the members of the committee. It is in our viewing notebook at the table outside, and will become a part of the meeting record.

I have also received two requests for all presentations. The request for this morning's open public hearing is from Cory Dubin, president of the Committee of Ten Thousand. Before Mr. Dubin starts talking, our chair has a mandatory statement to read.

DR. TELLING: Thanks, Bill. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

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

Likewise, FDA encourages you, at the beginning of

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

Mr. Dubin? Mr. Dubin is the president of the Committee of Ten Thousand.

Agenda Item: Statement of Cory Dubin.

MR. DUBIN: Thank you, members of the committee, Mr. Chair, members of FDA and staff. First of all, we are always glad to address the conflict issue. I own no stock, nor have no interest in any companies related to this issue or, in fact, any companies that are regulated by the Food and Drug Administration. We, a, appreciate the fact that that gets done and, b, are glad to do it.

Let me say this. The Committee of Ten Thousand has been in this process since 1992. We have seated people on the FDA BPAC and elsewhere. Dr. Colvin was involved in the original David Kessler sponsored special advisory committee on Creutzfeldt Jakob disease. We have been around this issue for a long time.

As I entered the room today, I was troubled by a sense of deja vu, wondering how much had really changed. As I look at the table, I Can see one thing that has changed very much.

I look out of my eyes and see four people I know and trust at the table that represent our community. That is a positive change. That is a change FDA is to be commended for.

That said, this issue troubles us deeply, very deeply. We are not interested in standing here and sounding the alarm in the sense of HIV or hepatitis. We do not want to frighten our people.

At the same time, we believe the British Health Agency issued a warning to the hemophilia community that I believe FDA referenced in its briefing papers.

. We believe this was an excellent document, well done in its breadth, well done in its lack of fear and its educational value to the members of the UK hemophilia community. We feel like that was a very, very good guidepost, if you will, to where we want to go.

That said, COTT remains deeply concerned regarding the risk assessment and the proposed statement regarding the risk associated with factor concentrates and variant CJD.

The federal government, the fractionators, the manufacturers, the blood banking community, has always treated what occurred to us in the 1980s as an unavoidable event, and they would assert they did the best they could.

We believe that the historical record has never

supported these conclusions. In fact, the Institute of Medicine stated very clearly that, at critical moments in the HIV crisis the federal government and its agencies consistently chose to take the least aggressive action available to them.

We are concerned that that continues today. We are interested in seeing aggressive actions that address some of the problems that we see.

Later today you will hear from our staff, Dave Cavenaugh. He will talk about out concerns about FDA and USDA, the question of food and biologics within the agency, and perceptions which we have developed over a number of years.

We feel we would all agree that the risk is low, but I think it is important to know the last time this process happened we were not present. Decisions were made and we ended up burying roughly 8,000 of our people.

We are here this time. We are in the process. We are trying to provide a somewhat different view than what we hear FDA saying, different information about our sense of what the risk assessment means.

Here is where we really have a problem. How can we make decisions like this, that essentially a world class agency in the United States saying basically that the risk to hemophilia is not there.

Do we know enough about the prion agent, the infective agent? Do we know enough about the nature of this agent to even trust the tests where we spike the material, fractionate, find out, the basis of the risk assessment, the basis of the fractionator's claim.

You can pick your scientist in the global community who you want to talk to you and you will find some that say, well, maybe it reduces the infectivity. You will find others that don't.

How do we know what that threshold is? There is so much unknown about this agent. In the Committee of Ten Thousand's world, that kind of unknown should not trigger a lack of aggressive action.

Again, we are using aggressive not to say get up on the roof and sound the alarm, but we are using aggressive to say, this is not good enough. It is not an effective way to come at it.

The community needs education and it needs serious talk. Example. COTT would feel like what we would really like to hear from you, rather than what we are hearing, is something that might go like this:

We all know there is some risk. We all agree that the risk is low, but there is some risk. We, the FDA and advisors to the FDA, believe that, in the name of the long-term stability and viability of the blood supply, that is

an acceptable risk.

We would like to hear that because then we can come back with this: If that is the case -- and we do agree that the risk is low, we are not contesting that -- if that is true, then are you all ready to recommend, and is industry, both the fractionators as well as the blood banking industry, ready to put the money on the table and say, anyone who may be afflicted with a blood borne TSE will be compensated for their injury in a timely manner and will have their health care taken care of until the end of their life.

That is the kind of trade off we would like to see. We were the canaries in the coal mine. We shouldered that risk. We feel like we have never even been thanked for shouldering that risk.

If people get sick, will they be subjected to the abuse, the indifference and the inaction we were? Will they have to go to court? Will they have to spend eight years trying to understand something or will we as a society change our vision. This is what I mean by this.

We think it is a disgrace that we lack a national blood policy. A national blood policy provides guidance that leads FDA and advisory committees to say, okay, we are going to take these actions, but we know they are going to be costly and they may fall on the shoulders of the blood

banking sector of the fractionation sector, and we are going to do some things to help you bear that responsibility and bear that burden. We are going to lessen the hit.

So, for instance, if the blood banks were ordered to start leukodepleting and we had this national policy, we would be able to work to help them shoulder that, because clearly that would raise the cost of the products they put out, platelets, red cells, whatever they may be.

We lack that policy. What we are essentially saying here is, no vCJD here, risk very low. Let's label it like this and say it.

We are extremely troubled and we feel like we have to continually qualify this so that you don't think we all want to sound the fog horn.

Aggressive doesn't necessarily mean sounding the fog horn. There are a lot of steps in the word aggressive in the way we see it.

We are here this time and last time there was no accountability on any of what happened. This time we are going to ensure there will be.

We would much rather come at it from a forward position and say, let's put our heads together and look at what we might do that will both further our understanding --more research, more dollars committed, more time

committee, more out of the box thinking from the medical community being funded.

I know this is a period where everything has kind of been dummied down, but we have to get back to critical out of the box thinking so that we can learn.

We depend on you all to learn about these agents, but it is hard for us to look at this in the face of the degree of unknown.

We have done our homework. We have talked to many scientists around the world, some very prominent like Dr. Aguzzi at Zurich and others, who believe that fractionation, that you cannot really define that threshold.

So, how can you conclude that we have come to a position of clearing enough of this agent to say that we are safe.

So, we would urge you to not adopt this at this time, to take some more time looking at this, and think this through a little bit better before you take action.

Maybe next time the canary in the coal mine won't hit hemophilia in the same way it did because so many of us use albumen free recombinant products, but what about the sickle cell folks? What about other communities where education is so much less than ours, where advocacy is so much less, where racism is a factor, other issues.

Just because we are the most vocal -- and we are, no question -- it is important to consider the other canaries in the coal mine who are not in this room.

We fear for their safety. We have added members of the sickle cell community to our board of directors to try to plug us together and work together on education. We did that in 1998 and we are hoping to add more.

We would urge you to take a big step back. In conclusion, we do not believe you have enough knowledge to conclude what we think you are about to conclude.

The last thing, I want to go back to the IOM and say one more thing, and we were instrumental in the Institute of Medicine report. We were the people who approached Kennedy and Graham, asked for a congressional investigation and were told that we couldn't have it, but we got the IOM.

The level of coordination that the IOM called for we do not see. We think the agency, between food and biologics, needs to tighten it up. We want to see more coordination. I thank you very much for your time and the opportunity to address you. Members of the committee, thank you.

DR. TELLING: We thank you for those very important comments. Is there anyone else at this point who would like to make a statement?

If not, then we will go to the next phase of the agenda. We are now going to hear the FDA questions for the committee from Dr. Weinstein.

Agenda Item: FDA Questions for the Committee, Open Discussion and Recommendations.

DR. WEINSTEIN: The first question is, does the committee have any comments on the technical aspects of FDA's assessment, including the risk estimates and uncertainties of plasma-derived factor VIII from U.S. donors. I guess we will have discussion on that.

DR. TELLING: I would like to open this discussion right now.

DR. GAYLOR: I would like to make a comment and then suggest something for discussion. I like it where you have calculated the number of years between cases, like you estimated one case in 35 years or 3,000 years.

I think that is a little bit more understandable than a risk of one in 20,000 or one in two million. That is a little hard for people to fathom, I think.

If I say, you have a risk of one in 20,000, what does that mean? That is the risk associated with bring hit and killed by lightning in the United States, one in 20,000. I doubt if many people in this room worry about being hit by lightning, unless you play golf or you are a fisherman or a farmer.

That is a relatively low risk that most of us don't think about. A thunderstorm, I try to get inside. Maybe it is because I know that number. I don't know. So, one in 20,000 sounds like a pretty low risk, but it can happen.

The comment or the suggestion that I have that I would like some discussion on, in the United Kingdom there have been around 160 cases of vCJD out of a population of 60 million people.

So, roughly that tells me that the prevalence is somewhere on the order of 160 in 60 million, more on the order of three in a million. There will be more cases, so maybe it will get up to four in a million. You have used the figure from your epidemiology report that was published in 2002, or the data were from 2002. You use this number of 1.8 per million as prevalence.

It seems to me that possibly that could be a factor of two higher. On the other hand, I think that the risk prevalence based on the tonsil and appendix tissues is way out of line. That is a factor of 100 higher. That doesn't seem to fit with historically what has happened in the United Kingdom.

We have got 160 cases and 60 million people, somewhere a risk of around three in a million. So, I think the epidemiology prevalence is pretty close for the

prevalence number.

I think this one out of 4,225 or whatever it is, is just way out of line. It is in all your reports. I wouldn't take it out of your reports. I wouldn't take it out of your calculations, but when communicating risk, I think you should emphasize the lower risk based on the epidemiology. I would like to hear some response.

DR. ANDERSON: All right, well, I think that probably the place to start is with the higher estimate. So, I think my perspective on that particular estimate is that is more of an infection prevalence.

So, you wouldn't necessarily see cases evolving from that, but a certain percentage of those might eventually sort of proceed on to cases.

Then you are talking about the estimate for specific cases that came from the epidemiological modeling estimate, which was the 1.8 per million. That actually was a case estimate.

So, we are talking about prevalences, but we are almost talking about two different types of prevalences. One of those is an infection prevalence, and then one is a case prevalence.

So, we think the uncertainty lies somewhere between those. Again, we are so uncertain that we don't know specifically, and that is why we presented both sides.

Did that answer your question?

Then probably -- I think the reason we arrived at 1.8 per million is we are talking about cases currently incubating.

Remember, we did have the 160 cases in the United Kingdom. Remember, those individuals are deceased and they are not in the prevalence calculation any longer.

What we are interested in is the cases going forward. So, now we are using an estimate of 70 cases, which is predicted from the epidemic curves and from the epidemiological modeling.

DR. GAYLOR: That is true, because it is certainly tapering off. So, the lower prevalence would be expected. I guess that it is probably in there. Maybe there ought to be more emphasis given, whether you are talking about the difference between infection and cases, or the case is really a terminal situation and the infections are not.

The appendicitis and tonsil tissues, I suppose, come primarily from children. So, that is really not totally from --

DR. ANDERSON: Actually, they came from individuals mostly 20 to 30 years of age.

DR. GAYLOR: It is a little bit younger than your blood donor population, but it is pretty close I guess.

DR. ANDERSON: it is probably around 20 to 40.

DR. GAYLOR: Yes, it is pretty close. Thanks for that answer, Steve.

DR. LILLARD: I had a quick question. I am curious on how the FDA accounts for some of the under-reporting that may occur from cases reported to a local health department.

Oftentimes anywhere from 20 to 25 percent of those cases go forward to be presented to the CDC, for example. Are there any concerns or methods used to account for that?

DR. TELLING: Would FDA like to comment on that question?

DR. SCOTT: I think if I understand the question correctly it is, how do we account for under-reporting of possible variant CJD cases? All right, that is actually very difficult.

It is hard to assess under-reporting, but the autopsy rate here is very low. We do have, in our guidance for industry, a request that CDC be contacted for any case of CJD in age less than 55.

There is no mandatory reporting of spongiform encephalopathies in humans here. We hope that neurologists and people who are taking care of people that may be at higher risk are aware of this, due to this committee and

the patient organizations, but I think it is difficult to do that.

For the purpose of the risk assessment, it is really all prorated to consumption of British beef or British products, either by visiting or travel there, and what proportion of people might be here. It is all prorated to the United Kingdom.

Now, the United Kingdom has a completely different type of reporting system, because they have a national health service.

It is assumed that the capture rate there would be higher than the capture rate would be here. So, for the risk assessment, it is really based on the UK risk.

MS. KRANITZ: I just also wanted to add to that, that there are silent, possibly silent, carriers. For example, in the United Kingdom, the NV phenotype, the last patient who passed away was asymptomatic. So, we really don't have good understanding. Also, the fact that as Dr. Scott said, it is not a mandatory reportable disease. So, there are a lot of risks that we can't even begin to measure.

MS. HAMILTON: Following up on those two comments, is there any way that there could be a strengthening of the reporting and maybe by listing the symptoms?

From my understanding, there are a lot of other things that emulate the same symptoms, and perhaps people don't, at the time of death, realize that that might be a vCJD case.

Is there any way that CDC could strongly encourage or make mandatory looking at those symptoms and, if those symptoms were present, request an autopsy?

DR. SEJVAR: I think we are kind of starting to get a little bit off topic here. I will say that, as you can imagine, CJD, variant CJD, these spongiform encephalopathies, are very difficult diseases to do surveillance for.

However, CDC does have a multi-pronged approach, including sort of the support of the national prion disease pathology surveillance center to bolster autopsy rates, which we are succeeding in doing, active case reporting of cases under the age of 55, to increase our ability to detect variant CJD.

It is not a perfect surveillance system, but we are very confident that potential cases of variant CJD or just CJD in general we are capturing very well.

Again, the issue of surveillance is one that I think is a separate topic from what we are gathered here today -- I would be happy to discuss with anybody about our surveillance activities.

DR. LILLARD: My point in initially asking that question wasn't necessarily -- it was more associated with the risk assessment that the FDA uses and how they formulate that risk assessment.

Even more specifically, I was speaking also toward the under-reporting at local health departments, definitely not the CDC.

DR. POWELL: Because the two prevalence estimates do estimate such different aspects of the disease, one prevalence essentially of the agent in tissue that could be recoverable versus an epidemiologic estimate of the current and incubating diseases, I would suggest that they be retained, and that also, given that we are going to probably be revisiting this issue in this risk assessment as it is updated and other risk assessments, we will have the advantage of having, through accumulation of evidence over time and the UK cases that we have observed, we will be able to evaluate after the fact the relative likelihood of these two estimates.

So, we will be gaining new data that will allow us to say which of these prevalence estimates is more likely given the number of cases that we have now observed in the UK population since the baseline year of 2002.

So, it will become more clear over time which prevalence estimate is -- obviously there is a lot of

uncertainty, but the relative likelihood will become apparent over time.

DR. COLVIN: I think similarly I would like to estimate that from the infectious disease perspective for a second, that both estimates should be considered as well.

If you consider that many infectious diseases, people can be infected and not ever have any symptoms from them and, over time, as one's cell mediated immunity usually diminishes, diseases becomes more prevalent as one ages.

So, in this case, actually, the epidemiology may actually suggest that the infection prevalence is much higher, but then in a certain subset of people, as their perhaps cell mediated immunity diminishes as they age, is more likely to come down with symptoms of vCJD.

We see that in many diseases, obviously, as we all know. So, at this point, we don't know, of course, the difference between the infectiousness and the contagiousness of the agent in somebody who may be latently infected, as perhaps is the case, but I think that it is always wise to err on the side of caution.

DR. TELLING: I think it is important to refocus the discussion on specifically the first point, which really asked us to address the uncertainties involved in the risk analysis.

Of course, the most important aspect of that analysis appears to be clearance. Of course, the experimental approaches that have been used to address clearance are based on artificial experimental models. This was brought up by the comments from the Committee of Ten Thousand.

So, I think it is important that we address whether or not we feel that these are reliable criteria on which the FDA can really base their risk assessment.

My first question is -- and I will get back to you, Dr. Manuelidis in a minute -- on what basis does the FDA -- I would like clarification on what basis the FDA considers this four log reduction as being in place with the currently available manufacturing involved in Factor VIII. Perhaps you could clarify that.

DR. SCOTT: We have some data from every manufacturer of plasma-derived Factor VIII involving TSE clearance studies.

A lot of that data is preliminary in the sense that we do not have it in the form of a submission for very detailed review. Some we do, some we don't.

Some of this data is preliminary in the sense that it has been done using binding assays as the input and output measure, whereas we feel that bioassays may be more definitive.

I will let industry speak, of course, but we understand that many of these, because the bioassays take at least a year, are beginning or are in process.

So, that statement is based on the data that we have. Dr. Kreil showed this data at the last meeting, and I think he will show a slightly updated version of the same information at this meeting and it should be in your handouts, showing you essentially where the studies are and what the assays were and what the spike preparation was.

DR. CREEKMORE: Before you leave, just another clarification. You made the comment that essentially all are in the four log reduction or greater sort of category at this point, or a great many of them are.

How many are in that upper level of log reduction? Are we basically saying that -- maybe to rephrase it a little bit -- of the ones that are in the four log or greater, what percentage of those are actually in the seven log or greater category.

DR. SCOTT: Before I give you the answer, I would like to consult my notes. More than one is what I recollect. Thomas?

DR. KREIL: I will have the information in the presentation that you see, I think, at 1:00 o'clock today. So, I wouldn't want to speak off the top of my head.

DR. TELLING: Dr. Manuelidis, can we get back to

your comments or questions?

DR. MANUELIDIS: My real question as the devil's advocate is the higher risk. I agree that the risk is probably very low, but I think that as a caveat it is important for the committee to take some sense of the higher possible risks.

One is, nobody has mentioned anything about Canada and the people who go to Canada, and the fact that Canada has actually a number of cows now that have been infected. What is the combination that we have with -- but they are concerned about this and I think there may be one or two cases. I haven't really traced them.

The second thing is silent carriers. I think there is a very important theme biologically with these agents. That is, once something gets into the population or once something gets into a certain species, it typically -- although not always -- becomes more virulent for that species.

I raised this issue years ago about when you have to decontaminate instruments from many things in blood. So, vCJD is a BSE derived agent in all likelihood. That is the best evidence. Once it is in the human population, it may spread more easily if people are exposed to it.

I somehow think that that has to be part of the understanding of the risk. So, a human to human

transmission is probably going to be more efficient than a cow to human transmission.

The second thing is the route. It is the route and the dose. In this sense, it behaves like a classic virus. If you give something repeatedly by a very lousy route, like the oral route, which is very inefficient, you are not going to have very many takes.

The reason I asked the question about the route and the number of shots that people get of some of these products is that you have accumulated material by a route, like an IV route, that is extremely efficient, as far as we know, from all the animal studies, in these particular infections.

So, I think that raises the risk. That is a second feature that raises the risk. I think one has to really sort of understand that.

The third thing is, I actually think that the advocates and the people on this committee have an obligation to sort of encourage the government agencies to fund certain kinds of fundamental research and not just epidemiological studies, which can address these things.

There are animal studies that show that repeated low doses, for instance, of scrapie orally give an animal something that will become an infectious disease, whereas one or two very large doses don't.

So, again, this becomes much more relevant for blood products and other things that we use medicinally. So, I somehow think that those things should be in.

Again, I think that surveillance has been very poor in this country for BSE especially, and it is a major concern to me, the way it is handled.

I am not criticizing the CDC but I think that, the autopsy rate being very low, if we don't look, we won't find things. I think this is again a risk that doesn't have to be there.

DR. TELLING: So, let me understand. Your contention is that basing the risk assessment on exposure to BSE may be a significant under-estimation and that possible iatrogenic propagation of the agent may be a significant factor, and has not been addressed by the risk assessment?

DR. MANUELIDIS: It is an unknown, but I think that it is probably increased from what would be the assessment from the prevalence of the number of cases from cows to human beings so far in the United Kingdom.

DR. TELLING: So, I will get back to my original question. How do we feel about using spiking experiments, which the clearance being the most important factor involved in the risk assessment, as a surrogate for possible clearance of the variant CJD agents in these blood

preparations?

MR. BIAS: I think it is a step in the right direction. I think we have to work toward making sure that those processes are a like and similar or the same, so that we have a legitimate measurement tool.

I think that it is only a step. I think there are a few other things that we are going to have to do before we are sure.

We have just got to continue to work at it. I mean, we have been doing that. This is the 21st meeting, as Bill said. We are just going to continue to work at it.

DR. TELLING: So, this is the best available scientific evidence at this point in time. I think that is an important point to make. The FDA is using the best available scientific evidence for their risk assessment.

DR. MANUELIDIS: I think there are enough models now of vCJD in animals where one could assess actual vCJD agents in the blood of animals for clearance.

DR. TELLING: That is possible, but those data do not exist. It is important to make that point.

DR. MANUELIDIS: All I am trying to say is that I think it would be nice to encourage that kind of data in terms of being highly relevant.

DR. TELLING: I completely agree.

DR. MASTRIANNI: I think all the data for

clearance is in animal models at this time, or do we have data for clearance in human models or blood from humans and spiking with human material?

There are a lot of differences between animals, mice and hamsters and humans, with respect to blood and clotting.

So, I think it is important that we at least try to shift the model to humans and at least use human source material to test clearance.

DR. TELLING: Thanks. I had a specific question about the risk assessment. I thought I was clear on what was being told to me, but I understand from the actual presentation that I perhaps wasn't.

My question relates to whether we are looking at the risk of exposure or infection, which are two very different things.

DR. ANDERSON: Well, we are looking at two different things. We are looking at the risk of exposure. So, the potential for exposure, but then ultimately we do take that animal dose response and then calculate the potential for infection. So, we are doing both, actually.

So, the actual exposure is the numerical ID50 numbers. I didn't present them in the presentation, but they are in the risk assessment. So, that is the actual exposure.

Then you multiply that by the .5 value for the ID50, which is the dose response, to get the potential risk. Again, the limitations are that this is an animal dose response. So, there is considerable uncertainty with that estimate. So, doing both.

DR. MASTRIANNI: I just have a question regarding the tables, table 5-2A versus 5-2B. Could you describe for me -- so, there is one case of vCJD infection in 405 years. That is a population based number. I can't really calculate that in my head, if I was one patient getting so many rounds of transfusion of factor VIII, what that means to me. Does that mean in 405 years I might have a chance to get it, or does that mean I am only one fraction of those 250 patients that are going to get it in 400 years.

DR. ANDERSON: What that table means -- that is on page 56, this table I am looking at, table 5-2B, which is von Willebrand's disease.

So, taking that as an example, we treat 250 patients every year. Doing that over a period, year after year, year after year, if we got up to year 405, we would only expect to see one case. That is what that actually means. That is a population-based risk. That is how you interpret that.

DR. MASTRIANNI: So, you estimate, in those 250 patients getting treatments, it is based on the number of

treatments. So, one patient may get one treatment, another may have two.

DR. ANDERSON: Right. So, we account for that variability in treatment for all those patients. Those are all driven by distributions.

So, we are accounting for the variability in types of treatments, the treatment regimens they could be on. That really is a sum total for those 250 patients.

Again, it is an estimate, a lot of uncertainties. So, don't look at that as gospel. Again, it is a relative estimate of the risk.

DR. MASTRIANNI: Just in communication to patients, that is probably not the number to give them. For me, anyway, if I were getting -- you can interpret it as -- you know, the number of treatments you receive, your risk is a certain percentage.

DR. ANDERSON: The message would be, again, the risk from the model, at least, is telling us that that risk is extremely small.

I would stick with that. If they want numbers, then you can sort of look at these numbers and then start. Again, if you pull these numbers out and put them in any sort of documentation, please, you know, insert the caveats for the uncertainty. Those really carry with these estimates. Did you have a question about another table?

DR. MASTRIANNI: No, just the numbers of one in 52,000 basically was the risk versus the numbers to years.

DR. TELLING: Are there any more comments or questions about point one?

DR. HOGAN: We had this come up when we were trying to look at how well donor deferrals were doing for corneal transplantation. How did you get the range from 85 to 99 percent in terms of efficiency for the donor deferral issues?

DR. EPSTEIN: Thank you, Dr. Hogan. that subject was discussed at great length at the September advisory committee meeting.

I can't instantly reproduce it all, but what we have looked at is parameters such as marker rates in candidate donors versus selected donors comparing general population to first time donors, to repeat donors, looking at risk factors in the pre-selected versus the selected population.

This was done for a variety of our deferrals. It was done for males sex with males, history of hepatitis and on and on.

So, what we found was that there was a fair level of consistency when you compare markers of various sorts, be they risk factors or laboratory tests to the preselected and selected population, that that was the range by which

the prevalence of markers was reduced.

So, it is evidence based and it comes out of a variety of epidemiological type investigations of our donor screening, including responses to questionnaire. Again, it is a set of data from a variety of different types of study.

DR. HOGAN: I bring that up because it is an awful lot better number than some of the studies that we were doing earlier because it is based on at least some evidence. So, I feel much better about that number. Thank you.

DR. TELLING: Anything else relating to key point number one? Let's move on, then, to the second key point.

DR. WEINSTEIN: Does the committee agree that the key points and additional information as described, a, capture the essential points of the risk assessment and, b, provide suitable and understandable interpretation of the results.

DR. TELLING: So, just to clarify, this is not the communication document. What precisely are you --

DR. WEINSTEIN: We are talking about principally the key points document and the questions and answers.

DR. TELLING: Around the question.

DR. WEINSTEIN: Yes.

DR. MC COMAS: I have some comments on the key

points and additional information, but I think that some of it also relates to the overall communication strategy.

I think that the strategy precedes the messages that you are trying to communicate. So, I can give some feedback on the points themselves, but I am wondering if it is more helpful in some ways to move to the larger question of the strategy before we talk about the messages.

DR. TELLING: Yes, could we take the two questions in tandem?

DR. WEINSTEIN: Sure.

DR. MC COMAS: In general, I greatly appreciated the improvement in the key points to the original briefing messages. I am assuming that, at this point, you are interested most in the ones that we got at the meeting today as opposed to the ones that were sent out earlier.

DR. WEINSTEIN: Actually it is this slide, right, that has been modified slightly as you look through it.

DR. MC COMAS: Because i had some issues with the earlier one. So, one of the things that I think is important to consider for the larger question is the overall goal of the risk communication about the risk assessment, the risk analysis, and who the different audiences are.

We have got physicians, patients, hemophiliacs, patients/hemophiliacs, and general public. So, the one size

fits all approach, I think, may not work as well in some of these cases.

I think that the key points fit for a more general audience, but I think that some of the issues that have been raised today by the patient advocates, for example, have noted some issues which aren't really addressed in these key points and which may not necessarily be important for a general public, but would be important for physicians and patients.

Those might refer specifically to the issues of being aware of previous stigmatization due to experiences with HIV/AIDS, the need to not treat patients differently, the need to reassure access to health care and health insurance.

These things are not part of the key points, key messages. I think that they perhaps belong in an overall communication strategy where you are targeting physicians and trying to increase their sensitivity to patient concerns.

That said, some more specific things that I found missing in the key points and messages speak to essentially what is the FDA doing to ensure the protection of the patient and the protection of the blood supply.

I think perhaps some of that is not mentioned because it is implicitly believed, well, we are going out

and we are doing this risk analysis to determine what the risks are.

I think that some of the information about the deferment of at risk donors as well as the protection and the -- I am sorry, I am not as well versed in the technical language as you all are -- but the reduction of the possible presence of vCJD in the plasma.

So, I think that, again, there is not that as a key message. What is the FDA doing to protect the patient and to protect the plasma supply.

I think that there is a discussion -- this goes, again, to the strategy. Is the goal to raise awareness so that people will go and talk to their physician. Is it to raise alarm about it.

I don't think that that is it, or is it to reassure people that the plasma supply is safe and that they don't have to worry when they go to get these products.

If it is to talk to your physician about these risks, in a risk benefit scenario, what are the alternatives to this treatment.

If you are going to tell people they are at risk, albeit it low, of contracting vCJD through this treatment and you are not going to give them any alternative, then you have potentially gotten a problem, especially if you

toss in the word mad cow disease, which I strongly recommend that you leave out of all messages at this point, because of the emotional affective connection with that.

I think, again, in these revised messages that has been largely left out, but people need to understand what the alternatives are, and the potential risk of the alternative, and the potential strain on these alternatives of people going out and requesting these alternative treatments.

Again, have these alternative treatments been examined the way that PD Factor VIII has been examined for the risk of carrying vCJD. I think at that point I will sort of let somebody else talk.

I think, again, there may be some different messages for the different audiences that need to be considered along these lines.

There are some just sort of specifies in the messages in terms of telling people about the key exposure period, but not necessarily giving them the dates. So, is that 1980 to 1996 as a key exposure period?

Then, again, referring them to read more about mad cow disease and vCJD, again, I think that increasing the resonance that these two sort of stick together is possibly going to raise undue alarm.

It is not that I am advocating at all that you

hide this connection, but even just the use of bovine spongiform encephalopathy instead of mad cow disease can have a better sort of impact or influence on perceptions.

DR. TELLINg: Thank you very much.

DR. MASTRIANNI: You just sort of made me think of a question. In reading the key points, there is no description of what Creutzfeldt Jakob's disease is. I don't know. Is there?

DR. WEINSTEIN: I think we mentioned it is an invariably fatal brain disease that has a long incubation period. That was one of the key points.

I think it is important to mention that, of course, a lot of points are covered in the questions and answers, that we do bring several of these issues to bear.

I am just sort of wondering what you might think -- we moved up, as you might notice, that we moved one of the issues about why are we looking at factor VIII rather than some other plasma derivative, from the original copy that you had, where that was put in the questions and answers. We moved that up into the key point area, because we had received feedback about that particular thing as being something that people really wanted to have in there. Do you think that things are diminished by putting things into the question answer format, versus what we have in the 16 bold point --

DR. MC COMAS: Actually, thanks for pointing that out. I did appreciate the question and answer section and I just had a couple of comments in relation to some statements.

When you talk about, for instance, that a person might be at risk, under additional information, if a blood donor unknowingly carried the vCJD agent at the time of donation, but at this point it seems that an opportunity is missed to talk about the screening procedures.

It raises the alarm about the risk but it doesn't talk about the screening procedure. I am not saying that it is all about reassuring the public that there is no risk, but when you constantly raise this sort of negative aspect and you don't answer it with what is the FDA doing, then people might feel a little bit unnerved, and perhaps rightly so.

DR. WEINSTEIN: That, I think, is one of the key issues with this whole document, that we want to have it balanced. We want to have people feel appropriately concerned, that here is what we know and here is what we don't know.

We can't be entirely reassuring. We say, the risk is extremely small but it is not zero, and we live with that uncertainty. I hope that was the point of what we are trying to convey here, not to hide things, not to

exaggerate and not be completely reassuring and say that there is no risk.

DR. MC COMAS: Right, and I think that in general the public accepts that there is some risk in every activity that they undertake every day, but when they undertake a risk, it needs to be relative to its benefits.

Since we are on the point of the question and answer, there is one question that I had issue with, and it is on page two at the bottom, answering the question, what is the risk of vCJD to patients who receive transfusion products like red blood cells and plasma.

Then it goes on to explain the risks, but the last sentence in the second paragraph talks about how hundreds of patients might potentially be affected with the use of a contaminated plasma derivative if there were not a significant reduction in vCJD infectivity during the manufacturing process.

I think this sort of blows out of the water all the reassurances that you made here. Again, I just think you might want to consider a way of -- this is talking about, again, what is driving your risk analysis here at FDA, which is the need to protect and ensure that this sort of bad scenario doesn't occur.

Here you have been reassuring them that the risks are low because there has never been a case that has

happened in the United States, and that in all the cases of plasma transfusion, there has never been a case that you know about.

In the end it is just sort of like, whoa, hundreds of patients might have been affected if we didn't take this. So, I think you might want to reconsider the placement of that statement and the use of that statement.

MR. SKINNER: I have a few comments on the revised key points. I guess they aren't numbered. It would be the third key point, top right on page two.

Again, this goes to the lack of reference to factor IX. People are going to want to know, what about factor IX.

I guess the question I have is, in that list of delineating factor VIII and then albumen and immunoglobulins, if you are able to, say, put factor IX in that list as being later in the process or comment no factor IX, but it seems to me that there needs to be some reference in the key points for the patients to explain why not factor IX now, and perhaps it fits into that paragraph, why there was VIII and not IX.

Then the next page, to me, the three most important key messages are buried at the bottom of the list of key points.

I would tend to lead with the conclusions and

then provide the background key points to provide the reassurance.

If you get through the process of reading all the bad things and then you get to the good news, I would rather lead with the good news, and that is really the first three bullets on page three.

The last bullet on page three, I think, is a point that troubles me not as much here, but I think perhaps the FDA can be useful in answering the question.

The last sentence of that bullet is redundant to the previous one, but maybe if they are rearranged, they won't seem so redundant where you talk about there is no test available.

What the bullet doesn't say, and what I think it says in the risk assessment or at least the issue summary, is that we can't provide a risk for the individual patient, nor can we comment on the risk of individual products.

I do have a concern down the road that this risk assessment could be used by the companies for marketing or commercial purposes, to say that their product, one is better than another.

I think it would be useful if the FDA, even though it is buried in the report, would make it a key message that the assessments can't be completely individualized, now should they be used to make judgements

between specific products, at least based upon the data hat we have at this point.

Then the last comment that I had is actually in the Q and A. It is on page three, I guess, of the Q and A. The question, should patients inform their primary health providers about a possible vCJD exposure, if you read that question in the abstract and without the other information, to me it tends to imply that actually something can be done or that there is some treatment available.

I think it might be useful to reiterate in the answer that we are really talking about things prospectively, but it doesn't include treatment, that there still isn't any treatment.

So, we are talking more about providing them with additional information, but I wouldn't want to give the false impression that, at that point, if they hadn't read the whole document, that there was, in fact, some treatment available.

I think those were -- my only observation as well is, the risk assessment does cover von Willebrand disease and most of the key points summarize on factor VIII.

I Don't know what the key message is on von Willebrand disease, but there really isn't the concluding statement for the von Willebrand disease patients in the summary key messages like there is factor VIII.

It seems to me that it might be useful to have a summary statement on von Willebrand disease, or to incorporate it into the key points.

DR. TELLING: Thanks. Anybody else from the committee have any --

DR. ROGALSKI-SALTER: I think it is just important to reiterate some of the comments that we have heard this morning, and that concerns the communication of benefit.

In the background reading that was provided to the advisory committee members, any portrayal of risk needs to be portrayed in contrast to the benefit that is gained. So, I would just like to reiterate that. I didn't see very much about any benefits in either the key points or the questions and answers.

DR. WEINSTEIN: Could you maybe expand on that a little bit as far as benefit, in what respect.

DR. ROGALSKI-SALTER: Of the products themselves. So, the products are administered because they confer benefit to the patient.

DR. MASTRIANNi: I just had another comment about, okay, so I did see that it is a fatal brain disease, but I still think that is probably not enough information.

It is just stated, fatal brain disease, in a couple of places, but that doesn't really tell the reader

much about what the disease is all about.

There are sites that they can go to if they are computer literate, but they may not have that ability to do so.

I think advising at least the primary health care provider in your Q and A is an important thing to at least get more information about the disease and things, so that they can have a direct communication about what they should or should not be worrying about.

That establishes the connection between the physician and the patient, to help with the communication of the whole risk benefit.

DR. TELLING: It is a really important point because there is so much confusion about the etiology of CJD and the relationship of sporadic CJD and familial CJD with bovine derived products.

DR. MASTRIANNI: Right. Every patient that I see with CJD thinks that it is mad cow disease, and that is what they call it.

MS. HAMILTON: I am just assuming -- I know you should never do that -- that after this meeting, that there will be another revision of the key points and questions and answers.

I would like to just echo some of the sentiments said earlier about the order in which they are presented

and maybe starting off with a positive statement, and then following through.

Again, because I said it this morning and Mark said it later, I really feel that Factor IX needs to be at least mentioned in there somewhere, and that we follow through with the recaps, so that we don't leave any gaps in what people perceive as the message.

Then just one final comment is, has it been decided at this point how all these key points and questions and answers will be disseminated and to whom?

DR. WEINSTEIN: I think that the overall plan, of course, is to put it on the FDA web site, to distribute it to the patient advocacy groups, to present it also to the hemophilia treatment centers, and again to work, to the degree that we can, with outside parties outside of the hemophilia treatment centers.

I think this has been a point that we heard a number of times here, that we have to broaden our reach here to beyond the groups here.

I don't know exactly how that is going to transpire, and exactly the way that our office of communication will handle that is something that is yet to be determined.

MS. HAMILTON: Thank you. Is there a time line for that?

DR. WEINSTEIN: As soon as possible.

DR. COLVIN: Given what everybody has been saying, I think there is one other important point that could go in the key points as well, that we are not making any decisions and we are performing -- as was sid over here, we are trying to reduce the risk and we are doing this in the context of what happened with the hemophilia community in the 1980s with HIV.

It is not that, again, we think it is similar, but I think that would be reassuring to a lot of people, that we actually learned a lesson from that and, in fact, we are trying to move forward in a different way in terms of assessing a risk and putting out some information that would allow people to take something away of the risk of the products they are using.

DR. TELLING: In the question and answer the FDA states that it believes that notifications such as those made to recipients of plasma derived products such as Factor VIII in the United Kingdom, that they have an increased risk of vCJD, and not necessarily in the United States. You might want to explain why and amplify on that point.

DR. WEINSTEIN: Repeat that again, please?

DR. TELLING: The point being that there is a difference between notification in the United States and

the United Kingdom, and that the FDA believes that the risk here is lower, and you might want to state why.

DR. MASTRIANNI: Just an aside question on the surveillance question is, what about the hemophilia population?

There was some ongoing surveillance at one point and a lot of autopsies were looked at, and no cases of CJD were identified.

What about an active ongoing surveillance now? Is there anything in place where it might just be voluntary, I guess, or is there anything formal about following every patient that gets factor VIII or IX?

MS. HAMILTON: There is the UDC study through the treatment centers and CDC. As I said earlier, I think it would just be great to strengthen that and make sure that the funding stays in place for that, and that it can go beyond what it has done at this point.

DR. MC COMAS: I guess my last question is, is there a message for the general public. What is the message for the general public in this.

DR. WEINSTEIN: I am not certain that the message for the general public is any different from what we are presenting to the patient population, because this is a product that is used by specific populations and so forth.

DR. MC COMAS: I guess what I see is, say this is

picked up in the news media and it talks about the risk of VCJD in blood products, plasma products.

Are people in a general public going to be concerned, thinking about previous contexts, that there is a way to get it from dental or surgical instruments.

Again, I am speaking on sort of a high level of ignorance and naivete, but is there a take home message for the non-patient population.

You said that your strategies were physicians, patients and general public about the risks of their either contracting it, or perhaps another message is in terms of vigilance in their donation of plasma in the future, be aware of these things if you go to donate.

DR. POWELL: I guess I am focusing on the same question and in particular on page two, bottom of that final paragraph.

I am ignorant of the manufacturing processes, but I think one obvious question that the general public is going to be interested in is what is the fate of the infectivity that is removed from that product.

DR. COLVIN: I just want to respond a little bit to Dr. Mastrianni in that there is an instrument in place, the UDC universal data collection that the CDC runs on the hemophilia population.

Unfortunately, it doesn't collect data on CJD or

vCJD in our population. I think one way -- the first thing to do is again start -- I think this starts at both educating the people at the HTCs, because that is where the data are collected.

They collect a lot of data and they collect a lot of serum. So, if we could start the process of the HTCs being educated, add CJD and vCJD to the list of diseases that are tracked, that would be a step in the right direction in terms of future surveillance of this disease in the hemophilia population.

DR. CREEKMORE: I might have missed this in reading, but an additional reassurance could be some expression in the communication of commitment to continue to reassess risk with new information.

MR. SKINNER: If we are talking about the communication strategy and the roll out as well, because I think the message is pretty clear in the Q and A on surgical and dental instrument, that this was the area of perhaps the greatest unanticipated consequences for the patients with hemophilia in the United Kingdom, that they were denied colonoscopies, endoscope procedures, dental procedures.

Hospitals were quarantining them. They were saying, well, you can use the one that the previous hemophilia patient used because you are already at risk.

I think we need to be prepared with a proactive message for either the institutions that administer those procedures or the dentists, and not wait for them to come to us.

I would hope that, whether it is the patient groups or someone else preparing a letter to the dental associations, but they clearly need to be put on notice.

We don't want to have to correct the problem, but we need to be proactive there as well as other communications, and take note of where the patient suffered the greatest access to care following the UK's risk assessment announcement.

MR. BIAS: That was an issue that at least I discussed at length with the FDA, was the possibility that people would be denied care. That is the weakest link in terms of organized care for hemophilia.

The primary providers of medical care will certainly hear these messages and incorporate them into the treatment of patients.

That secondary tier of folks who take care of patients, dental and others, FDA didn't seem to have a clear method of communicating with those medical providers.

There didn't seem to be a mechanism out there by which we could clearly send a message to that group of physicians or medical providers to protect this patient

population.

That was one of my biggest concerns about the release of the risk assessment, was how do we impact that group of providers who are, by the way, the least reimbursed of anyone who treats patients with bleeding disorders, and what would be their incentive to continue to treat those patients. Would this be a further disincentive to treat those patients.

So, it is a missing link in terms of the communication piece. Although I echo what everyone else says about CDC needing to add this to the UDC, I think that is going to be a fairly easy process. They have been a part of many of the phone calls as far as this communication piece.

They have agreed to absolutely participate in collecting information from treatment centers. I think it is just a matter of having another discussion with them about what needs to be added to UDC

Keep in mind, UDC only captures about 70 percent of the patient population. It is the other 30 percent of the population who are not specifically connected to hemophilia treatment centers, who live in rural areas, that we need to find some other mechanism for contacting them.

Certainly we are going to capture the lion's share of people who have young children with bleeding

disorders. That is not the question.

The question is, those who have already been trained to deal with their bleeding disorder and primarily do it on their own, that is the patent population that we may be missing, and those are the ones we need to figure out how do we reach them, how do we reach the physicians that treat them.

Even though the patient organizations can write those letters to the Dental Association, to the national hematologists society and all of that, it is going to be much more profound if it comes from the government.

MS. HAMILTON: I don't think we have to wait to be concerned about the dental community. They are already talking about it.

I had a call a couple of weeks ago from a writer who was writing for one of the dental journals, who had picked up the information from the release.

They are already concerned about instruments and disposal of instruments, since some cannot be autoclaved or whatever.

So, the message is already there in the dental community. I don't think we need to shun whether we need to talk to them. They are already concerned about it. I think that just emphasizes the fact that we do need to get to those other tiers, as Val was saying and also, as I

mentioned earlier today, to those who do not go to treatment centers or hematologists. That is the lost population that we see. Not even the three major national organizations communicate to all of those. I mean, we catch some of them, but not all of them.

MS. KRANITZ: I have a question. They are not going to treatment centers but they are obviously getting blood products or plasma products. Maybe that is the place that that message needs to come from.

MS. HAMILTON: If they are getting them, they are either getting them from an HTC or from a home care company. So, you know, maybe that is another tier that we need to think about. That might be an inroad to get to those people.

MS. KRANITZ: Just sort of a commercial message, the CJD Foundation is now completing their second and third medical education -- this is aimed at infection control -- where we touch on this issue.

What we found was frustration and a great sense of the need to carry this message. We had to reach every level that we could and do it in every way possible.

I think that the FDA has outlined your plan and you have mad a wonderful inroad, but again, the urging has to be that it has to -- you have to keep going until it is perfect.

It is probably never going to be perfect, but the perfection has to be inherent, that you are trying and the communication to patients and physicians and any other medical care provider should permeate in every way possible, through patient advocacy organizations who speak so eloquently on behalf of their membership.

If that message is unified, then I think we have a chance of at least educating that the problem exists, and this is what we are trying to do to eliminate it.

DR. TELLING: So, we have about 10 minutes left. Are there any other comments or questions or burning issues that the panel would like to raise?

DR. COLVIN: There is one thing and it keeps being unclear whenever I look at the risk assessment. When we think about the pool size that we are considering in terms of when the fractionators are making the plasma-derived factor VIII, when you go back again looking historically, initially they said it was about a few thousand donors.

Ultimately, after hemming and hawing for a decade, basically they found it was upward of 300,000 donors in a pool size, which that would obviously change by a factor of two or three what we are really dealing with in terms of the risk of any agent in the blood supply. So, that is the first thing.

I think what is done in the risk assessment pretty well is considering different levels of use of factor VIII by people who use it.

I just speak for myself for a second, who is a relatively low end user. I can show one slide up there. For somewhat severe hemophilia, I infuse on average probably at least once a week 2,000 units on average.

Over the course of the year I probably go through three or four different lots, because that is what gets delivered to me, and they are never the same.

At least at this point I use the recombinant factor, but imagine for a second somebody who is similar to me or perhaps uses more than me for whatever reason -- people use different amounts.

They could use twice as much, three times as much, four times as much easily, or if they are on prophylaxis as a child they may even use more than that. They will have many different lots as well.

There is going to be a wide variability in that group as well. So, ti is just one of those other things to consider as we think about this, that this is -- the breadth of the differences may be bigger than we think and it may vary individually as well.

DR. MANUELIDIS: I think what is interesting to me is, a lot of this discussion is based on epidemiology.

It is on certain people who work with the drug industry, which is fine, doing certain kinds of experiments.

I really sort of have a question. Why doesn't the FDA have any money to sort of say, look, we have some things that can be answered experimentally or in other ways to direct, or certain studies that should be directed. Isn't that also part of this report, that we need certain information and it is not going to come from the usual types of channels.

That is really sort of a question. Otherwise, one is just talking with sort of not the real data that one may want to have.

DR. TELLING: Is there someone who can address that question?

DR.WEINSTEIN: I guess the issue here, I think that in fact we aren't doing that, and in the second portion of this meeting we are, in fact, asking industry about clearance.

That, again, is the primary way to reduce infectivity, and the pool size issue, as you saw in the tornado estimate there, was relatively small, but there are these other -- the clearance -- we are asking industry for more information regarding --

DR. MANUELIDIS: I don't think industry has all of the resources or cares about getting involved in certain

kinds of things. Their agenda is one thing, which is valid, but I think that there are questions that are being asked about, for instance, should we spike blood, should we use a different model. Those are really up to people who are scientists and industry is not interested, as far as I can see, in supporting that kind of fundamental research which really plays into risk and into control.

DR. MASTRIANNI: I also think that it is inappropriate for industry to do the research if it is based on their own products.

You need confidence in the data. If somebody is trying to sell a product and they are performing the research that says it is completely safe, you know, the confidence in those findings is not as high as in an independent researcher with no bias.

DR. GAYLOR: Thirty years ago the FDA set up the National Center for Toxicological Research in Arkansas, to conduct research that industry was not interested in doing, or the private sector or universities, or research was not being done.

It was set up as a center to conduct experiments that were of concern for solving problems and issues that FDA was faced with.

They have -- I don't know whether I will get this right -- a level three laboratory for working with

contagious -- I think level three is right. Anyway, pretty high level. They can deal with infectious agents down there and they do have a microbiology division. So, that is a possibility for future research.

DR. TELLING: I think Dr. Epstein had some comments. I don't want it to get too far beyond the actual -- then I will get back to you, Dr. Powell.

DR. EPSTEIN: It seemed that we were approaching a closure to the discussion. So, I wanted to make a comment that we very much appreciate all the specific feedback that we are receiving about the communication strategy and the specifics of our messages, and that we envision a process where the PHS would continue to interact with experts to develop our messages.

If the members would like to communicate to us individually in writing to give us specific suggestions, it might be very, very helpful in that process.

On the question of research that Dr. Manuelidis has just raised, we do have research resources within the center for biologics, which we have focused on critical issues regarding TSE.

Some of the most important work in that area has dealt with issues of decontamination. As you have heard, we have been very active, cooperating with outside research efforts, including at NIH, with DOD and with the industry,

to help answer some of the most critical questions, such as about clearance.

We are not, at this point in time, funded adequately to be, ourselves, an external funding agency. It is not unheard of historically for the FDA to put out a grant, but at the present time, most of our external affiliations are through collaboration rather than through grant offering.

Beyond that, I think what would be of tremendous value is suggestions from the committee members about where the effort could be best placed.

What are the most important research questions that are amenable to an approach at the present time. That would help us in our interactions and also in our dialogue with other agencies that may be offering funding to the FDA or to other parties.

I am not in a position to comment whether the FDA Center for Toxicological Research has a program of significance in the CJD or TSE area. I believe they do not. I believe part of that may reflect their primary mission, which is toxicology.

This is really infectious disease pathogenesis detection and so forth. There are other sources. The NIAID has invested very heavily in this, DOD has invested very heavily in this.

I really think that the core issue is direction. In other words, what are the important questions, how are they best addressed, and there are various fora where that kind of issue is taken up. This is one of those fora.

DR. POWELL: I just wanted to confirm, I had a lot of very kind of detailed technical questions and comments on the risk assessment and I didn't want to get the committee lost in the weeds there. I am presuming that there will be an opportunity where we can provide feedback to the analysts.

DR. TELLING: Apparently so, yes. Okay, at this point, I would like to adjourn for lunch. We will reconvene here at 1:00 p.m.

[Whereupon, at 12:02 p.m., the meeting was recessed, to reconvene at 1:00 p.m., that same day.]

A F T E R N O O N S E S S I O N (1:15 p.m.)

DR. TELLING: So, welcome back from lunch. We are going to visit topic two now, which relates to levels of TSE clearance in the manufacture of plasma-derived factor VIII and this is revisiting some points that were discussed at the last meeting of the TSEAC. So, Dr. Scott is going to summarize those discussions from the September 18 meeting.

Agenda Item: Topic II: Levels of TSE Clearance in the Manufacture of Plasma-Derived FVIII. Summary of 18 September 2006 Discussion.

DR. SCOTT: Good afternoon. This afternoon we are going to address a couple of questions that we asked the committee at the last meeting.

You requested that we defer these so that you could consider the level of TSE clearance in the context of having seen the Factor VIII risk assessment.

So, that is what we are going to do today. This is Dr. Anderson's slide, just indicating that the log reduction of the vCJD agent during manufacturing substantially impacts risk in the risk assessment in a favorable way. That is, it diminishes risk. That is why we are focused on this particular area of risk management.

These are very similar to the questions that you had last time. The first one is, based on available

scientific knowledge, please discuss whether a minimum TSE agent reduction factor, demonstrated using an exogenous or spiking model and scaled down manufacturing experiments, can be identified that would enhance vCJD safety of the products.

We added this little a. If you ask what TSE agent reduction factor is most appropriate, and the second question which we will come back to later because I would like to expand on some of the portions of this question is, if you identify a minimum TSE agent reduction factor that would enhance vCJD safety, what action should FDA consider in cases when a licensed plasma-derived factor VIII has a lower reduction factor.

So, going back to the first portion, what I would like to talk about first is the exogenous or spiking model, especially what we covered the last time, to summarize that discussion, and how one might think about identifying a minimum TSE agent reduction factor. I will be doing that second.

Just as a reminder, this is a typical exogenous or spiking experiment model. Here I have the example of cryoprecipitation, but it really could be for any plasma or manufacturing intermediate, and any manufacturing step or even series of steps.

So, in this example you have a TSE agent spike,

some TSE infectious agent. This is usually brain material or brain sub-fractions, although spleen in theory could be used in these experiments.

That is added to your manufacturing intermediate here, but with starting plasma, and then the manufacturing occurs, cryoprecipitation, and the amount of agent remaining in the cryoprecipitate and the supernatant from that is assayed and compared to the original amount of starting material, and this gives you a level of clearance that is achieved.

What is the ideal spiking material? Well, it would physically and chemically blood infectivity, it would be easy to prepare and widely available, and it would be high titer material.

I think we have the last two covered here somewhat, but this has been called into question, the degree to which spiking agents replicate the TSE agent in blood or plasma, and we just simply do not have that information. As far as we know, nobody does.

We asked a series of questions about spiking experiments last September. The first of these is, what would be the optimal spiking material and its preparation.

The committee, some members opined that brain subfractions might be better than whole homogenate, although I have to say, in our experience, we haven't

really seen much of a difference when these two have been compared in certain types of manufacturing steps. That doesn't mean that this will always hold true.

You also asked whether higher titer infectivity fractions that might be more relevant to blood infectivity form could be generated, for example an LDL DLDL bound fraction from plasma. This is based on Dr. Sejvar's study or series of studies that he presented last time, showing that the agent may be preferentially associated with these lipoprotein fractions.

There also may be other purification methods for infectivity, such as a solubilized homogenate, which might, again, more replicate what is in blood.

That, again, isn't certain and Dr. Priola stated there is no pending resolution of the physical form of blood infectivity.

Spiking studies use human plasma and intermediates.So, they are highly process relevant. It is possible that animal plasma may fractionate differently.

We also asked you to comment on the selection of TSE strains in animal models for spiking experiments. Some members of the committee thought that the most relevant strains would be TSE and vCJD related, although a well characterized and practical variant CJD model in rodents is not widely available.

Transgenic mice, that is, mice that are prion protein transgenic for specific animal TSE strain, may provide greater sensitivity or shorter incubation periods.

For example,what I mean is use of BSE in bovinized mice, mice with a bovine PRP, or scrape into ovinized mice. Human TSE studied in humanized mice continue to be developed.

We also asked for these spiking or exogenous experiments, what the committee thought about the use of bioassays or immunoassays to assess the level of clearance.

Immunoassays are inevitably based so far on the binding of PRP TSE to an antibody. They can be rapid, but we wanted to point out that some examples of infectivity without detectable PRP TSE can occur.

There are examples of the abnormal PRP TSE without infectivity. It is generally less sensitive than bioassay. It may be that the confirmation dependent immunoassay provides an exception to this.

Bioassays also have their down sides. In particular, they are slow. They take many months or even over a year to do, and they require large numbers of animals for infectivity titrations, whereas these binding assays don't require animals other than for input material.

These are some of the things that you discussed. One is that the enhancement of binding assay sensitivity

with protein misfolding cyclic amplification may be possible.

Replacement of bioassays with binding assays would require very careful validation, and it is still current important to assay infectivity.

Tissue culture bioassay models would be terrific because they may have a very short incubation, but these really are developed for use in titrating infectivity and clearance studies. They probably hold out a good deal of promise.

Then Dr. Colvin pointed out -- and I think that is some of the theme of this morning -- that we really don't have the kind of assays, and we really don't have even necessarily the kind of model that might be optimal.

He said we are never going to have the best assay. That is the nature of science, we keep moving ahead and making things better.

We felt that was very optimistic and also that whatever we are doing today might be changed another day based on having more scientific information.

Now I am switching to the second sort of aspect of that first question. That is, how does one think about defining a minimal clearance that would enhance vCJD safety of plasma-derived factor VIII product, or really of any product that is plasma derived.

There are two things that you have today to look at. One is the analogy of TSE clearance to validation studies, and how is viral safety demonstrated. I will go into that in a minute.

The other is the information that you haver gotten from the plasma-derived factor VIII risk assessments, in specific, the sensitivity analysis for clearance levels. How much difference does that make in the possible risk.

Viral safety or viral validation experiments are similar to TSE clearance experiments. In this case, they are spiking of infectious virus into plasma or a manufacturing intermediate depending on what step you are going to study, and an assessment of removal of that virus or inactivation of it at the end of the step.

Now, I would point out that, in contrast to TSE -- and these numbers have changed a little, basically they have gone up because we have got additional published information -- but just to give you an idea of the contrast, for the envelope viruses that have infected plasma and some blood products -- HCV, HIV-1 and HBV -- the maximum titers expected in blood for viremia -- so that is in a plasma or blood donor -- is four to nine logs. For the non-envelop viruses, about seven logs for HAV and up to 13 or even 14 logs for B19 virus.

Here we are, with TSEs, we are just guessing, based on the animal work that has been done, two to 30 intracerebral IUs per ml, or infectious units or infectious doses have been estimated for TSEs.

So, if you wanted to estimate the amount of TSE infectivity in plasma, based on the animal models, you could take the amount of infectivity that might be there, multiply it by the highest volume of plasma you may get from a donor, 800 mls, and you end up with a titer of 3.2 to 4.4 logs total in that whole unit of plasma.

Do we know this is true? We don't, because we don't know the amount of infectivity in human plasma for variant CJD. I just want to give you an idea of where this might fall.

Viral clearance, usually these studies are designed, or rather, the process is designed to achieve, at least to cover or remove the maximum amount of virus that is expected, based on these kinds of numbers, plus an added margin of safety.

So, what is this margin of safety? In he past it has often been at least two to three additional logs of clearance.

It is obviously preferable to have more than that, say three to five. This may be prudent because manufacturing conditions cannot be identical in every

respect for every lot.

So, there are small changes, for example, in pH protein concentration, ionic strength, ethanol concentration, and other parameters that manufacturers use within a range for any given step.

These, obviously, because they have ranges, each lot is going to be slightly different. The point is that you might get a little more or a little less clearance at any given time.

Also, the viremia range could be higher in a donor than has previously been reported. So, there is that to consider.

Also, even for these, virus models are usually used and they are not identical to the field virus, even if they are the same type of virus.

Sometimes they are not even the exact type of virus. For example, hepatitis C virus cannot be studied due to the lack of culture methods for HCV. So, similar model viruses such as bovine viral diarrheal virus may be used as surrogates for HCV.

I am going to switch from that way of thinking about clearance to make the point that Dr. Anderson has already made about sensitivity of the factor VIII risk assessment to the amount of TSE clearance.

We generated these ranges that we thought would

probably cover all of the products, based on what we knew and based on published studies of certain manufacturing steps.

I have just excerpted a portion of table 5.3.A. At random, more or less, I picked this particular type of patient, episodic, no inhibitor and the two prevalence ranges, the lower estimate of prevalence and the higher estimate of prevalence in the United Kingdom that were used to generate this risk assessment for U.S. products.

What you can see here is that you get an extremely low risk for the seven to nine logs of clearance, very low risk, or extremely small, for the four to six logs of clearance, one in 9.4 million, one in 105,000.

If you really go down to a lower level of clearance, it makes a substantial impact in the estimated risk.

It has been stated this morning, but I will say it again this afternoon, that the available data suggests that all the U.S. licensed products are likely to have a TSE clearance of four logs or greater. Again, there are some caveats to that, that we can discuss, but this is based on the current data that we have and Dr. Kreil will be showing some of that information in just a few minutes.

Now, on to the second question -- and I will try to make this brief because I think I am running out of time

-- if you identify a minimum TSE reduction factor that would enhance vCJD safety, what action should we consider in cases when a licensed plasma derived factor VIII has a lower reduction factor.

Labeling that would differentiate the higher clearance products from other products, we talked about this a little bit at the last committee meeting, and I think we may hear those opinions and some additional opinions here today.

Recommending addition of TSE clearance steps to the manufacturing method. One thing I would like to point out about this is that adding a clearance step or adding any major step to manufacturing is considered a major manufacturing change, and this would require special validation studies, potentially clinical studies, and might impact the product.

I can't really tell you all of that for sure without knowing what those additional clearance steps that are proposed might be, if any are, performance of TSE clearance experiments using the endogenous infectivity model or any other actions.

So, I am just going to talk a little more very briefly and expand on A and C. We have already been over he labeling this morning that concerns the CJD agent in blood.

This is the recommended labeling that plasma-

derived products have. I am not going to read it to you because you heard it this morning and we are low on time, but it does give the warning that theoretically this is a risk.

Then we have the voluntary labeling in the description section for manufacturers who have submitted their detailed studies to us so that we could thoroughly evaluate them.

This tells you that the manufacturing process was investigated, and it characterizes the study as investigational, and it introduces the concept of models for vCJD and CJD.

The second part of that labeling for manufacturers can claim the actual amount of material they removed. This also has a statement that provides an estimation of the effectiveness of this removal in the context of low levels of infectivity. So, that is the reason for the wording, reasonable assurance and low levels of infectivity.

To remind you, here is the endogenous and TSE clearance type of study. This is where plasma will be taken from a TSE infected animal and subjected to a manufacturing step, and the cryoprecipitate, in this instance, would be assayed for infectivity as would the cryo-poor plasma supernatant, and that is how you would get a level of

clearance.

Now, comparison of results from endogenous and exogenous infectivity studies so far suggested similar reductions for some precipitations.

I would like to point out that there is a very limited number of endogenous studies that have been done and there aren't very many for all of these manufacturing steps. So, that is a caveat here.

The endogenous infectivity characteristics in plasma are small size -- it is difficult to sediment in its native form, it is poorly aggregated and, as we heard last time, it may be lipid or plasma protein associated.

The relevance of infected animal plasma to human blood, at least the form of the agent in that plasma, is highly likely to be relevant to the form of the agent in vCJD, but since we don't know exactly what the agent is like, I can't promise you it would be identical.

These studies are limited because the starting infectivity of the material is low. In other words, if you have a high level of clearance, it would be very hard to see it, given the way that these assays have to be done.

You can use large numbers of donor and assay animals to compensate for these low titers but, as I showed you in the last meeting, for 100 mls of plasma, to titer all of that into animals, you probably need 5,000 mice if

you are using mice, or 2,000 hamsters.

It was suggested -- and there are a lot of problems so far with the logistics of large animal models, but these are probably doable but very difficult.

At the last meeting, also it was asked, can studies be done using a large animal plasma donor with a small animal assay, and this was a very interesting idea, for example, using sheep plasma and fractionating that and assaying it in ovinized mice.

Then the question was brought up, does animal plasma fractionation equate to human plasma fractionation. Finally, since I am way out of time, I will leave you with the questions, and I would also like to introduce Dr. Kreil, who spoke here the last time about the industry perspective and also the current state of their TSE clearance studies and the amount of clearance they have been seeing using various models and studying various manufacturing steps. Thank you.

DR. TELLING: Thank you, Dr. Scott. So, Dr. Kreil?

Agenda Item: Updated Information From Manufacturers.

DR. KREIL: Good afternoon, ladies and gentlemen. First of all, I would like to, on behalf of PPK's pathogen safety steering committee, thank you for the opportunity of

having us part of this dialogue. We really appreciate that.

What I would like to discuss with you today again is the TSE clearance studies that amongst the industry have been performed, with a specific focus for the purpose of this meeting on plasma-derived Factor VIII products.

This is an acknowledgement of the industry partners who have contributed to conduct of these studies.

The meeting, as we said, today is going to focus on plasma-derived factor VIII which is the fraction that, when you thaw plasma, precipitates here and then is separated from what we call cryosupernatent by typically centrifugation.

This part of the products actually fall into two categories. One is they do contain von Willebrand factor in addition to factor VIII, others that are factor VIII only.

Then the cryosupernatant here goes on into further manufacturing processes to give rise to, for example, factor IX or the more classical product.

Now, experimentally, to work with these processes and to investigate prion reduction, for example, we can obviously not do these experiments on the large manufacturing scale.

This is done at the typically thousands of liter scale. What we do is, we reduce from the manufacturing scale to a scale that we can perform in pathogen safety

laboratories, but where this process is actually conducted in an equivalent way to the large scale process.

Then, as Dr. Scott as pointed out, we take intermediate from the manufacturing plant, spike it here, as you call that, by addition of prion agents, run through the process at the small scale and determine how much of the input prion infectivity, or surrogate marker for prion prisons, makes it at the end of the process through it. This is how we determine the log reduction factors.

Now, a number of things need to be said about the conduct of such studies. First and foremost, how do we set up a down scale for these studies.

It is important to stress that the intermediate that is used in such down scale studies is obtained directly from typically the production scale or a pilot scale. So, it is fully equivalent to regular manufacturing operations.

Secondly, we do determine a number of product parameters, that being activity as well as physical parameters, such as concentration of protein or protein impurities for that purpose, to ensure that our process, again, is fully equivalent to the large-scale process.

Finally, we do determine a great number of process parameters to, again, ensure that we have full equivalence between production and laboratory scale

because, really, this is the prerequisite of applying the prion reductions as determined at the lab scale to the process as it is conducted in routine manufacturing.

Now, with respect to the investigational prion clearance studies that we are going to discuss here, an important list is obviously the right set up in terms of using prions and detecting prions.

First, you end up with the choice of the spiking agent. This is you need to figure out which is the source of your agent.

Secondly, the preparation of the spiking material is critical, in that from a more crude, for example, brain homogenate down to a much more purified fraction, everything has been used, and I think under the right circumstances, is appropriate to be used.

Finally, there is a choice that needs to be made regarding the assay for quantification of prions, with the choice being here the more time consuming, but maybe somewhat more close to the real agent, infectivity assays versus the more readily available but maybe only a surrogate to the real prion agent, the in vitro assays.

Regrading the prion quantification, we do believe that we have really good control about this,and that control has been established by controlling the reagents used during these assays by applying the principles of good

laboratory practice, by using standard procedures for all the detection methodologies for the preparing of the spiked material, for the conduct of the assay, for the acceptance of the assay results.

So, all in all, we believe that the suitability of assay results as obtained by such a well controlled set up, can be guaranteed.

So, in summary, these prion clearance studies, we are using validated down scales fully equivalent to manufacturing processes.

We are using controlled prion spike materials and controlled prion assays for the purpose of making sure that this is a reproducible assay that we perform and that we come up with reliable results.

We feel strongly that further standardization would in fact inhibit process specific investigations. Just to give you one example, it might be quite appropriate to use a more crude prion preparation when you are investigating a more upstream manufacturing step when, also, your intermediate will be more crude, whereas it might be quite appropriate to use a more refined prion spike if you are investigating a more downstream step with a more purified intermediate also.

We feel that the standardization also would lead to the fact that novel approaches could not easily be

taken. In fact, we feel that it would discourage the application of improving understanding and, as has been pointed out a number of times during this meeting, there are still gaps in our knowledge. As they are filled, we are going to adapt our research approaches.

Another thing that is important for us to stress, even virus reduction studies at this point are not fully standardized, and for a very good reason.

As has been pointed out by Dr. Scott, some of the target viruses that we have an interest for we are using, such as, for example, HIV.

There are circumstances when other target viruses that we can use, such as hepatitis A virus, are not being used, for example, when antibodies to that virus are present and, therefore, would convolute your research findings.

A third option would be that we are actually using viruses that have never been used before, and that was, for example, the case when we wanted to verify that our processes did, in fact, also cover emerging virus such as west nile virus. So, standardization, we believe, is not a replacement for expert knowledge.

Before going into the presentation of company specific data, therefore, I would like to point out that what you are going to see is data obtained for different

manufacturing processes.

From these manufacturing processes not necessarily all steps of the entire manufacturing process have been validated.

Detailed data for the U.S. licensed product that you are going to see here have been shared with the agency and further research is still ongoing.

I would like to echo here what Dr. Telling has said before. I think the data that I am going to present to you really represents the best scientific evidence generated on a voluntary basis by the industry, and we are going to keep up this commitment going forward.

This is the presentation for a product that is licensed in the United States. There are two steps that contribute to a reduction of prion infectivity in this instance, and the total reduction factor is given here at the bottom.

Company B, also that product is licensed in the Untied States. For this product, three different steps have been investigated and, again, here you can see a total reduction factor that has been added for ease of reading, basically, for this committee.

Company C, this product is not licensed here in the United States. There are two steps that have been investigated, but we have not given an overall reduction

factor here.

Here, another company C product that, again, is not licensed in the United States but, again, two steps have been investigated.

Here, company D, this product again is licensed in the United States. Two steps have been investigated and, again, you can see here the total reduction for the process as it has been validated.

Company E, also a product licensed in the United States, here again you can see the total reduction factor that we have added here. I should stress, though, that this is the reduction factor for only part of the process that has been validated.

Finally, here, company F, this is yet another product where a single step has been investigated. That product, however, is not licensed in the United States.

In summary, what I would like to say from all of these studies that have been performed actually over a number of years, I think what we can say is that plasma-derived factor VIII manufacturing processes do remove prions.

The specific reduction factors obtained will depend on a number of variables, the first being a specific manufacturing process for the specific product, secondly, the number of steps that have been investigated throughout

the process, finally, as I pointed out, on several aspects of the experimental design.

Secondly, we would also like to point out that we agree with the agency's judgement on the level of risk, which is not fully known, but very likely low.

What we think is particularly strong evidence is that there is absence of evidence for the transmission of prions by any plasma product, but certainly also for plasma-derived factor VIII and that, despite a very high level of pharmacovigilence, particularly in the United Kingdom where the majority of prion disease cases in humans have occurred.

The exposure to these prion agents, I think it is important to keep in mind, is low and getting lower still. I would like to substantiate that with the next slide.

Again, reduction is a common feature for all plasma-derived factor VIII manufacturing processes. So, finally, we would like to conclude by saying that the quantification of reduction versus an unknown but low level of risk, is an open equation. Therefore, putting a threshold requirement in there would really be very arbitrary.

This is what I mentioned before. The exposure is low and getting lower. This is a version that has been published in the mid of this year by the United Kingdom

Health Protection Agency.

Just to reiterate what that means is, that this is the occurrence of one case of variant CJD per quarter worldwide.

As PPTA, we would also like to offer our comments to the questions that the FDA has asked to this committee, the first question being whether a minimum TSE agent reduction factor would enhance the safety of products.

Our response is that while the variant CJD risk is considered very low, although not fully understood and quantified at this point, we believe that really any level of reduction that we could demonstrate is reassuring.

We got into further questions that sort of hinge on the first one and we would like to also offer comments. Where the agency has asked which further actions the agency should take when a plasma-derived factor VIII product has a lower reduction factor, one option is to introduce labeling that would differentiate TSE clearance for products that have more of it versus a product that has less of it.

We feel that where these reduction factors are derived from investigational approaches, labeling cannot really be meaningfully assessed without having all the experimental details available to the person assessing the label.

Also, we are afraid that these labelings may

suggest a safety differential which, quite frankly, where we don't know the exact level of risk, we could not substantiate it versus any reduction that we can demonstrate.

Another opportunity that has been discussed has been the recommendation to add additional clearance steps to the manufacturing method.

As industry, we feel that the introduction of additional steps would vary like the clinical testing of other product features, such as safety and efficacy.

That would involve patients in these investigations and, quite frankly, we believe that they would involve patients with an unsubstantiated benefit to them because, again, the risk that we are talking about has not been substantiated either.

Also, we feel that these production processes would very likely be negatively affected with respect to the yield that they can produce.

Question number 2-C, it was asked whether it would be appropriate to require performance of studies involving endogenous infectivity models.

As we have discussed last time, we feel that using these low titer endogenous infectivity models would actually generate reduction factors very likely lower than those already demonstrated with exogenous infectivity.

Also, we would like to stress the point that we made the last time. Animal and human plasma are very different, indeed, and therefore the data derived from fractionation of animal plasma are very likely irrelevant to the situation in humans.

Therefore, we believe that such experiments would only cause the use of large numbers of animals, but without changing product safety.

Just as a reminder, one of the models that last time was discussed, is a newly derived transgenic mouse model, where the PRP protein does not have the GPI anchor. Therefore, this PRP protein is very soluble and produces rather high levels of infectivity also in the blood.

In the initial publication of those model it was suggested that it should be used for the investigation of effectiveness of methods for removal.

We were not convinced of the value of this model in the last meeting, as we felt that this truncated version of the PRP protein would very likely also behave dissimilar to the PRP protein that we are really concerned with.

Just as a good point of evidence was the natural PRP SC as a rather hydrophobic protein, this GPI anchor less PRP is a rather soluble molecule.

So, whether the data derived from using this is any more relevant than anything else we have used so far we

would question.

Beyond that, this is data that compares the presence of certain coagulation factor concentrates in mouse plasma versus human plasma.

As you can see here, mouse plasma contains two-and-a-half times more factor VIII than human plasma. So, we would argue that an investigation with mouse plasma will not generate data that would be meaningful for human plasma.

Here you can see pieces from a publication. Here you can see functional clotting assays, and over here you would see rat and guinea pig. That is probably the most close data that we get to mouse or hamster.

As you can see, the value for these functional clotting assays are way higher than for the humans over here.

The same is true also for the presence of coagulation factor concentrates. This is for the presence of factors V, VIII and XII. Again, you can see that rat and guinea pig have much higher levels of these as compared to humans which would, to our belief, render any investigations with these animal plasma models irrelevant for the behavior of human plasma.

The final question is whether there should be any other actions taken on behalf of FDA. What we would like to

emphasize is that, yes, there needs to be further action, and we are going to take this action.

We are going to remain committed to doing further investigations into the behavior of prions during our manufacturing processes.

We would also wish that we can continue the dialogue between the agency and the agency's advisor, so that we can address together the remaining uncertainties.

At this point, though, we feel that, given the uncertainties that we first need to experimentally address, and the reassuring epidemiological information that we are getting more and more, that at this point further actions would not be justified.

So, in conclusion, we feel that the level of prion risk for plasma-derived factor VIII at this point remains unsubstantiated, which we feel is not a rational basis for taking any additional measures at this point.

Specifically, a minimum TSE reduction factor versus an unquantified but considered very low level of risk we don't feel is necessary.

The implementation of a quantitative prion labeling versus a threshold, we feel, would not provide meaningful safety information.

As I said before, the introduction of additional manufacturing steps might possibly impact other clinical

product characteristics and very likely lower yield and, therefore, would require very likely patient exposure in clinical trials with really very unclear benefits to these patients.

Finally, on the endogenous prion reduction studies, we feel that this would certainly not change the safety profile of the product, but also the data generated would not be a meaningful addition to the data that have been generated so far.

The bottom line, we do commit to working with you. We do commit to trying to, as well as we can, fill the gaps. Thank you.

DR. TELLING: Thanks, Dr. Kreil. There is a question here.

DR. LEITMAN: Can I ask a technical question of Dr. Kreil? You may have mentioned this. These are technical questions, again. Where does the infectivity go in the first step when you separate the cryoprecipitable to the non-cryoprecipitable? Does it go into the non-cryoprecipitable?

DR. KREIL: This is not a black and white cut. So, part of it goes into the cryoprecipitate and part of it goes into the cryosupernatant, but this is not really a very sharp separation step.

DR. LEITMAN: Then the procedures, eh

chromatography and the precipitation and the filtration, are those applied to the mix before the separation into cryoprecipitable and non-cryo, or applied to the separated?

DR. KREIL: These are steps that are applied in the downstream processing of the cryoprecipitate.

DR. LEITMAN: Okay, and then this question came up at the table at lunch. I don't think any of us could answer it. Is the material, the infectivity, inactivated or segregated and still active? If it is segregated but still active, what happens to it then?

DR. KREIL: Prions happen to be very sturdy agents. So, inactivation of prion infectivity is something that takes very, very harsh measures, quite frankly, measures so harsh that none of the biological activity of our product would survive them.

So, it is not inactivation. It is separation away from the biological entity that we are interested in. So, in our waste fractions you could argue that there you would have the prion infectivity, would it occur in plasma to start with.

DR. LEITMAN: How do you sterilize that, then, and reuse your equipment?

DR. KREIL: Two things. The waste fractions, they are discarded. In our instance we actually put it into a plant and burn it to produce energy. So, that would take

care of this.

As to the equipment, there are first cleaning procedures and then later sanitization procedures, as we call them. Those have been investigated with respect to also a potential prion contamination.

Just to give you a perspective on this, cleaning at least in our company has been defined to at least require a 1,000-fold reduction of any residual protein where prion agents would be residual protein. You would have at least a 1,00-fold or three-log reduction of any potential prion that should sit around after your manufacturing process.

Then secondly, for the sanitization, we have just as an industry published the results of a collaborative study that has shown that even very low concentrations of the sanitizing agents as we have used them for your stainless steel equipment, for example, can very effectively inactivate prion infectivity. So, by these two measures, that is taken care of.

DR. EPSTEIN: I just wanted to add an additional comment about the cryoprecipitation. It is correct that it is not a clean cut and it is also correct, however, it is not a robust procedure.

In the majority of experiments, about one log or 90 percent of infectivity goes down to the cryo. However,

there have been some experiments in which it has been reversed. So, it depends on the methodology.

We tend to think that there is more infectivity partitioned into the cryo, which is part of why we focus first on factor VIII rather than factor IX, because factor IX comes from the cryo soup and factor VIII comes from the cryo.

DR. MASTRIANNI: I was just going to add to that, if you put infectivity in, if you spike with a certain level of infectivity, can you recover all the infectivity that you put in? It is another way of basically looking at where it goes.

DR. KREIL: As I was trying to point out, what we are doing to determine the reduction factors across a processes is compare the input to the output.

The input is not a theoretical assumption, meaning to say that we put this and that in so it should be in, but it is an actual determination of the levels of the agent upstream, and that is then compared to the actual determination of the agent downstream. So, we can recover and we confirmed that.

DR. MASTRIANNI: Okay, but you recover what is left downstream. So, in other words, if you start out with nine logs of infectivity and you recover two logs of infectivity, where are the other seven? Can you recover

those?

DR. KREIL: That is actually a requirement for all validation studies for viruses, and we have used the same conceptual approach also for prion reduction studies.

What you in fact do is, you determine it not only for the input and your output, but also all the fractions generated throughout the process, so that you are able to understand where does your prion infectivity go.

DR. MASTRIANNI: One other questions regarding the log reduction. I think I asked this last time, too. Do you use them additively and can you do that?

So, if you have two different procedures within a total fractionation clearance, can you add those log reductions?

DR. KREIL: This is something that needs to be substantiated for every individual case. Again, expert judgement comes into play here.

To use the phraseology that the agency has suggested, if these steps work by orthoganol mechanisms of action, then you can assume that it has been removed from the first step, but one step would not be the same as would be removed by another mechanism of action by the second step.

To be more direct here, certainly one of our member companies has done rather extensive investigations

where first individual steps have been investigated and then the combination of these steps has been investigated in one goal, and it has been shown that if, again, the mechanism of action is orthoganol, it has led to a very nice additive effect.

DR. SIEGAL: What is the order of magnitude of product yield lost that you pay for reductions in so and so many logs. Obviously, it varies by the process.

DR. KREIL: Exactly, it does vary very much by the process. I think from a principal's perspective, it is very difficult to see which steps even you could implement to remove specifically prion agents.

As I said before, for viruses, some of the inactivation procedures that we were able to put in place were very, very effective.

Where prions are so resistant to inactivation, this is not going to be a good methodology. If you are looking more at removal, then typically what you would be thinking of is things like filtration.

Then there is the first aspect that is a little arbitrary, that you start to validate filtration with a very small molecular form of the prion affectivity and you might not get a very good reduction.

If you took a physicochemically larger form, you might get a good reduction. So, it becomes very case by

case. So, it is impossible to answer this with a straight number, I am afraid.

DR. MANUELIDIS: I have a couple of comments to make. The first is that what is very worrisome to me is that you have a point of view which is still somewhat hypothetical.

There are people who don't believe in prions. You are making certain assumptions. For example, you say the high blood infectivity is not worth working on, a model, because the PRP is different, but that is assuming that PRP is infectious, and there are many people who think it is not.

The second thing is that, despite what has been said in this meeting, and the last time when you were here, people have said that PRP is not a measure proportional to infectivity in many, many instances.

Yet your best graph here shows nine logs, but it is all by western blot and there is no infectivity data to back it up.

Now, I think that it would be appropriate, when you give a talk, to say some of these caveats. I think by saying at the end, it sounds, the way you have given this, that there is a justification for no more work. You don't want to see work done on the endogenous model, et cetera, et cetera, et cetera. I appreciate your work but I also

think that you must be aware that there are these caveats.

DR. KREIL: I would like to answer first by saying that I hope to have said a couple of times that we do remain committed to doing further work.

It is not that we suggest that no further work needs to be done. The caveats about the endogenous infectivity model on this mouse model was more about the differences between mouse plasma and human plasma, and therefore doing fractionation with the mouse plasma would not render information meaningful to the situation with human plasma.

DR. MANUELIDIS: I just want to add something to that. I was in this FDA meeting years ago when I said, blood is infectious and we have known that since 1978.

The people around here from industry said to me, well, you know, mouse blood and guinea pig blood, it is different from human blood.

I would like to know what exactly that you were thinking of that is so different about mouse blood and hamster blood from human blood.

DR. KREIL: The data that I have shown you is that certainly the coagulation factor concentrates occur in very different amounts in human versus mouse blood.

Therefore, if you do studies specifically targeting the behavior of factor VIII for example, then

that starting point makes it impossible to result in comparable data.

DR. MANUELIDIS: But cryoprecipitation and the processes, too, are something that are independent of that.

DR. COLVIN: Also, I think, just to think about this in biological terms, a two-and-a-half fold difference when you are talking about a fractionation process, having done a fair bit of fractionation, that is nothing.

DR. KREIL: I would actually disagree with that. Our processes are very well controlled and differences of two-and-a-half fold are certainly not within the variation that would be acceptable for a controlled manufacturing process.

MR. SKINNER: Thomas, I am just wanting to probe your definition of unsubstantiated level of prion risk, if you could define unsubstantiated.

In the data you showed three-and-a-half logs of clearance and higher, and is three-and-a-half logs reduction the level where the risk is unsubstantiated, or can you quantify that for us?

DR. KREIL: No, what I was trying to say is that certainly not any level of reduction is good enough or not good enough, because that is exactly the problematic point. We don't know the level of reduction that we need to achieve.

To compare that with the virus situation, there we do rather well understand what the concentrations of viruses are as they occur in plasma and, therefore, also you can determine how much reduction it needs during a process to result in an appreciable safety margin of the final product.

I guess it is some of this information that we don't have at this point for prions. What we do know is that we have not seen transmissions through plasma proteins. Therefore, I would argue that risk, at this point, is unsubstantiated.

I don't argue that we know everything and it cannot occur, but it is not substantiated at this point. In other words, we are comparing an unknown load with a reduction capacity, whereas in the virus world we have a clear number for the load and a clear number for reduction and that allows you to calculate what is your safety margin. That is what I was trying to say.

DR. LILLARD: I was happy to hear that you are moving toward hopefully adopting something more standardized and uniform, log removal criteria in your process.

I wanted to understand more about the barriers that prevent some of these companies -- like I am looking at the total log reduction, say, in company B that is over

nine logs and some of the other ones are significantly less.

What are some of the barriers? Are they intellectual in nature in terms of trade secrets or patents and processes that prevent some type of standardization, something more uniform.

If it is cost, could you elaborate on what it would cost to move from the four to six log reduction processes to something over eight log.

DR. KREIL: At the point when these manufacturing processes were designed, we did not know about a prion concern.

At that point, which is typically decades ago when the principals have been designed, variant CJD did not actually even exist.

So, these processes were designed primarily to purify from plasma or from cryoprecipitate as a starting material for factor VIII, this biological entity for some of the products, including von Willebrands, for some of the products, not. So, in other words, the focus has been clinical efficacy.

Now that we are aware of the prion concern, we are trying to understand what our manufacturing processes do in terms of removing prions.

As it turns out, some have a more high capacity

to remove them. Others have a somewhat lower capacity to remove them.

It is just the differences of the manufacturing processes that are reflected in these prion reduction factors. It is not that everybody was trying to define the very same process to get a maximum prion reduction factor.

DR. LILLARD: Trying to get a better understanding of the barriers as a manufacturer you would encounter in reducing clearance, increasing clearance, are they regulatory in nature? Have you guys done any studies, perhaps, to quantify cost associated with that?

DR. KREIL: As I tried to point out in my presentation, every change to any manufacturing process, say for the purpose of increasing the prion reduction factor, would be viewed as changing also potentially the product characteristics and therefore, very likely, would require re-licensure of that product, including clinical testing of the other product characteristics such as clinical efficacy and clinical safety. Therefore, it becomes a very complex task. In reality, ti would be the development of a new product.

DR. COLVIN: I have a simple thing. I think, going back to what Cory Dubin said a little while ago, are you so convinced that these things work well that you would put your money where your mouth is?

In that regard, if somebody did use these products and ends up with vCJD or some other TSE, would you be willing either to compensate that person and/or continue to provide them health care to the end of their life, which would inevitably be a relatively short course?

DR. KREIL: At this point, the products as they are licensed in the market are obviously considered safe by both industry and regulatory authorities. So, at this point I would actually not want to speculate on this more political question.

MR. BIAS: Can you comment further on your speculation about yield? I don't even know if it was a speculation.

You said that, looking at the process, that it would somehow impact yield. Do you have measurements? Is it severe? Are you losing 50 percent of the product or more? What?

DR. KREiL: As I was trying to say before, the change in a manufacturing process that one could contemplate to increase prion reduction capacity is not known. It is very theoretical to comment on this.

I guess the only example that we can quote from history would be that when virus reduction steps have been implemented in manufacturing processes for biologicals, that typically the yield was removed.

A typical example would be for factor VIII, if I am not mistaken, the reduction from roughly 250 units per liter down to 150 units per liter.

Some of that has been recovered as we have gained more experience and were able to fine tune the processes, but that is roughly something that has at least happened with the introduction of virus reduction steps.

MR. BIAS: I appreciate your presentation and the work that you have done, but you have used a couple of hot button topics when you are talking to the consumer groups, in terms of when you use terms like reduction in yield, which was the argument that was used in the 1980s for not moving forward with certain tests and so forth, and that you can't do it because of this and you can't do it because of that.

I think this group has been very motivated to try to work with industry to, you know, find some way that we can measure these things and we can provide the public with some assurances.

Perhaps you probably shouldn't have tried to answer the questions for us from your point of view, but I am just a consumer here. It is not flying. I am not feeling that you are interested in doing this and, therefore, I think one of the goals here is so that the industry can have a label that says, hey, we can remove

this and, therefore, you should feel safer.

So, you have got to help us get there, because that is not what I am hearing based on your presentation. I am hearing more about what you can't do, how it affects yield and you can't really tell me exactly how it does that.

There are just so many unknowns. We have to make a decision in the end. We would like it to be a decision that benefits both the patient population that we are trying to serve and the industry. That presentation didn't help. So, wherever you can meet us halfway would be very helpful.

DR. KREIL: I guess one argument that I would like to stress again that it is certainly a fact that this industry has done all the work that shows reduction of prions through manufacturing process.

All the information that we have has actually been provided by industry. So, it is not like we are trying to work on this.

We are trying to, probably with a dozen slides or so, show the work we have done. On two slides we did also mention, for the sake of completeness, that any change in manufacturing process would involve very likely clinical testing of that product to assure that it is still efficacious, that we are not running into, for example,

inhibitor problems, that we may also have to compromise on yield.

These are just manufacturing realities. I did not want to hype that. I just wanted to make sure this is also mentioned.

DR. TELLING: I think it is valuable to have you answer these questions now while these issues are still fresh in our minds from your presentation. That is why I have allowed us to go some extra time. It is going to take away from our discussion time later, but I am going to allow two more questions.

MS. HAMILTON: I want to say amen to what Val just said. Dr. Lillard brought up a point a while ago and I was just getting ready to raise my hand.

If it is possible for one company to exceed nine, why can't the others do the same? What is keeping them from that?

When Val brought up the point that he just did, it echoed in my mind that for lack of 13 cents a unit, 10,000 people got AIDS.

I think we need to really think about that and we are very much aware of the expenses of the manufacturing process and what you have done, but we need to go farther.

I think that has come from several different points today and we just need to emphasize it, that we are

not there yet.

Again, I would go back to, if one company can do plus nine, why can't the others. We don't want to hear that you can't do it because it is going to do something with the yield. I mean, if one can do it, everybody else should be able to do it.

DR. KREIL: One of the differences might be that, for a process that will achieve the higher prion reduction factor, we would also have a more rigorous purification applied to the factor VIII molecule such that the final product contains factor VIII only.

For other manufacturing processes you would have factor VIII together with von Willebrand factor, which would change the clinical usefulness of that product.

Therefore, if you wanted to apply the same rigorous purification, you may also change the clinical efficacy of that product with respect to, for example, von Willebrand content.

MS. HAMILTON: Which is better, safety or efficacy? I mean, if you have to do another product for von Willebrand factor in order to make the factor VIII product safer, what is the decision?

DR. KREIL: As I said before, these fundamental changes would really be new products that need to be developed from scratch.

DR. MASTRIANNI: So, reading number of independent runs per sample preparation, in most the cases, well, in half the cases there are one and in the other half of the cases there are two. Does that mean one or two experiments or what does that actually mean? Have these been replicated or at least done in triplicate to get an idea what the average is?

DR. KREIL: The experimental design worked such that you did duplicate runs and, when your results are equivalent, you know that this is a robust number that you end up with.

The alternative is that you start with, for example, using different spike preparations and, if you do one run with the one and you do another run with the other and you end up with an equivalent number, then that tells you also that, regardless of what spike preparation you use, that it is a number that reflects your process.

I should also point out that what you have seen are numbers on a log scale. So, in other words, a one means a 10-fold difference.

So, the numbers that we give you here, I believe, are very robust and that variations such as two or three-fold, you would not see as variations in these numbers.

DR. MASTRIANNI: I am not sure I understand. Number of independent runs per spike preparation. Again,

does that mean -- maybe I am not getting it but does that mean one experiment, one spike preparation and one run through to measure the log reduction, or is it a summation of multiple runs.

DR. KREIL: For in vivo assays, for example, you would very likely just do one run with infectivity because you would end up injecting the product into literally hundreds of hamsters.

So, to repeat that is not considered a wise choice. What you would do is, you would repeat that maybe with an alternative readout and use waste involved in addition, to confirm that, with that, you would get equivalent results.

DR. MASTRIANNI: I know I couldn't get a paper accepted with an experimental number of one. So, I don't know how we can really assess the data with one or two experiments, really.

The other issue is, you know, the additive log reduction. It seems that all the differences here between different companies are the different methods of preparation of the product, essentially. There may be some difference in quality control.

So, if there were another preparation or another method to add to what other companies have ongoing that could add another log reduction of two or three, that could

get us to the four to six log reduction that most people will probably accept, that might be an easy thing to institute for other companies to accept maybe. Do you think that is possible?

DR. KREIL: As I said before, the introduction of additional steps into the manufacturing process of a licensed entity would very likely be viewed as a very substantial change to the product and therefore would very likely require revalidation of also the clinical usefulness of the product involving patient trials. So, it would be more like a new product, really.

There are really only very rare exceptions where this has been accepted as a variation rather than a new process.

DR. MASTRIANNI: Can somebody assess the cost to a company on adding a manufacturing procedure step, so we maybe could get an idea of what kind of an expense this would be? Is it really something that is not possible or is it possible?

You are kind of answering that, well, this is an impossibility. I think you have to look at what the potential possibilities are so that we can assess the situation better.

DR. KREIL: I hope I didn't say that this is impossible, because new products are being developed. So,

this is something that can be done.

What the specific price tag is, I am really not in a position to comment, but we are certainly talking many millions.

DR. TELLING: I think I would like to finish it here because I am aware that people have probably made bookings to travel home and we are running a bit late. I would like to thank you very much for answering the panel questions here and for your presentation.

At this stage I want to move on to the second of the two open public hearings. I believe there has been a request to speak.

Agenda Item: Open Public Hearing.

DR. FREAS: Yes, Mr. Chairman, I have received one request from David Cavenaugh, government relations director, Committee of Ten Thousand.

DR. TELLING: Once again, both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency in the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open

public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that he may have with any company or any group that is likely to be impacted by the topic of this meeting.

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

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Agenda Item: Statement by David Cavenaugh.

MR. CAVENAUGH: Thank you. As Dr. Freas said, my name is Dave Cavenaugh. I am the government relations staff for the Committee of Ten Thousand. We have no financial conflicts of interest like anybody else in the room today.

I appreciate the chance to present a second time for our organization today. I know that we are running behind.

Listening to the discussion this afternoon, I am trying to integrate it so that we leave the day with a combination of the uncertainties of the morning and the

uncertainties of the afternoon, if you will.

There was a mystic in about the 1400s or 1500s who went by the name, the Cloud of Unknowing. The thirteenth century, pardon me.

Between the humor of that, I was once given an ice breaker sign on my back saying that is who I was, and I had to ask questions to determine who that was. I had no idea. I wasn't one of the religious historians. My wife was.

The other thing that we all can relate to is, above all, do no harm. The kinds of things we heard today, the data gap slides that show, well, there are many, many variables and the second bullet is, but the risk is extremely low.

I am sorry, but those two statements don't go together. You can't say the one unless you can eradicate the other first.

We have just had too many examples. Dose response for humans in vCJD in this morning's slides, challenges for determining dose response.

Human data absent, quantity agent in human blood plasma present throughout incubation period, genetics and susceptibility of humans, threshold or not, accumulation of agent in humans.

The FDA risk assessment model assumes that the

vCJD agent present in the last half of the incubation period, linear dose response, no threshold, accumulation of infectious agent in body. Okay, that is some of the things.

The results of one slide this morning dealing with the risk communication model was to give the two things that I have just mentioned.

My conclusion was that the risk communication strategy was to confuse, because you can't reconcile the two together.

To go back to the prepared remarks for a little bit, I guess first I would like to invoke one more piece of history in context.

Consider our knowledge of retroviruses in 1973, say. Consider our knowledge of what my sister-in-law has, reflex sympathetic dystrophy syndrome, and how no HMO that she could go to could find out what that diagnosis was. So, she had to pay her own $5,000 way to the Mayo Clinic to get it diagnosed.

Syndromes, you know very well, are multiple symptom manifestations. This woman is suffering greatly. There are many people with fibromyalgia. These are unknowns that have crept in on us. There are unknowns around in medicine.

FDA has determined that the majority of risk

associated with TSEs for blood product users is reduced through the fractionation process, according to the papers that we have been given, average four log.

However, the concept of the prion is still quite new in scientific terms. Abnormal disease causing prions are seldom found in nature.

The charting of the disease from infection to death is still little understood and research is hampered by small case numbers, post-mortem ethics issues, and the almost complete lack of data on pre-clinical characteristics.

The behavior of the disease vector within and across species is little understood, and it is difficult to predict the contagiousness and disease course of the human disease, as the characteristics of the various prion diseases vary greatly between species.

None of what we have heard in the last hour has specified which TSE is being used at each stage and in each spiking.

Recent data, for example, suggests greater human to human infectivity levels for CJD than is generally recorded for TSE transmission across species. This has serious implications for estimation of future potential incidence.

Reliable reporting of incidence and prevalence

within and across TSE infected species varies widely as well.

There is one state that has just started requiring that brain samples be taken by the state agents of any hunter's deer caught in that state. Some other states are doing something like that now. We are beginning to improve our tracking of CWD at least. That may not be true of any of the other TSEs.

There are a great number of unknowns. The wide confidence intervals that are called for and the resulting gross modeling estimates that have to be made as a result cause concern that FDA is focused on the proof of risk reduction through fractionation alone and they may miss the mark due to unknown factors or those known but not satisfactorily included in the model.

We, as representatives of the consumer community, deeply believe from past experience that the precautionary principle has never been more appropriately invoked than in an instance such as this where, once a threat bringing many knowns have been identified, efforts are being made to nevertheless identify selected safe practices within the threat arena.

It is in the United Kingdom that the vast majority of vCJD cases have been found. It is in the United Kingdom that the three cases of blood transmission of the

disease have been found.

Without regard for the modeling fractionation, it is in the United Kingdom that the health agency sent warning letters to hemophilia families, considering them among the highest risk groups for contracting the disease by virtue of their past infusion of fractionated clotting factor possibly contaminated before pooling.

Here it seems we don't even factor into our risk thinking the reality that people who eat beef give blood. While FDA concludes that U.S. licensed PDF factor VIII products probably achieve at least a four log level of CJD clearance, the discussions in the European Science Board as to the need for better data on the preclinical stages of the disease suggest the hemophilia population may be a good reservoir to collect such information, tacitly admitting that the UK government is correct, that we are in one of the highest risk groups and the risk was communicated through fractionated plasma.

It is important to collect blood from preclinical and clinical vCJD patients -- quote -- for use in assessment of the efficacy of blood tests and to assess the point in the incubation process where blood becomes infectious.

Blood collected from individuals -- quote -- at risk of vCJD for public health purposes -- unquote -- as

the 4,000 people receiving those letters in hemophilia households are now labeled, will provide a valuable source of blood for potential preclinical cases.

FDA's model is based in part on assumptions of low prevalence of BSE in US cattle. They quote USDA BSE data as if it were true without question.

Quote, draft risk assessment, page one. Because BSE occurs at an extremely low level in the United States -- parenthesis -- two native-born cows and one cow imported from Canada -- close parenthesis, close quote.

Yet the USDA's survey methods have drawn much criticism over several years. Stories like, one company slaughtered 350,000 animals in 2002 and 2003 and tested only three.

Inspector General details flaws in mad cow testing. USDA admits to 1,000 violations of mad cow rules. House committee presses agriculture officials on mad cow screening.

These have not been hidden stories. These have been all over the press for three or four years now. They reduced their testing last summer of one tenth of what it had been. What it had been was less than one percent of the herd tested every year.

There are folks that we have talked to, folks that we have in our organization, many that we can find on

the internet who will tell us the common practices among those in agriculture who think they may have an infected cow. That cow does not see the rendering plant. That cow gets buried. You do not want to risk losing your whole herd uncompensated.

So, we have to kind of act as though there might be some around, even though the USDA says no. The USDA itself says, their methodology was tantamount to a safety check on meat processing plants, not a search for the first sign of an animal disease of major potential threat to humans.

The USDA's mandate is animal health only. The FDA's is human health, assuring safe treatments for the sick and safe food for us all.

The FDA's methods should, thus, be by far more rigorous, if need be questioning even another federal agency's products when its charge is protection of human lives. theirs is the agriculture economy, especially when so much criticism has been raised about their methods.

There may, in fact, by one informed estimate, be in excess of 100 live BSE cases in the United States at the present to be slaughtered and eaten by future blood donors, among others.

In another example of what may amount to granting too much trust, hardly one of the tools usually found in

invoking the precautionary principle, FDA claims on page three of the topic II summary that the average four log reduction data that it accepts for industry would render products safe if there were known CJD positive donor units in the plasma used.

Research on various TSEs and surrogates for CJD behavior is dangerous. Spiking is needed. It is understood. CJD samples are rare.

In notes from the September meeting of the SCAC, the European TSEAC, if you will, preliminary evaluation of the specificity and the sensitivity of tests could be achieved using blood spiked with brain or spleen from vCJD cases, or blood from animal models. However, it is very important that the final evaluation include testing of blood from the vCJD cases.

I grant you, this is discussion of blood testing, not blood clearance. However, I think some of the concepts are very parallel.

As noted at the outset, we are pleased that FDA has undertaken this review, that it entirely warrants use as proof of safe practices, given the many areas of great uncertainty surrounding prions and the associated diseases.

Identification of strains of CJD other than classical or sporadic or variant have underscored this need for caution. BASE, bovine amyloid spongiform

encephalopathy, is an example, from the animal form of the disease.

Discussions of Alzheimer's disease as possibly being a TSE is another. We ask that you recommend revocation of the policy of exempting plasma collected from persons who have traveled to high risk areas for the CJD donor bans. Thank you.

DR. TELLING: Thank you, Mr. Cavenaugh. I think I have to move on now to revisiting the FDA questions for the committee.

MR. TEMPLE: Could I add a quick comment?

DR. TELLING: I am sorry. I didn't realize. Yes.

Agenda Item: Statement by Chris Temple.

MR. TEMPLE: I have no financial gain from any pharmaceutical manufacturer or entity at all. I am a dairy farmer. My name is Christopher Temple(?) and I am from Burborough, Pennsylvania, and have basically half my life spent in the agriculture industry.

As David alluded to earlier, if we have a downer cow, the biggest incentive for us to do is to get rid of it. A couple of years ago, I used to euthanize them, take them over to MOPAC, throw them off the truck, and you get rid of them for free. Now they charge you $200.

So, that is $200 to take it to MOPAC. It takes $5 worth of diesel fuel to dig a hole with a back hoe and kill

it and throw it in the hole, cover it up and it is gone.

Depending on if it didn't have any antibiotics, you take it to a custom butcher shop and you get the thing butchered and somebody eats it.

I was just at a cattle auction yesterday and you should have seen some of these ragged old cows going through the cattle auction.

I think the USDA is doing a terrible job and the USDA and the FDA need to work together. Every head of cattle needs to be tested and quarantined until the test result comes back.

As was pointed out earlier, the cigarette warning label comparison to factor warning label, people that smoke, if they get cancer, they chose to smoke. If they get cancer, in my opinion, too bad.

Somebody like myself with hemophilia, I was born with it. I take the factor, stop the bleeding. I get to live to see another day.

That is about all I really had to say. I think every head of cattle needs to be tested, whether the risk is super duper low or super duper high. It is a tragedy. One human life. Do any one of you kids give factor to your kid knowing that it could be infected?

DR. TELLING: Thank you for your comments. Are there any other comments? I am sorry, I should have asked

this before, in the open public hearing phase of the meeting?

If not, then I will move on now to revisiting the FDA questions for the committee for the second topic.

Agenda Item: FDA Questions for the Committee. Discussion.

MS. SCOTT: The first question is based on the variable scientific knowledge. Please discuss whether a minimum TSE agent reduction factor, demonstrated using an exogenous or spiking model and scaled down manufacturing experiments would enhance vCJD safety of the products. If yes, what TSE agent reduction factor is most appropriate?

DR. TELLING: So, I throw the question open to the panel for discussion.

DR. GAYLOR: I have a question about spiking experiments and the fractionation process. Fractionation, what is being assumed here is that we have a first order process, meaning if you spike high, say you start with nine logs and you get down to five logs, great.

Suppose you start with five logs. Will this same process get you down to one log or does it get harder to get an equivalent amount of reduction as you get down to lower levels that are more like the human exposures.

Can you still expect four log reduction? You get four log reduction if you spike high and bring it down. Are

you still going to get four log reduction when you start at very low levels?

Maybe the answer to this is known. Maybe the experiments have been done. I don't know. To add logs, can you go through the process twice and get an eight log reduction?

DR. MASTRIANNI: I don't really know the answer and I did ask this question myself before. I think it gets harder, but nobody could give me a clear answer last time.

So, I think basically it gets harder when the log of infectivity is reduced. So, you don't get the same benefit.

However, if you can guarantee four to six logs of infectivity reduction and you are already below what you consider a safe level, then I guess it is a moot point.

DR. TELLING: Laura, do you have any insight into that question?

DR. MANUELIDIS: Actually, it is sort of interesting you asked that. One of the first papers that we wrote that said that prions were not the infectious agent is, we found that there was aggregation of PRP and we found that we could keep reducing the infectivity by putting something through a column again and getting more and more abnormal PRP back but without the infectivity.

So, I think it is an extremely good question and

I think it is a difficult question to answer. Nobody really knows when you go down.

Again, this is one of the reasons why I am so interested in having a real sort of support for an effort on fast tissue culture models of infectivity that are sensitive enough to pick up low amounts of material and to be able to do these experiments in a timely way. It is an excellent question.

DR. TELLING: I think there is a comment or maybe a clarification.

DR. KREIL: There is only one comment that I would like to offer on the removal. If you started with a very high spike, you need to know that one log removal means removal of very much more than if you started with the lower spike.

Just to give you an example, if you went into a step with the six log challenge and you had one log removal, that is the removal of 900,000 of these units.

If you went in with, say, five log, then the removal by one log is only the removal of 90,000 units. So, that high challenge to be used for these steps is actually a very much worse case, because we need to remove much more to demonstrate a one log reduction as if you went through with a lower challenge.

DR. TELLING: Let me refocus the question. Do we

believe that exogenous spiking experiments have direct relevance to enhancing the safety of variant CJD, safety of the products in question?

DR. MANUELIDIS: I think if you are going to do a spiking experiment, why not do it with vCJD. Again, I am not talking about endogenous.

There are mouse models of vCJD and one can at least make that material. It is clearly a strain that is different from some of the other strains. Whether it is going to behave -- let's say in the murine model, it is one thing.

It is very consistent and everybody knows that that agent breeds true. So, if you are going to do spiking, why not do it with that. I personally would prefer, as I say, if you are looking at blood, you should look at blood.

Those models are in progress or available. They have been made in the United Kingdom. They have been made here. You should be able to make some plasma, at least see what the infectivity of blood is and what the infectivity of cells and serum are, for that particular agent.

I think that is probably a good start, because it is not going to be like sporadic CJD, which has a much, much lower infectivity in circulating blood.

The ideal would be to take blood from a known infected individual and to fractionate the material from

that individual and bioassay the infectivity using the most sensitive biological readouts, which would be probably transgenic mouse models.

So, develop both of those -- well, these materials appear to be not available. Certainly the biological assay, the ability to biologically assay variant CJD using transgenic mouse models, for example, is extremely difficult.

So, we are left with whether or not we believe using surrogate infectivity, such as SC235 -- did I say that right, hamster prions in any case, 263, sorry, 263K -- bears any relationship to how variant CJD, not from brain but in blood, would behave.

DR. MANUELIDIS: Again, Glenn, I don't want to disagree with you, but there are murine models of vCJD that are not transgenic.

The Edinbrough group doesn't have transgenic animals. They have actually just ordinary outbred mice that are infected with both BSE and vCJD.

DR. TELLING: Then the starting material is mouse.

DR. MANUELIDIS: It is mouse but with that agent, and that agent behaves differently than scrapie agents.

DR. TELLING: I couldn't agree with you more. Also, the plasma from mice, as we have heard from industry

representatives, behaves completely differently to --

DR. MANUELIDIS: It may behave differently for certain things that industry wants to give people, but it may not behave differently with respect to how the infectious agent fractionates. That is the key.

DR. TELLING: We now have those models? The data from those models is not available. We are discussing data that involves spiking from materials derived from experimentally adapted scrapie in hamster, and whether or not we believe that that is a relevant and accurate means of relating to variant CJD in blood. In my opinion, it may be the best that we have, but I don't think it necessarily equates.

DR. MASTRIANNI: I agree. We are limited in what we can do at the moment and the model isn't perfect, but it certainly is relevant.

It is using the same general agent. It may not be exactly the same strain, but certainly replication in other models would be of benefit to compare with what is more readily available. So, the vCJD models in mice would still be a valuable source of information.

DR. TELLING: So, I would be of the opinion that, whereas we should not abandon these studies because they could shine some relevant light, I am not convinced that they give us enough information to adequately address point

number two. Would anybody else like to comment? In my opinion, point A becomes moot.

DR. MASTRIANNI: Would you restate your opinion, Mr. Chair?

DR. TELLING: I think that you are right. It is not irrelevant to study these experimental models. However, whether or not they bear relationship to variant CJD infectivity in blood of human beings is a big unknown.

I think that it is too much of a stretch to use those data based on those assumptions to give a concrete number relating to point 1-A.

DR. MANUELIDIS: Yes, I agree. That is basically what I was trying to get at, the same thing. There are better models to be able to do that.

DR. TELLING: Do you think FDA can still label appropriately and appropriately, based on the label, it can be said that spiking and clearance studies have demonstrated this.

DR. MASTRIANNI: I agree. The spiked model -- I am sorry, the question on the spiking. The volume and what material you are spiking into blood, it is a volume of how much at this point, your small down scale system?

DR. KREIL: That will differ from process to process as it is investigated. Typically we are talking about a range of a liter roughly. That would be the

dimension.

DR. MASTRIANNI: So, what is to prevent us at least from taking variant CJD from brain of patient and putting it into a human blood, you know, one liter of human blood and do some spiking assays with that material at least?

DR. MANUELIDIS: Because there is no infectivity assay for that. There is only a PRP assay.

DR. MASTRIANNI: Why aren't there infectivity assays?

DR. MANUELIDIS: Because you can't inject human beings with vCJD.

DR. MASTRIANNI: You can inject mice as a bioassay.

DR. MANUELIDIS: There is a species barrier. So, basically your incubation time and your takes are going to be much less. From the literature, that is basically somewhere between 290 days and 500 days.

DR. MASTRIANNI: Well, currently all they are showing is western blots anyway. I agree that the bioassays need to be done.

DR. MANUELIDIS: Again, how much of a label do you want. When you are talking about spiking experiments you say, well, this cuts out the protein, but we don't really know about the infectivity. I think that is a more

honest way of labeling that product, then.

DR. MASTRIANNI: Again, it is an extrapolation. If you see a western blot and you can take the western blot data with animal data and then do bioassay from that data and extrapolate to the western blot --

DR. MANUELIDIS: But they haven't done the bioassay.

DR. MASTRIANNI: I know. So, I agree with your point earlier that somebody needs to do a bioassay. I think mice is not out of the question and cell assays are still not out of the question, and whether we can use a quick bioassay in cells.

DR. TELLING: So, you know as well as I do that the humanized transgenic mouse models are not going to reproducibly read out variant CJD titers; right? We could use certainly bovinized mice.

DR. MASTRIANNI: There is transmission to methionine mice.

DR. TELLING: To R3 mice? I think Laura is right, you have a species barrier and very long incubation times. I think that is one aggressive study that could be pursued and should be pursued in future years to address these unknowns, the developments of much more sensitive and reliable bioassay models.

I think probably also CDI could be used. There

are some very nice experiments from the Pruson(?) Group showing direct correlations between bioassay infectivity data and the CDI. I think you are right. If you are going to spike, why not spike with variant CJD brain.

DR. MASTRIANNI: Exactly, and then figure out how you are going to do the bioassay after, maybe develop better bioassays.

DR. ASHER: I just wanted to remind the committee that some of these issues -- these are important issues that you are discussing, some of which have been discussed before.

I think at our last two meetings we have stressed the fact that the absence of infected human blood, not to mention a validated assay for infectivity in human blood, both constitute tremendous problems for evaluating filters, for evaluating tests, and for evaluating reduction processes in plasma derivatives.

A number of other things -- and the WHO has as an official goal trying to develop collections of infected blood materials but thus far has had much less success, essentially none, compared with having limited success, but some, in developing human brain materials.

Another couple of things, transgenic mice, the sensitivity of transgenic mice for detecting human infectivity, including the bovinized and other mice, may

well turn out to be very good, but their sensitivity relative to a human being -- the sensitivity relative to each other has never been adequately examined, which is one of the values of having reference materials, so that the titrations can be compared in various models.

Finally, although in principle cell culture assays would be very attractive, in fact, so far as I know, neither variant CJD nor BSE agents have been adapted to growth in cell cultures, certainly with a usable read out.

Even those models that have been adapted to cell cultures, there are certain logistical problems, including loss of susceptibility to infection by the cultures and propagation of the agent to relatively low titers.

At least in this country there is an additional logistic problem in using variant CJD and BSE derived materials, and that is that they require containment facilities that, for most laboratories, are very difficult to support.

DR. MANUELIDIS: Actually, that is not true for vCJD because vCJD is under the CDC and has no other special things than other CJD agents. Only BSE is impossible to work with, well, almost impossible. You take your fingerprints and then you have to build a new laboratory and then you are not allowed to leave the laboratory for 19 hours, et cetera.

DR. MASTRIANNI: It still has to be handled under containment.

DR. TELLING: All prions do, but not under level three.

DR. ASHER: For the variant CJD?

DR. TELLING: That is correct.

DR. MASTRIANNI: It is BL2 with three practices.

DR. ASHER: We had to get ours past CDC and it took over a year. At any rate, the point is that there are logistical problems that make it more difficult to work with. I shouldn't have diluted it. We are going off on something of a tangent but there are logistical problems involved in doing this, but I am sure we all agree that modeling studies should be made as relevant to the practical problem as possible, and using the agents of interest or agents derived from them, in an assay as comparable as closely as possible to human beings would be desirable.

DR. TELLING: Okay, I would like to get a show of hands from the committee and a sense of what people feel about point number one, which will inform us as to whether we can actually move on to the other points in any meaningful way.

So, based on the available scientific knowledge, can we agree on whether -- who believes that a minimum TSE

agent reduction factor demonstrated using exogenous spiking models in scaled down manufacturing experiments enhance vCJD safety of the products. All those in favor of that? All those who agree with that?

DR. LILLARD: I am not sure what the alternative is.

DR. TELLING: I am just saying, based on the available scientific evidence, do we believe that is a meaningful means of addressing safety of vCJD in blood?

DR. MASTRIANNI: The phrasing is whether it would enhance variant CJD safety, not whether it is a meaningful model.

DR. TELLING: Believe it enhances vCJD safety.

DR. MASTRIANNI: Or illusion of safety. You know, I just feel it is a model, it is something, and it at least is close to -- it is better than putting in hepatitis B and trying to get infectivity out and assuming that that is relevant to variant CJD.

So, ta least it is the same agent that we are looking at, and ideally not the best system, but I think it does say something.

If you can effect a significant loss of infectivity after a procedure, to me, if I were having to take the product, I would feel more comfortable knowing that.

DR. HOGAN: The reason I voted for that, the issue here, we know the problems with the models used the problems with the starting materials and the problems with the assay. We have talked about that now for several times. The issue, does it enhance safety? Well, how much enhancement? Who knows, but probably some.

DR. GAYLOR: I would second that last comment. It is a pretty weak statement, enhance. Yes, I think so, but how much? Who knows.

DR. TELLING: I would agree it enhances safety, yes. Is there general agreement from the committee, then, that it does enhance safety? Do you want to move on to point number A then?

MR. BIAS: It probably does enhance safety? I don't know, if I were asked to do an up and down vote, I could say, you know -- you guys have a lot of scientific background you can weigh your answers on. I have to look in the face of a mom with an eight-year-old kid and say, did I do the best thing I could when I was sitting at this table? I can't vote on that.

DR. TELLING: Well, we will move away from the up and down vote, but let's just get a sense of how the committee feels in general. My sense is that the committee feels that, yes, it does enhance safety.

DR. HOGAN: Given the caveat that this is an

imperfect experimental model.

DR. TELLING: Dr. Powell, did you have something to say?

DR. POWELL: I just wanted to comment on part A under question one. I am sorry, I thought we had closed discussion on point one and I have a comment relative to point A under question one.

DR. TELLING: Okay, I have just been told that an up and down vote would be useful. You can vote yes, no, or abstain. Let's go around the table.

DR. FREAS: I will call out the names. Dr. Leitman, we are going to start with you. This is on question number one.

DR. LEITMAN: It is hard to have a very strong feeling about this because there have been no transmissions documented.

I listened to Dr. Kreil's presentation and his point was, whatever we are doing right now appears effective. The committee was not very happy with that conclusion because is a reactive conclusion rather than a proactive conclusion.

Still, there have been no transmissions. So, I find myself agreeing with the industry presentation that what is going on now appears to be effective. So, it is hard to ask for a higher log removal for increased

efficacy.

So, I am not sure that I Feel it would enhance the safety to set something other than what we have right now, which appears to be three-and-a-half to four-and-a-half log from the industry presentation. So, you want a yes or no answer?

DR. FREAS: Yes, no or abstain.

DR. LEITMAN: I think I am going to abstain.

DR. FREAS: Thank you. Dr. Mastrianni?

DR. GAYLOR: Some of us have to leave. Can I vote?

DR. FREAS: Yes, you can vote out of order. Dr. Gaylor?

DR. GAYLOR: I vote yes.

DR. FREAS: Is there anyone else on the way out? Dr. Creekmore?

DR. CREEKMORE: I vote yes as well.

DR. FREAS: Now I am going back to the order of the voting members at the table. Dr. Mastrianni?

DR. MASTRIANNI: I am sorry, I have got to say something just very briefly, though. I don't think this implies whether there is a bioassay done or anything. It is just implying if we can designate a minimum requirement of log reduction in TSE, would that enhance safety of the product, and I vote yes on that.

DR. FREAS: Ms. Kranitz?

MS. KRANITZ: I don't like the question. So, I am not clear that I can vote yes or not. I am going to have to abstain.

DR. FREAS: Dr. Sejvar?

DR. SEJVAR: I question strictly as the question reads, I would vote yes.

DR. FREAS: Coming around the table, Dr. Siegal?

DR. SIEGAL: I abstain.

DR. TELLING: Again, as the question reads, I vote yes.

PARTICIPANT: Could you read the question once more?

DR. TELLING: Based on available scientific knowledge, would a minimum TSE agent reduction factor, demonstrated using an exogenous spiking model in scaled down manufacturing experiments, enhance vCJD safety of the products. I am paraphrasing the question that is up here.

DR. FREAS: The next voting person at the table, Mr. Skinner.

MR. SKINNER: I vote yes, and the word minimum is what is important to me. I don't know what the alternative to minimum is. So, I vote yes.

DR. FREAS: Dr. Lillard?

DR. LILLARD: I vote yes.

DR. FREAS: Dr. McComas?

DR. MC COMAS: I would vote yes.

DR. FREAS: Mr. Bias?

MR. BIAS: I am going to abstain.

DR. FREAS: Dr. Powell?

DR. POWELL: I think I will also abstain.

DR. FREAS: Dr. Manuelidis?

DR. MANUELIDIS: My tendency is to abstain, but because the assay is not on infectivity, I have to vote no.

DR. FREAS: That is a no vote for Dr. Manuelidis. Dr. Colvin?

DR. COLVIN: I agree with Dr. Manuelidis, and I vote no as well.

DR. FREAS: Dr. Hogan?

DR. HOGAN: Given the caveats we have talked about, yes.

DR. FREAS: That is a yes vote from Dr. Hogan. There were five people who abstained, two no votes, nine yes votes.

DR. TELLING: Dr. Mastrianni?

DR. MASTRIANNI: I have a problem because I am not seeing that there is a requirement for proving infectivity there. It is not saying that you don't need to prove infectivity. It is saying a TSE agent reduction factor.

DR. MANUELIDIS: Is not safety infectivity?

DR. MASTRIANNI: No, I am saying, why does that exclude infectivity? Just because we haven't seen the data yet doesn't mean that we shouldn't see it.

DR. MANUELIDIS: That is why I said I would go for abstain, except that I think what is being used is something that has not yet demonstrated infectivity and, without that, I can't say that the current types of experiments have been helpful.

DR. MASTRIANNI: Well, it says available scientific knowledge. It is not data.

MR. SCOTT: Can I make a clarification? We have said in psst committee meetings, a while ago, admittedly, and we have currently only permitted labeling claims where we saw an infectivity readout.

I know that the studies you saw from industry, but many of those are not necessarily finished and they may or may not have been submitted to us for a clearance claim.

DR. TELLING: Thank you. It was my understanding that the assays involved were bioassays, and you are clarifying that. You just clarified that. There are bioassays studies; right?

DR. MANUELIDIS: In that case, I would say yes.

DR. TELLING: Since Dr. Rogalski-Salter was not a voting member, do you have any comments you would like to

make?

DR. ROGALSKI-SALTER: No, I think the information, based on where we are with the scientific efforts today, the information adds to the body of knowledge. So, I would vote yes.

DR. TELLING: Okay, I am going to move to point A. If yes, which I think we did vote yes, what TSE agent reduction factor is most appropriate.

DR. POWELL: On that, I have a comment. I think I alluded to in the previous meeting that I think we need to be aware of the implication of the log reduction factor when we are dealing with a continuous measurement metric of the ID50.

The implications of that are quite different from the implications when you have a discrete metric for viruses or bacteria.

An average concentration less than one per administered dose unit in the microbial viral domain means that a large fraction of those doses would be absolutely free of the contaminant. The same inference cannot be made when you are dealing with a continuous metric, the ID50.

DR. TELLING: Thank you. Any other comments?

DR. MASTRIANNI: I am not sure, just by saying yes to question one, that we can still answer part A.

DR. POWELL: Yes, I guess I got hung up on

question A. The reason I abstained is, if it had stopped at, would a minimum TSE agent reduction factor enhance VJD safety, I would have no problem answering yes.

I don't feel qualified to comment on whether that attaining a nominal minimum TSE agent reduction factor can be demonstrated by the means you stipulated.

DR. TELLING: So, does the committee feel comfortable stating that it is not appropriate to set a specific log reduction factor at this time?

DR. MANUELIDIS: Surely not with exogenous spiking. I mean, not with necessarily everything, but not with that particular model.

DR. LEITMAN: I would like to comment on the fact that the reason I abstained is that I couldn't give an answer to A. So, it seemed not productive to state that we should establish a minimum reduction factor when we couldn't advise the FDA on what that was, since there is not enough data to suggest that. I think we just heard that, but that might be one of the reasons for some of the abstentions.

DR. TELLING: I apologize if I was equivocal on that, maybe. You can change your vote if you like.

DR. LEITMAN: So, everything I know about viral reduction in the way one makes fractionated components suggests that one should establish a minimum log reduction,

but I couldn't find that in the material that was presented today.

So, yes, there probably would be a minimum reduction. So, sure, I will change one to yes, but not able to answer A based on data presented.

DR. TELLING: Just to clarify, my understanding of question one is its relevance to the spiking approach. FDA, does this render question number two moot or not?

DR. EPSTEIN: I think question two is moot if we do not have a recommendation to establish a minimum clearance level based on the exogenous spike.

The question here, we discussed after the voting that FDA to date has only allowed clearance labeling based on bioassay demonstrated clearance.

So, the question is, had that been the understanding before you voted, would you vote differently. If FDA had said, please discuss whether a minimum TSE agent reduction factor shown by bioassay using an exogenous spiking material in a scaled-down manufacturing experiment would enhance vCJD safety of the products, under that understanding, removing the ambiguity of whether we would equally regard results of immunoassay, would that have affected the votes.

DR. TELLING: Can I ask the committee that question directly?

DR. EPSTEIN: Sure. Is there anyone who would change their vote if the FDA had first clarified --

DR. MANUELIDIS: I already changed my vote on that basis.

DR. EPSTEIN: Yes, I heard that, but you were the only one who responded when Dr. Scott ---

DR. COLVIN: I would have to say yes, too, because then we have a real correlation.

MR. BIAS: I would change my vote as well.

DR. EPSTEIN: So, both of the no votes have disappeared. How about the abstentions? Would any of those who abstained?

MR. BIAS: Mine was an abstention.

MS. KRANITZ: I would also change my abstention to a yes.

DR. TELLING: We still cannot assign an absolute value, which I think is fine.

DR. EPSTEIN: We just need to record what was voted with the changes in votes, and I will just read it is: Based on the available scientific knowledge, would a minimum TSE agent reduction factor by bioassay, demonstrated using an exogenous spiking model in scaled-down manufacturing experiments, enhance vCJD safety of the products. So, that is the question that was voted.

I was a little bit losing count, but I think what

happened here, was it two or three abstentions turned to yes?

DR. LEITMAN: I think the entire committee voted yes. I was watching the process. You have no --

DR. EPSTEIN: Could we just have a quick show of hands to verify the count? Well, the other way around. How many abstain still? Two abstentions. Okay, how many vote no?

DR. FREAS: Just to give the names, Dr. Powell still abstains and Dr. Siegal still abstains.

DR. EPSTEIN: Then how many vote no with the modified question? Zero. We can assume that the balance voted yes.

Again, we usually require roll call votes, if it is unanimous, it is simple. Is it the unanimous opinion of the committee that the committee cannot recommend any specific reduction factor at the present time? Are there any who would disagree? Okay, so that is unanimous. I think that again renders question two moot.

DR. TELLING: So, with that, if there are any other points of discussion, then they should be raised now.

DR. EPSTEIN: The only issue, since we have only a small number of abstentions and no no votes, just for the record, why those who continue to abstain continue to abstain might be informative to us.

DR. TELLING: Let me ask Dr. Powell and Dr. Siegal.

DR. POWELL: Again, as I was just saying, I think a performance standard is always good in principle, but it often simply shifts the problem from now how do you demonstrate that you have achieved that performance standard.

Now, I don't feel qualified to speak to the laboratory experiments that would be necessary to demonstrate achievement of a performance factor. I could propagate that through a model given that this is the performance that is being achieved, what would the risk reduction be, but I don't have any unique knowledge on the experimental side to say, well, what demonstrates that that performance has been achieved.

DR. SIEGAL: I think if this were HIV I would consider myself qualified to vote one way or the other but, since it isn't, I would rather abstain.

DR. ROGALSKI-SALTER: Just a clarification question. By rewording this question, we didn't just negate the scientific information that is presented without the use of a bioassay, the information that was just presented. Is that correct?

DR. TELLING: My understanding is that at least a subset of that data was based on a bioassay. Am I correct

in that assumption? Yes.

DR. POWELL: The spiking versus the bioassay are two separate issues.

DR. TELLING: The spiking is just the input, and then the read out is --

DR. POWELL: Exactly, but the question about the relevance of spiking as well to the clearance mechanisms.

DR. TELLING: Yes. Is everyone happy? I want you to be happy. Is FDA happy? Okay, I am going to adjourn the meeting and thank you all very much, safe travels home and happy holidays.

[Whereupon, at 3:15 p.m., the meeting was adjourned.]