UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE

and the

BLOOD PRODUCTS ADVISORY COMMITTEE

+ + + + +

JOINT MEETING

+ + + + +

THURSDAY,
JANUARY 17, 2002

+ + + + +

The Advisory Committees met at 8:00 a.m. in the Versailles I/II Room of the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. David Bolton, Chair of the TSEAC, presiding.

PRESENT

DAVID C. BOLTON	Acting Chairman, TSEAC Chairman
KENRAD E. NELSON	BPAC Chairman
ERMIAS D. BELAY	TSEAC Member
JOHN M, BOYLE	Temporary Voting Member
MARY E. CHAMBERLAND	BPAC Member
DEAN O. CLIVER	TSEAC Member
STEPHEN J. DeARMOND	TSEAC Member
LISA A. FERGUSON	TSEAC Member
G. MICHAEL FITZPATRICK	BPAC Member
PIERLUIGI GAMBETTI	TSEAC
LIANA HARVATH	Temporary Voting Member
F. BLAINE HOLLINGER	Temporary Voting Member
RICHARD T. JOHNSON	Temporary Voting Member

PRESENT: (continued)

RICHARD J. KAGAN	Temporary Voting Member
JEANNE V. LINDEN	Temporary Voting Member
PETER G. LURIE	TSEAC Member
J. JEFFREY McCULLOUGH	TSEAC Member
DANIEL L. McGEE	BPAC Member
MARK A. MITCHELL	Temporary Voting Member
STEPHEN R. PETTEWAY	Non-Voting Industry Rep.
PEDRO PICCARDO	TSEAC Member
SUZETTE A. PRIOLA	TSEAC Member
TERRY V. RICE	BPAC Member
TOBY L. SIMON	Non-Voting Industry Rep.
DAVID F. STRONCEK	Temporary Voting Member
SHIRLEY J. WALKER	Consumer Representative
ELIZABETH S. WILLIAMS	TSEAC Member
WILLIAM FREAS	Acting Executive Secretary

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(8:04 a.m.)

EXECUTIVE SECRETARY FREAS: Mr. Chairman, members of the Committee and the audience, welcome this morning to this joint meeting of the Transmissible Spongiform Encephalopathies Advisory Committee and the Blood Products Advisory Committee.

I am Bill Freas. I'll be the Acting Executive Secretary for today.

At this time I would like to go around and introduce to the audience the members who are seated at the head table. They are, starting on the audience's right hand side of the room Dr. Jeffrey McCullough, Professor, Department of Laboratory Medicine and Pathology, University of Minnesota.

If the members would raise their hand as we go around so we could identify you.

Next is Dr. Mary Chamberland, Assistant Director for Blood Safety, Division of Viral & Rickettsial Disease, Center for Disease Control and Prevention.

Next is Dr. Peter Lurie, Medical Researcher for Public Citizen's Health Research Group, Washington, D.C.

Next is Colonel Michael Fitzpatrick,

Deputy Director Armed Services Blood Program Office.

Next is Dr. Stephen DeArmond, Professor, Department of Pathology, University of California, San Francisco.

Next is Dr. Daniel McGee, Medical University of South Carolina, Professor, Biometry & Epidemiology.

Next is Dr. Pedro Piccardo, Associate Professor, Indiana University School of Medicine.

Next is Dr. Richard Kagan, Associate Professor of Surgery, University of Cincinnati College of Medicine.

Next is Dr. Ermias Belay, Medical Epidemiologist, Centers for Disease Control and Prevention.

Next is Dr. John Boyle, Senior Vice President and Partner, SRB, Incorporated.

Next is Dr. Elizabeth Williams, Professor, Department of Veterinary Service, University of Wyoming.

Around the corner of the table is Dr. Liana Harvath, Director, Blood Resources Program, Division of Blood Disease and Resources, NIH.

Next is Dr. Pierluigi Gambetti, Professor and Director, Division of Neuropathology, Case Western

Reserve University.

Next is the Chairman of the Blood Product Advisory Committee, Dr. Kenrad Nelson, Professor, Department of Epidemiology, Johns Hopkins University School of Hygiene & Public Health.

Next is the Chairman of the Transmissible Spongiform Encephalopathies Committee who will be acting as Chairman of the entire joint meeting for today, and that is Dr. David Bolton, Head of the Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

Next is our consumer representative, Shirley Walker, Vice President of Health and Human Services, Dallas Urban League.

Next is Dr. Blaine Hollinger, Professor of Medicine, Baylor College of Medicine.

Next is Dr. Richard Johnson, Professor of Neurology, Johns Hopkins University School of Medicine.

Around the corner of the table is Dr. Suzette Priola, Investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories.

Next is our non-voting industry representative, Dr. Toby Simon, Chief Medical Officer and Chief Operating Officer of TriCore Reference

Laboratory.

Next is another non-voting industry representative, Dr. Stephen Petteway, Director of Pathogen Safety and Research, Bayer Corporation.

We will soon be joined in the empty seat by Dr. Mark Mitchell, President, Mitchell Health Consultants.

Next is Dr. Lisa Ferguson, Senior Staff Veterinarian, U.S. Department of Agriculture.

Next is Dr. David Stroncek, Chief Laboratory Service Section, Department of Transfusion Medicine, NIH.

In the empty chair we will soon joined by Dr. Carmelita Tuazon, Professor of Medicine, Infectious Diseases, George Washington University Hospital.

Next is Mr. Terry Rice, on the Board of Directors Committee of Ten Thousand.

Next is Dr. Dean Cliver, Professor, School of Veterinary Medicine, University of California, Davis.

Next is Dr. Jeanne Linden, Director Blood and Tissue Resources Program, New York State Department of Health, New York.

I would like to welcome everybody here

this morning.

And now I would like to read in the conflict of interest statement for this meeting, and it's a lengthy one.

The following announcement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting.

Pursuant to the authority granted under the Committee charter the Director, Center for Biologics Evaluation and Research, has appointed Dr. John Boyle, Blaine Hollinger, Richard Johnson, Richard Kagan, Jeanne Linden, Mark Mitchell, David Stroncek and Carmelita Tuazon as temporary voting members for this meeting.

Based on the agenda made available it has been determined that the agenda addressing general matters only. The general nature of the matters to be discussed by the Committee will not have a unique and distinct effect on any of the members' personal or imputed financial interests. However, the following interests are being disclosed so that the public can evaluate any comments made by meeting participants.

Dr. John Boyle is an unpaid trustee of the Immune Deficiency Foundation, IDF. His wife is Vice President of IDF. IDF receives funds from various

plasma product firms.

Dr. Boyle is also an unpaid trustee for PSI, a subsidiary of IDF which distributes plasma products. IDF has contracts and grants from companies which manufacture and distribute blood products. Dr. Boyle has no involvement with these contracts and grants.

Dean Cliver served as an expert witness regarding toxoplasmosis.

Dr. Lisa Ferguson is employed by the U.S. Department of Agriculture as a Senior Staff Veterinarian.

Dr. Michael Fitzpatrick is employed by the U.S. Army's Blood Program.

Dr. Suzette Priola has a patent with her employer, NIH, for inhibitors of formation of protease-resistant prion protein.

Dr. Stephen Petteway is serving as a non-voting industry representative. He is employed by Bayer and, thus has interests in his employer and other similar firms. In addition, he is the scientific advisor for Intersouth Partners and Biolex and holds mutual funds.

Dr. Toby Simon is also serving as a non-voting industry representative. He's employed by

TriCore Reference Laboratory. Dr. Simon and his spouse own stock in effected firms.

Dr. Peter Soul is a guest and is head veterinarian for TSE Team, Department of Environmental, Food and Rural Affairs in London England.

Dr. Hester Ward, a quest, is employed by the National CJD Surveillance Unit, Western General Hospital in Edinburgh, Scotland.

In addition, listed on the agenda as part of the Committee updates are speakers making industry presentations. These speakers are employed by industry and, thus have interest in their employer and other regulated firms. The speakers who were invited to make presentations on clearance of spiked TSE infectivity and protease-resistant prion proteins by plasma processing. These speakers were not traveled by FDA nor were they screened for conflict of interest.

The Committee will discuss general matters only. In the event the discussions involve specific products or specific firms for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the

public record.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current and previous financial involvement with any firm whose product they may wish to comment upon.

That's the end of the conflict of interest statement.

Dr. Bolton, I turn the microphone over to you.

EXECUTIVE SECRETARY FREAS: Dr. Goodman, could you come to the microphone at this time?

DR. GOODMAN: Good morning. It's a very large Committee here, and thank you all for coming.

And I'm up here today particularly to thank retiring members of both advisory committees. And as you all know, the FDA and the public as a whole use these advisory committees to provide outside expert advise from various perspectives that help us make important public health decisions.

The TSE Advisory Committee I think we all recognize is particularly important. Not only does this effect the Center for Biologics, but all the centers of FDA, the entire Department of Health and Human Services and very broadly public health and the

U.S. economy. Plus, it's a difficult area scientifically so we have frequently called on the TSE Committee and when relevant, the Blood Products Committee for help.

So these contributions have been very important. From my observations at some of the committee meetings I've been at, as well as reading transcripts and talking with others in the agency about your advice, I can say that advice has been good. It's been important and it's been used in agency and government decision making. So, I really do want to thank all of you who are here today as well as these retiring members. And I know that the Commissioner Dr. Schwetz and Kathy Zoon the Center Director feel the same way.

Today we have two retiring members, Dean Cliver and Peter Lurie who are here, and I would like to come up and join me. I'm very happy to present them a plaque and letter from the Commissioner of the FDA.

Peter Lurie. Peter, thank you very much. Yes, it says Dean Cliver, and I apologize. The plaque looks like Cliver. I'm sorry.

You want a picture. The famous handshake. Thank you.

DR. LURIE: Thank you.

DR. GOODMAN: Again, I thank you all, whatever your name is. But it does Cliver here, so it's my fault that I misread that.

Well, again, I'd like to thank both Dr. Cliver and Dr. Lurie for everything they've done. And this has been about, I guess over three years that they've been in the Committee since '98.

Okay. There's two people who aren't here today who are also retiring, and Dr. Donald Burke and Bruce Ewenstein. And maybe everybody could thank them for their work, too.

Also at the last meeting there are a couple of members who are also coming off the Committee who weren't able to be there, and I believe they're both here today. So I'd like to present them a similar token of our appreciation. And that's Dr. Marion Koerper and John Boyle.

So at this time I'd like them to come up and, again, thank them for the Center, for the Commissioner, and indeed for the public for their service.

Thank you very much.

And also Richard Kagan.

So first, Dr. Boyle. Thanks, Dr. Boyle.

Thanks for your service.

Thank you very much, Dr. Kagan.

And that's it. Okay. Dr. Koerper couldn't be here.

Thank you all very much. We can get on with work. Thank you.

CHAIRMAN BOLTON: Well, as Chairman of the TSE Advisory Committee, I also would like to add my thanks to Dr. Cliver, Dr Burke, Dr. Lurie, and Dr. Ewenstein who are stepping off of our Committee. Their work has been valuable both to the Committee, to the FDA and to the general public. So, I thank them for coming and sitting through many long meetings and enduring endless stream of Power Point presentations and other things to try to get to the heart of matters that are of concern ultimately to the general public.

We have an agenda today that's not too packed. I hope that we'll be able to stay, more or less, on time, although probably not meet all of our breaks. At least maybe ultimately adjourn by somewhere in the neighborhood of 4:30 go 5:30.

And with that in mind, I'd like to open the meeting and begin with the Committee Update, the revised FDA Guidance on Preventive Measures to Reduce the Possible Risk of Transmission of CJD and variant

CJD by Blood and Blood Products. This is an update of the final guidance. And Dr. Dorothy Scott will present to us this morning.

Dr. Scott.

Following Dr. Scott's presentation, we will have an open public hearing. I have three individuals who have requested time to speak at that, but we will also any comments from the public in open forum.

So, if you have things that you would like to say, please formulate your thoughts and be ready to come to the microphone.

Now, Dr. Scott.

DR. SCOTT: Good morning. I'm going to reintroduce the guidance. This is now the final guidance which as published early this month. It's the "Revised Preventive Measures to Reduce the Possible Risk of Transmission of CJD and variant CJD by Blood and Blood Products," and you can now find this posted on the Internet.

I just want to briefly recapitulate the history of geographic donor deferrals, which is the primary change in this new final guidance. However, I also want to point out that the differences between the draft guidance and the final guidance are mainly

technical. They're important but they are technical. We have kept the same donor deferrals and the same implementation times that were in the August draft guidance.

Just briefly the history of geographic donor deferrals. In August of 1999 we published a guidance which was updated in November of 1999 containing a recommendation to defer donors for variant CJD risk. And at that time this was defined as residence in the United Kingdom for 6 months or more between 1980 and 1996. You're going to hear a lot today concerning this 1996 cut off date for the United Kingdom.

In January 2001 this Committee met to discuss expanding these donor deferrals in the context of BSE spread to Europe as well as the increasing number of cases of variant CJD in the United Kingdom

In June 2001 you evaluated the risk and benefit of expanding geographic donor deferrals and you made recommendations which were incorporated in the final guidance.

In August we published a draft guidance incorporating your advice. And on January 9th we published a final guidance after a period of public comment.

Just going to review the donor deferrals in the draft and final guidance.

We had two phases of implementation to help attenuate the impact on the blood supply. And the first set of deferrals is here: Residents in the United Kingdom for 3 months or more between 1980 and 1996. And this, of course, is because of the variant CJD and large BSE epidemic in the UK.

Residents in France were 5 years or more between 1980 and the present. This is not only because of the French BSE epidemic which, to our knowledge, is not as large as the epidemic in other parts of Europe, but also because France is the only other country which has had variant CJD cases. It's also known that the French consumed a lot of British beef between 1980 and 1996, and it's believed that accounts for their variant CJD cases.

Residents on a U.S. military base for 6 months or more between 1980 and 1990 north of the Alps, there are four countries there, or 1980 and 1996 south of the Alps. There are five countries, I believe, there. And this is because U.S. military bases had the British beef to Europe program and so they consumed a moderate proportion of British beef, estimated worse case to be as high as 35 percent.

But, of course, in my places it was less than that.

And finally, a deferral for recipients of transfusion in the United Kingdom. Again, because of the variant CJD epidemic there.

The second phase of donor deferrals is for implementation in October 31, 2001 or by that time. And this is for deferral of blood donors who have lived in Europe for 5 years or more between 1980 and the present.

I want to point, and we'll be talking more about this today, that donors of source plasma for plasma derivatives who have lived in Europe for 5 years or more during this time period remain eligible. And I'm going to go through the rational for that, and we're going to hear some presentations that have bearing on that after the open public hearing this morning.

We know that model TSE agents are partitioned and removed during plasma fractionation. There's a moderate amount of published data in peer review journals which show us this, and these are model agents such as GSS in mice and hamster scrapie. Today we're going to hear some about the variant CJD agent partitioning during plasma fractionation, and this is not published data.

We also know that the European risk of variant CJD is low because they have currently a small BSE epidemic relative to that of the United Kingdom. Therefore, European donors have much less exposure potentially to the BSE agent.

In addition, the magnitude of the risk reduction that you can achieve by fractionation at a minimum is estimated to be approximately a couple logs greater than that that's possibly achievable by donor deferral.

And finally, we do have a concern that there would be an effect on nationwide and worldwide plasma supplies with the European donor deferral. Not because there are so many plasma donors in the U.S. that have been to Europe for five years or more, but rather because of the perception of safety of European plasma. That's also an issue that we plan to discuss further at future meetings, or we hope to discuss further.

I want to point out, because it's important, that source and recovered plasma are differentiated. That is people who donate blood from which plasma's recovered will be deferred because of the 5 year European deferral. And people who have lived in Europe for 5 years can still donate source

plasma. But this differentiation is only in order to prevent potential errors in the use of nonplasma components or cellular components from this whole blood collections from which recovered plasma is made. So, this is really a technical reason. We don't believe currently that there's any difference in the level of safety between recovered and source plasma in terms of the 5 year European donor deferral.

I also want to let you know that we will continually reevaluate this recommendation in the light of additional epidemiologic evidence, transmission studies for blood and for plasma and advances in understanding of the removal of TSE agents by manufacturing of plasma derivatives.

There were, certainly, some changes between the draft guidance and the final guidance, and I've listed most of them here.

The final guidance clarifies the reporting or the recommendations for biological product deviation reports.

There's donor question streamlining and we think improvements. We have our many public comments to thank for that.

We've clarified donor questioning methods and frequency.

We've added a summary table that you'll see at the end of the guidance which can help you navigate through the many complexities of donor deferrals and recipient notification, consignee notification and so forth.

We've also added definitions, additional references and we've articulated a general approach to non-European TSE.

I want to mention that again. I mentioned at the last TSE Advisory Committee. But as most of you know, the first case of endogenous non-European TSE was documented September 2001 in Japan. This was confirmed. The diagnoses was confirmed in the United Kingdom, and the USDA announced an import ban in that same month.

We believe, or we know, anyway, we have heard from news reports that meat and bone meal from the United Kingdom was shipped to many non-European countries. I think one of the Committee members on the TSE Advisory Committee asked me last time well what were these countries and how many were there. We don't have official reports. We only have news reports. But it look as if meat and bone meal may have gone to over 50 other countries on all continents except for Australia.

There are a lot of complexities to this and it makes it very difficult to figure out which countries might be at more risk for BSE. Because there's also trans-shipment. So even if the UK shipped to a certain country, you don't know if the meat bone meal ended up there.

And also we don't know how the meat and bone meal was used. It could be used for feeding to ruminants or cows, or it could have been used for feeding to fish or chickens. So, there are a lot of complications with figuring out whether and how to defer donors from non-European countries.

But at any rate, we feel currently that we need to assimilate the deferrals that we've recommended, and we need to consider in the future additional deferrals depending on the BSE epidemic and perhaps depending on additional information that we might be able to get.

I just want to mention that the spread of BSE emphasizes the importance of food chain controls, which will be discussed as part of topic one later on in the day.

We recognize that there are a lot of continued issues, and I don't think this final guidance is the ultimate final guidance.

We do need to evaluate the need for future deferrals.

We need to think about assessing food chain controls in the context of existing deferrals and possibly future deferrals.

We need to monitor prospectively and retrospectively the impact of deferrals on blood and plasma derivatives.

And, of course, we are continuing to monitor TSE blood and plasma transmission studies. The partitioning and removal of TSE's by plasma fractionation including variant CJD, diagnostic testing for donors and the epidemiology of these diseases.

I just want to introduce in advance the talks that are coming up. These are sponsored by the Plasma Protein Therapeutics Association, and there will be presentations on the clearance of spiked TSE infectivity and protease-resistant prion proteins by plasma processing.

As I mentioned, we're expecting some variant CJD data for the first time. Introducing the topic will be Mr. Healey, then we will be hearing from Dr. Lee, Dr. Vey and Kreil about the science and the experiments have been done to demonstrate whether or

not plasma processing can remove TSEs in variant CJD in some cases.

So thank you, and I'll take questions.

CHAIRMAN BOLTON: Thank you, Dr. Scott.

I will now open this up for questions from the Committee if anyone has brief questions for Dr. Scott about the update on the guidance.

While you're formulating your thoughts, I just want to thank Dr. Scott for presenting this, but there are people behind the scenes somewhere at FDA that take all of our sort of nebulas recommendations and our attempts to achieve something and they formulate this down into a document that's, hopefully, not always a half an inch thick.

But it becomes language that means something to lawyers and possibly not so much to us. But I want to thank them for doing that and trying to translate what we're trying to achieve, and I know the FDA is trying to achieve, into something that can be meaningful at a different level.

Questions from the Committee.

DR. BELAY: Dr. Scott, I was wondering if there's hope that the American Red Cross would potentially embrace the FDA proposal? Have you approached them recently or it might be a done deal?

DR. SCOTT: To my knowledge, we haven't spoken to them about this potential for harmonizing our deferrals. Jay might know more.

MR. EPSTEIN: Well, I think that's a question that has to be answered by the Red Cross. However, there have been informal suggestions that current leadership may wish to reconsider their existing plan.

CHAIRMAN BOLTON: Let me warn the Committee. It's a big Committee today. So if you have trouble getting my attention, you may have to waive your arms or jump or down, or something. Because I'm going to have a hard time discovering the entirety of the assembled group here.

Other questions? Especially those of you in the corners of my peripheral vision. Other questions?

Okay. Well, then we'll move on to the open public hearing. And we have three speakers who have requested time in advance.

The first of those is Dr. Robert Jones, who is President and Chief Executive Officer of the New York Blood Centers. Dr. Jones, you have the floor.

DR. JONES: Good morning.

With the release of final guidance on blood donor deferrals as a precaution for transfusion/transmission of variant Creutzfeldt-Jakob Disease we again assessed the blood supply horizon through the phases of implementation of this new policy.

At the October meeting, if you recall, in the immediate wake of the disasters in New York and Washington, blood donations were at all time highs nationally and the supply was far overrunning out ability to distribute for medical need. At that time it was hard to remember blood shortages or imagine that we would have any difficulty managing large dents in the donor base from the variant CJD deferrals.

Today, however, just four months after the largest surge of blood donations in history, we look at a depressing picture of blood donor apathy and rapidly dwindling supply that could, and probably will, soon impact the ability of our hospitals to deliver medical care.

The current picture goes beyond the usual pattern of soft donations and shortages that follow the holiday season or that accompany severe winter weather and seasonal illness. The compounding factors today include: The poor economy resulting from 9-11

and preexisting conditions leading to corporate layoffs and low community moral; a poorly defined general community malaise that is reflected in low charitable contributions as well as low blood donation rates; and, three, frustration with blood care organizations due to recent negative publicity as well as the attention on blood wastage after 9-11.

There are regional variations in severity with the greatest intensity being in New York and the Washington area. But informal surveys on my part indicate a national phenomena: a disturbing instability in the national rates of blood donation and supply.

For us we now see blood donation rates dropping well below levels experienced before 9-11 and our December whole blood collections were below our previous year. This figure here shows our whole blood collections up until August of last year. You see a very stable line, a very tight predictability factor here. And that was, actually, an unprecedented rate of donations, acceleration of donations over this period as we added capacity to collect more blood.

This slide includes those figures plus September and October. You see the huge surge in blood donations experienced in New York in both September

and October.

This slide shows to the present, including November and December. You can see there's been a huge drop off in blood donations in New York. We're sort of the canary in the coal mine here. We follow this data almost on an hourly basis. So, I'm sure that other figures will start to be confirmed from other blood carrier organizations as well.

This figure finally shows our projected. Given our current percentage of people showing up at blood drives and the blood drives we have booked, which would be up on this line, this is the rate we project over the next three months.

The black area you see here is May 31st of 2002, which is the date for the implementation of the first phase. So we're always keeping our eye on that date and trying to make sure that we're in the 40,000 per month range. And that's so we can, with the agreements we have from other blood carrier organizations, provide for the community.

Prior to 9-11 we were very confident that with the agreements for U.S. supply from blood care organizations such as ABC, BCA and the American Red Cross, plus our own collections growth that we would have no supply problems for the New York area

resulting from implementing the guidance released just in draft last fall.

As we now project this new reality into our planning, we are now much less confident. Our latest understanding from our Euroblood partners is that the Swiss and Germans will cease their shipments at the end of March. This is due to liability concerns on their part and their inability to implement the questions around residents in France.

What is most disturbing is the current instability and unpredictability of blood donations. We simply don't know whether our donation rates will return to previous levels and whether our existing agreements with other U.S. providers will be fulfilled to fill this void.

We are certainly doing everything we can to revive blood donations in our area. We assume all others are working similarly. However, we believe it is important for these committees to understand that there is some real danger that this situation could extend into the period of phase 1 implementation and that severe blood shortages could result both nationally and in New York City.

Given this, we urge the Committee to consider the following:

1: Advise FDA that current uncertainty around blood donations nationally warrants delaying phase 1 implementation until at least the date for phase 2. This would allow for a better understanding of how blood donation rates will stabilize.

2: Perspectively access specific triggers for modifying the guidance in order to adapt meaningfully to evolving events such as:

1: Low blood supply related to the deferrals;

2: Implementation of food controls assuring that the infectious agent is not entering the food chain; and

3: variant CJD attack and prevalence rates that indicate that the precautions blood donor deferrals that excluded so many willing donors worldwide are no longer necessary.

We continue to fully support and participate in the agenda to make America's blood supply as safe as possible. We also believe that continuous assessment of the trade offs involved in this agenda is necessary to avoid causing patient harm in the name of blood safety.

Thank you.

CHAIRMAN BOLTON: Yes. Dr. Nelson?

DR. NELSON: I have a question.

Shown on the graph are just collections in New York City. It does not include Euroblood, is that right?

DR. JONES: No, this is just our collections.

DR. NELSON: Is that the bulk of our supply?

DR. JONES: It does include Euroblood.

DR. NELSON: What proportion of the New York supply is Euroblood? It was around --

DR. JONES: Well, it's beginning to be a smaller proportion and it will become a very much a smaller proportion. But of our total supply it has been historically as much as 40 percent, now down to 20/25 percent range.

DR. NELSON: So at the same time there's a declining proportion that is Euroblood?

DR. JONES: Yes, that's been true for 3 years or more. But it's still substantial supply. That's why we've been concerned for, as you know, this Committee for some time.

CHAIRMAN BOLTON: Briefly. We need to move on to the rest of the public hearing.

DR. DeARMOND: Is there a brief explanation of how this dip in the New York blood supply predicts the changes throughout the country. Because New York seems to be atypical to begin with. They've required so much outside European blood.

DR. JONES: Well, the source of European blood and the reason we've had that is historic going back for 25 years or more. And in my estimation one of the reasons we're trying to replace Euroblood is because I believe it's always suppressed our own willingness to collect. So I don't think it's not related to that.

But related to the curve we see here, I get anecdotal reports that other people are seeing the same thing, maybe not to this extent, but we don't see the data. I think we're, again, the canary in the coal mine here and we're collecting this data much more intensively than other people. So, we may be having this data before others.

Do you have another question, please?

DR. LURIE: What the data show are a 20 percent increase in blood collection shortly after September 11th, right? And, in addition, there were all these people who were turned away whose names, I presume, you've collected before you turned them away.

DR. JONES: Yes.

DR. LURIE: I guess my question to you is given all of those resources, 20 percent plus of new names potentially, of many new names, how come you were so far at least unable to turn that into increased collections?

DR. JONES: We have been working diligently from day one. We had a list of 30/40,000 names. Our yield on that at the moment return is -- these are people who did not donate because we turned them away, is about 8 to 9 percent of those who have come back and made donations. This is after several attempts at calling, letters, carrier pigeon, whatever it was it took to contact these people.

We also have a discouraging rate of approximately 50 percent of the people who came in after 9-11 were first time donors. And that's, obviously, a group you want to try to embrace and get back. As we've done the same in contacting them, thus far -- this is about a month ago or so -- only one percent of those have come back to donate again.

We do have some time to see how that plays out, and further appeals will likely bring in more. But it's still a very low rate.

And this is not unusual. People in the

blood banking world who have seen disasters and have made similar efforts to get people back after the surge have also had similarly discouraging results.

CHAIRMAN BOLTON: Thank you, Dr. Jones.

As a personal comment, I am a regular blood donor. And I have to admit that I was due to donate in September and since there was a glut I didn't, and I have not been back to donate. And so I know how people get diverted and it's been difficult, I think, since September 11th to get back on track.

Our next speaker is Dr. Celso Bianco. Dr. Bianco, you have the floor.

I should emphasize the presentations are limited to 5 minutes and the presenters are asked to state any financial involvements that they have with any firms or products they plan to discuss.

Dr. Bianco.

DR. BIANCO: Hi. I'm Celso Bianco. I'm the Executive Vice President for American's Blood Centers. And my livelihood is totally derived from my salary from American Blood Centers.

America's Blood Centers is a national network of locally-controlled, non-profit community blood centers that collect about half o the US blood supply from volunteer donors. Collectively, we

operate in 45 states and serve more than half of the nation's 6,000 hospitals. America's Blood Centers' total blood collections exceed 6.7 million pints in the year 2000.

ABC members thank FDA for incorporating some of our comments into the newly published Final Guidance. However, some important questions remain unresolved.

One, we are concerned about the impact of the donor questions and the way they're formulated in the guidance. We hope that FDA will take into account the studies and proposals being made by the Donor History Task Force of the American Association of Blood Banks. We also hope that the Task Force recommendations will be considered in a speedy manner.

While there is opportunity for change by asking FDA for permission for the use of alternative procedures, these concessions, if granted, are not granted quickly. A community that is driven by regulatory compliance and appreciates the importance of prompt implementation of new guidelines will find it easier just to follow the new rules than to change them.

The other open issue is the actual impact that implementation will have on the blood supply, as

Dr. Jones just mentioned. When this Committee last October, we were still in the height of the public response to the September 11 terrorist attacks.

Blood bank refrigerators were full, we had two weeks of supply, and it was difficult for the public and even for some blood bankers to envision future shortages. However, the donors' enthusiasm predictably waned, and we now are back into a very severe post-holiday shortage situation.

We believe that these shortages are be.ng aggravated by he implementation of unjustifiably stringent deferrals by the American Red Cross, affecting about half of the blood collections in the U.S.

I want to reemphasize the position of ABC member center regarding variant CJD deferrals. They strongly believe that FDA made an enlightened decision in its approach to balance safety and availability. All but one of ABC's 74 member centers based in the United States plan to implement the FDA recommendations as recommended in the Final Guidance. Over 99 percent or almost 7 million collections made by ABC member centers will be performed according to the FDA recommended criteria.

ABC members want to reaffirm their support of

FDA as the agency responsible for setting the national blood safety guidelines. We strongly disagree with the more restrictive approach implemented by the American Red Cross because it may reduce the donor base by 8 to 9 percent without the benefit of additional protection. Both the FDA algorithm and the ARC algorithm achieve statistically identical protection from theoretical risk. The difference -- and it an important difference -- is in the donor loss.

ABC member centers have embarked on an aggressive donor recruitment effort that we call the Member Donation Initiative, or MDI for short. We have engaged a marketing consulting firm, performed extensive research on donor behavior, and developed an advertising campaign that is now being launched by the majority of the centers.

We have also been placing substantial effort to the recruitment of individuals who donated or who attempted to donate in the days following September 11. Our success has been, at most, modest. Our research, plus the experience of past events such as the Gulf War, the Oklahoma bombing suggest that most of these individuals promptly respond to national emergencies, but rarely because regular blood donors.

We are optimistic about MDI, and expect that our substantial financial investment will go a long way to help compensate for the expected donor loss caused by the variant CJD deferrals.

We also believe that blood availability must be monitored, in order to assess the health of the US blood system. We applaud HHS in its efforts to monitor the blood supply in hospitals and transfusion services. In order to complement this effort, we have implemented a system for monitoring the supply of ABC member centers. We call it "The Stoplight."

Every morning, through an automated e-mail system, members report the status of their inventory: Green, for a three day supply or more; yellow, for a two day supply; and red for one day supply or less. The results are compiled automatically and aggregate results, calculated for regions of the country that match those of the HSS survey, are posted on our website.

The system is being tested internally, and the data will become public in the next few weeks. Essentially, the public, the healthcare system and the regulators will have a daily picture of the status of the blood supply among ABC member centers by simply logging into the ABC website. It is important we

monitor the impact of the variant CJD deferrals, and take action to change them if the system cannot tolerate the donor loss without affecting healthcare.

Finally, we commend FDA and these Committees in their efforts to correlate variant CJD deferrals with the implementation of national policies on food chain controls. Let's not forget that the recommended pan-European deferral is additive. Donors who donate next November may take one more winter trip to Europe that prevents from donating in the following February and ever after. It is critical to increase the specificity of the deferrals by limiting them to the actual periods during which the theoretical risk is highest.

We ask that this Committee continue to evaluate the potential for transmissibility of variant CJD by transfusion. And we are encouraged by the lack of evidence of transmission as the observation period is extended, and by the recently published studies predicting that the number of cases of human variant CJD will be small.

We are also encouraged by efforts being applied in the development of tests for detections of prions in humans. We hope that epidemiology and screening tests will help us eliminate geographical

deferrals with limited specificity in the foreseeable future.

Thank you.

CHAIRMAN BOLTON: Thank you, Dr. Bianco. I apologize for mispronouncing your first name.

DR. BIANCO: Oh, no, that's fine.

CHAIRMAN BOLTON: Brief questions? Yes.

DR. SIMON: Dr. Jones in his statement called for the FDA to delay the implementation because of the serious concerns about blood shortages, and I would certainly echo that. From what we are seeing dealing with hospital transfusion services. Do you support that?

DR. BIANCO: I personally -- obviously, New York Blood Center is one of our members. That is the proposal that we made at the meeting of the TSE Advisory Committee this past October 24th -- or 25th, I believe. And that proposal was not accepted by FDA, so we have accepted the determinations of FDA in this latest published guidance. But, certainly, it would be a relief if we could delay the implementation for two reasons.

One, because it would give us room for keeping up with the donation process.

Two, because of the immense burden that is the implementation of new procedure for so many donors, that is we will have to prepare new SOPs, retrain staff and do everything so that the deferrals are applied appropriate twice in the year 2000. So certainly it would facilitate things. But we have accepted the FDA determination.

CHAIRMAN BOLTON: Other questions?

Okay. Dr. Bianco, thank you very much.

DR. BIANCO: Thank you.

CHAIRMAN BOLTON: Our next public speaker is Cheryl Hayden representing the National Hemophilia Foundation. Cheryl?

MS. HAYDEN: Good morning. My name is Cheryl Hayden. I'm the Director of Government Affairs and Blood Safety at the National Hemophilia Foundation, or for about a month I've been in that position.

The National Hemophilia Foundation would like to take the opportunity to thank you for our ability to provide comments on the guidance document. A written copy of the comments has already been provided to you, and I won't read it in its entirety, but just summarize it.

The National Hemophilia Foundation

commends the Food and Drug Administration, the Centers for Disease Control, the NIH and other areas in the Public Health Service, as well as the Department of Agriculture for the high profile that they have placed on preventing an outbreak of BSE and variant CJD in the United States.

We commend them for their aggressive multi-pronged approached for preventing these diseases in the United States, but however we remain concerned that the current guidance document which will be discussed today leaves patients with bleeding disorders vulnerable to an avenue of transmission by failing to require deferral of source plasma donation from individuals who would meet the donor criteria if they donated whole blood.

The reason for taking this position, which differs of course a great deal from the previous two speakers, is that of the experience of the population of individuals with bleeding disorders. In 1983 many of the same kinds of comments that people will use today, such as "theoretical risk," and the like were used to describe the possibility of individuals with hemophilia and other bleeding disorders contracting HIV and hepatitis through the use of clotting factor products.

And we know that that was not the case; that instead of it being a small theoretical risk nearly 10,000 people have died, and many more people continue to attend NHF annual meetings who are both HIV as well as HCV position. And for that reason the National Hemophilia Foundation urges the advisory committee to take the greatest care in making decisions that will protect this vulnerable population from a possible infection with variant CJD.

Thank you.

CHAIRMAN BOLTON: Thank you, Cheryl.

Are there any questions for Ms. Hayden? From the Committee? No?

Now I would like to open the microphone up to members of the public. And if you would, come to a microphone, give your name and affiliation. And, again, state any financial involvements that you may have with any firms or products that you plan to discuss.

Yes.

MS. O'DAY: Good morning. I'm Miriam O'Day. I'm with the Alpha-1 Foundation.

And individuals who suffer from the genetic lung disease, Alpha-1 antitrypsin deficiency are frequent and lifelong recipients of plasma drug

products. We support the final guidance with respect to plasma.

And I'd like to ask that this statement that we delivered to the TSE Advisory Committee in June of 2001 be resubmitted for the record because it still stands.

Thank you.

CHAIRMAN BOLTON: Thank you.

Next?

MR. SAYERS: My name is Merlyn Sayers, and I'm CEO at Carter Blood Care, which is the community blood program for the Dallas/Fort Worth region.

My blood program pays dues to American's Blood Centers of which Dr. Bianco is the Executive Vice President. I doubt that much of that money, though, contributes to his luxurious lifestyle.

I'm tempted by something that Dr. Bianco and Dr. Jones said to make the following comments.

Dr. Jones, in particular, made mention of why it is that donor recruitment is becoming increasingly difficult. And what I want to add to those difficulties is that at every turn it appears that as far as volunteer donors are concerned, we are increasing their level of disbelief when it comes to confronting them with reasons for their either

temporary or permanent deferral.

Bare in mind that something like 40,000 volunteers a day in this country donate blood. They're subjected to questions and testing which for many of them is an experience in intensity which is not even mimic in their annual physical.

Whether we like it or not, community blood programs are becoming centers of public health. And as such, it's important that the information that we give to them, particularly with regards to their temporary impairment deferrals, be information that they can immediately understand, appreciate. And it's important that it's information that they do not feel flies in the face of their own sense of good health.

When I think of the question in particular that Dr. Bianco referred to relating to deferrals for individuals which go from 1980 through to the present, it's inescapable that some donors, those visiting Europe, are going to earn deferral during their donation history. They'll be eligible for a donation on one occasion, they'll go and spend a couple of weeks in areas, well have topped out over their five years, and at the time they return for their next donation, we are going to permanently defer them.

The quality of the information that we

then give those individuals is going to be problematic. They're going to argue that we should have announced up front that they will be deferred at their next donation should they have spent time during the intervening between donation periods overseas. And they'll assume that the deferral that they have subsequently earned will be as a result of a hamburger that they had in Brussels during their most recent trip.

This is not an appeal for discontinuing any contribution to transfusion safety, but it is a reminder that whatever the new interventions are that are introduced, are going to be introduced or should be introduced in a way that's going to be most appreciated by donors recognized as contributing to transfusion safety and not just issues which are contributing to their increasing incredulity with the process.

Lastly, I'd just like to thank the FDA and the TSEAC for continuing to visit this really problematic issue.

Thanks.

CHAIRMAN BOLTON: Thank you. A question?

DR. SIMON: I'd ask Dr. Sayers since he's from the middle of the country and not from New York,

the disturbing news that Dr. Jones brought us that serious shortages are occurring and the future restrictions could cause serious harm to patients, do you see this happening also in the middle of the country in your area?

MR. SAYERS: Yes, we had an opportunity to look at two really disastrous events. Three years ago in Fort Worth there was what was referred to as the Wedgewood Baptist Church shooting. A gunmar went into a church, shot and killed a number of co:gregants. Needless to say, there was an outpouring of community anxiety, dismay and blood donation in the wake of that event.

So we compared and equivalent period of time after that tragedy with the period of time after 9-11, and we saw that something like 20 percent of regular donors who came out after the Wedgewood Baptist Church disaster returned to donate, as did 20 percent of first time donors who merged after that tragedy in the church.

It has not been the case with what happened on 9-11. Certainly 20 percent of the regular donors who donated around about that period of time have come back. But it's only 7 percent of the first time donors that have come back, and that's probably

average for first time donors in our blood program anyway.

We've actually gone back to those individuals who appeared at the time of that donation who were first time donors who have not come back and asked them why they haven't. And 40 percent of them said "Well, we thought you were throwing the blood away." And that was a disconcerting observation. But I think it is true that behavior is different for donors who respond to a local crises when you compare that to donors who respond to an awful tragedy, but a tragedy which happens remotely from their community.

CHAIRMAN BOLTON: Yes.

MR. CAVANAUGH: My name is Dave Cavanaugh. I'm Government Relation Staff for the Committee of Ten Thousand.

CHAIRMAN BOLTON: Please move closer to the microphone.

MR. CAVANAUGH: Is that better? My name is Dave Cavanaugh, I'm Government Relation Staff for the Committee of Ten Thousand. And I'd just like to reiterate a little bit some of the points that we made in our comments on the guidance that were not incorporated.

There's still issues, the FDA acknowledges

continuing issues and so do we.

One is the difference between the FDA's guidance and the announced intentions of one of the largest blood collectors in the country, the Red Cross. We're concerned that confusion between those criteria will defer people from even considering whether or not to donate. I take into account what Dr. Sayers just said about the types of criteria.

I understand if is more stringent, it's going to defer more people; that's the idea. We definitely favor the more conservative position.

The second comment we have with regarding the plasma exemption, and that's been mentioned a little bit already by NHF. We are quite concerned that the final guidance changes the draft language of "transmission of BSE has been experimentally achieved by transfusion" to "transmission of BSE appears to have been experimentally achieved by transfusion." We'd like to know what changed between last summer and now to weaken a finding that was prior to that.

The model for fractionation reduction is an incomplete model. It is based on spiking and does not go all the way through the process, in the words of the author of the published report on it himself. And therefore, I have to also reiterate that we are

concerned about the exemption of source plasma. There are a number of ways in which that could be a problem; this is merely one of them.

The guidance alludes to another one, which is confusion of whole blood collected that may be used in plasma and recovered plasma. Down the line this may happen. Down at the level of moving a supply. If you'll recall the error rate in use of autologous blood is well above 20 percent; that's why it should be tested and is not. So errors do happen.

The guidance admits that in terms of cleaning of equipment after processing of variant CJD blood there is no known decontamination method. There's steam, there's pressure; several are given in the guidance. But this is the same guidance that says it's okay to use source plasma, so we're concerned about this.

And lastly, as with the example on autologous blood, recalls do happen from the plasma production process. We have two in the last two weeks. They come with some frequency and they're related to some problems with CGMP that don't seem to go away overall. So, that's one more reason we would like very much for the Committee to be conservative and for the FDA to be more conservative in its

discussions.

We, finally the third point we make, requested that there not be a phased approach for some for some of the same reason, however our reasons were not based on the need to defer phase 1 until October in order to develop recruitment programs. We're saying if you want recruitment, get Dick Cheney on the television, get popular figures. I know there was a real problem in the fall between CDC's leadership, Surgeon General's leadership and the like.

And actually in a conversation with FDA about our comments, which were like 4 days before December 11th, we said can we get one of those figures on the television on the third month anniversary, because after that people are going to stop kind of identifying back with the disaster. And we even put out a press release on the 10th, a few days later, mentioning this problem regarding the lack of coordination, federal as well as the major processing organizations.

And to our knowledge, it seems to be a problem on the federal side, we know the coordination problems on the private side, that there's no agency responsible for increasing blood supply in this country; not CDC, not NIH, not FDA, not HRSA. And we

think that should be addressed.

Referring to October, you know, between the draft and the final guidance we had Japan with its first case. We also have learned in the final days that we now have variant CJD in the U.S., although the person was only visiting. Things will change, and the longer we wait, the riskier we're being with what's in the final product.

Thanks very much.

CHAIRMAN BOLTON: Thank you.

Are there any other speakers from the audience? Members of the public?

Steve, you have a question?

DR. DeARMOND: I'm not sure it's a question or a comment. It seems to me it's hard enough for us to make decisions about theoretical risks of varying CJD or BSE, or anything in the blood supply. And what I got from some of the readings that we were given and these comments from the last speaker, is that there are additional problems of misuse of 20 percent errors in the presentation of autologous blood; that there's a possibility that in the process of manufacturing or purifying plasma products that someone will make a mistake and contaminate the product at the end or in the process

of collecting blood that is going to be used for plasma, that someone will make the mistake and actually give that blood to somebody and therefore create a potential for transmitting variant CJD.

So, it seems like we have two problems. One is our charge to understand the theoretical risk and to make recommendations. And now another one that really sloppy methods out there can compound that. But that seems to be a different issue, and is that our charge also; to deal with deal with people making mistakes when 20 percent autologous blood, people making mistakes if blood is taken for plasma that they give it to somebody?

CHAIRMAN BOLTON: No, I think that's reasonable. You're looking at me for an answer. I think our charge is to recognize that the real world process of blood collection and processing is imperfect.

And that when we consider what things should be done to improve the safety, we have to recognize that the system is imperfect and built into that needs to be some compensation for the fact that errors are going to occur. And the question is how often will they occur and when they occur, how will they impact the margin of safety that we're trying to

build into the system.

So, I don't think we should assume ever that any of the systems that we work with that involve human beings and/or even those that involve computer systems are going to be perfect and without error. So, the protections that we build in have to account for that as well.

Yes, Dr. Epstein?

DR. EPSTEIN: Well, first, I think that Dr. Linden has data on error rates in blood collection and in hospital unit release. I believe there are more reliable figures that we could hear, if you have a moment.

Let me just answer Dr. DeArmond by saying that the FDA recognizes the importance of maintaining adherence to standards through good manufacturing practice, that we have periodically brought to advisory committee discussions on where we stand.

For example, at the last meeting of the Blood Products Advisory Committee we did a review of the current status of consent decrees in the blood industry.

We also are mindful of the problem of medical error, and there's a very large public health initiative toward reporting of medical errors,

assessing of medical error and developing improved strategies to reduce medical error. And at the FDA we are involved with the sister agencies in the public health in developing strategies related to transfusion error.

So, I think that all of your points are valid and from time-to-time there will be relevant questions that we bring to advisory committees, such as whether strategies that are put forward are, in fact, valid and useful and appropriate. But I do think that it would be important to hear a little bit of more accurate data from Dr. Linden if she's willing.

CHAIRMAN BOLTON: Yes.

DR. LINDEN: The error rate in the transfusion setting, be it either the collection side or in the administration side, is in the range of 1 in 10,000 or less in our experience. And we monitor this closely in New York. Yes, there are problems with autologous units. Perhaps at a slightly higher rate than other units, but basically in the same ball park range.

I believe that the previous speaker may have incorrectly interpreted American Association of Blood Bank Survey that found that 20 percent of

facilities had had at least one episode during a one year period. But that's not 20 percent mistakes if they transfused a 1,000 autologous, it meant one of them had a problem in 20 percent of the facilities. So I think that may have been a misinterpretation.

The rate is 1 in 10,000 or less, but it's certainly something we're very concerned about because it probably exceeds the risks of all the different transmissible diseases put together. And as Jay says, it's certainly something the agency does need to look at.

CHAIRMAN BOLTON: Thank you for that clarification. Certainly 1 in 10,000 is a little better error rate than 20 percent.

It occurs to me that from several things that were said by members of the public and our speakers that there is a need to educate the public in several aspects. And whether that initiative comes from the FDA or comes from the industry is not clear. And maybe a partnership between the two would be the most productive. But clearly the public needs to be educated continually on the need for donations for blood and really on the blood supply itself and how it comes to be available.

And I guess a companion issue in there is

the safety and/or health risks associated with receiving blood and blood transfusions and blood products.

This is not a regulatory issue. It's really an issue of education, and how that comes about I'm not certain. But I think it would be important for both the industry and the FDA to begin to formulate thoughts about how to improve the public's knowledge in these areas.

I think we've run close to our time for the public hearing. If there are any other speakers, would they come to the microphone. I see none.

Are there any questions from the Committee or comments from the Committee? Yes, Dr. McCullough.

DR. McCULLOUGH: When the Committee made the recommendations to the FDA there was a substantial discussion about the impact on the blood supply. We've learned a lot more since then about this, and national events have certainly changed the outlook.

And I guess we've heard more specific data now. So my question I guess is whether we know anything now that would cause us to consider anything different from what we have been thinking about our knowledge of the impact on the blood supply? There certainly is more information than we had at the time.

CHAIRMAN BOLTON: Colonel Fitzpatrick?

COLONEL FITZPATRICK: I guess the information is very difficult to interpret at this point. The compounding effect of 9-11 makes it very difficult to assess the impact of implementing CJD deferrals.

The miliary experience is similar to the civilian experience with large outpouring of blood donations after 9-11. The Department of Defense implemented the deferral at the same time about as the Red Cross, in October. So we have already implemented the FDA guidance.

We are seeing an increased requirement for blood collection to maintain inventories that we are shipping overseas, and we are maintaining those levels and trying to assess the impact of implementing the deferral policy. It's very difficult to because of "self-deferrals."

We know that it's a larger effort to recruit donors than it has been in the past, even in our circumstances that we're able to maintain the levels we need at the moment with a redoubling of recruitment efforts. And we've asked our facilities to assess the impact of the deferral. But getting good hard data is extremely difficult.

The information campaign to educate the donors about who can and cannot donate appears to be working because we're not seeing an increased deferral rate at the donor center of large proportion. There's an increased deferral rate, but not a huge one. But what we don't know is yet a long term impact, and it's too early to tell that.

We receive numbers from both ABC and the American Red Cross to look at the national inventory of blood. And while there is concern about the decrease in those numbers, as Dr. Jones has stated, if we compare those levels to the same time last year prior to 9-11, the blood supply is in better shape than it was last year.

So, there a lot of compounding factors that we really don't have a handle on yet in order to assess the impact of the deferral, the aftermath of 9-11 and what to me from a biased perspective from a Department of Defense level is going to be a continued increased need for blood in support of the operation.

So we are trying to monitor that closely, work with the Red Cross and the ABC centers. And while there may be spot geographic regions where there is greater concern than others, if we look at the national supply as a whole, while I would say there's

concern, I wouldn't say there is panic at this point.

I don't know if that helps or not.

CHAIRMAN BOLTON: Thank you.

Any other comments or questions? Yes, Dr. Nelson?

DR. NELSON: There's a special deferral for military service in Europe recommended. I don't know if that's implemented now. Has that had an impact or will it have more in the military than --

COLONEL FITZPATRICK: When we implemented, we choose not to phase the implementations. So we implemented the entire guidance at the same time. And we are deferring from within our own centers those individuals who were stationed in Europe, such as myself. And there is an impact, yes. There's been an increased deferral rate. And we've looked at focusing our collections and increasing recruitment at those sites where we recruit and train as opposed to those sites where we have stable populations that rotate frequently back and forth between Europe and the United States. So that's how we're addressing that today.

CHAIRMAN BOLTON: Yes, Dr. Mitchell?

DR. MITCHELL: Dr. Fitzpatrick, I wasn't able to follow. You said that you think that the

situation as far as the supply is concerned is better now than it was before 9-11. Are your donor collection rates, how do they compare now between now and before 9-11?

COLONEL FITZPATRICK: Well, we've had to increase our collection rates about 25 percent to meet the requirement to ship blood to Southwest Asia and Europe in support of the operation. So we gear our recruitment to meet a normal health care need, and then a contingency need for shipments. So we've been able to incorporate that increase without having to impact the civilian blood sector by either purchasing or asking for blood from the civilian sector, and been able to meet that need within the Department of Defense.

CHAIRMAN BOLTON: Okay. We're beginning to run short on time, so brief questions if they're right to this point on the guidance, changes in the guidance. Okay.

Yes, Doctor?

DR. LINDEN: Well, relevant to the questions of current supplies, I think it would be useful to the Committee if we could get some data. If there's anybody from Red Cross, they have implemented the guidance already. In fact, even more stringently

since October. I'm wondering how they're doing with their collections. And also I see Dr. Nightengale is here. Since they are doing monitoring of the supplies of the nationwide, do they have data that show what the status is presently? I think that would be useful.

DR. STRONCEK: I guess I do want to make a comment. I think that looking at Red Cross data is a waste of time. I think after the events of the 9-11 the Red Cross over collected blood for several weeks. They then had to outdate a lot of that. That's been well publicized in a very negative way by several major newspapers. And I think that compounds all of this issue on whether or not we have a real shortage. Because that message is out that blood was over collected. And it's going to take several months before that message goes away and this all washes out.

So to look at three months worth of data where there's been so many mixed messages I think is just a waste of our time.

CHAIRMAN BOLTON: Well, I will concur at least in part, because it's not going to be resolved at this meeting in the next 15 or 20 minutes. What I would like to say, and then I will give Dr. Jones one minute to comment, is that in response to Dr.

McCullough's question, something that we know now that may be we probably knew or maybe it wasn't quite at the level of our perception yet, is that with the recent events in Japan we can see that looking down the road things are probably going to get worse rather than better. It's very likely that more countries will experience cases of BSE, and then we will revisit this issue again, and again as time goes on.

If we're very lucky, things will not get worse and they will stay the same. But it's very likely that the issue of donor deferrals, the issue of the questions of exposure to BSE in the food supply of other countries, therefore leading to potential risk of variant CJD in the populations of those countries or visitors to those countries will become more of a concern as time goes on.

So we are at a point now where things look bad, but they get worse. So it's important, I think for those in the industry to recognize this and while it might be nice to think about deferring or delaying the implementation of the guidance, that is a process that might help the collection part of the equation, but does not help the safety part of the question.

So we've spent a lot of time in this Committee hearing testimony, if you well,

presentations both scientific and on the economic side and the result of all of that deliberation is the guidance as presented. And I think the best thing that we can do now is to go forward for a period of time and see how things work. And I'm sure that we will revisit this, if not at our next meeting, we'll probably revisit it very shortly after that.

Dr. Jones.

DR. JONES: I just had one last comment on the issue of supply versus donation rates. What I've showed from our data was our donation rates and the actual blood donations, it didn't really reflect our supply. Although our inventories have dropped from a 40,000 level, you know, peri-9-11 down to around 13,000. It's a reflection of future supply, these donation rates. And that future is somewhere in the month to two months out as inventories get depleted and those donation rates are still not back to replenish the supply.

So, even in New York, we have cut our shipments of O negative blood and other Rh negative blood, but overall the supply remains okay. Even better than it was before 9-11 -- well, it was about a little bit less than it was before 9-11. But the point is that these donation rates do not reflect

supply today. They effect supply a month to two months from now.

CHAIRMAN BOLTON: Okay. This concludes the open public hearing portion of the meeting.

And we're going to move on now to a Committee update. This is a PPTA presentations on clearance of spiked TSE infectivity and protease-resistant prion proteins by plasma processing. Dr. Christopher Healey will present the introduction.

MR. HEALEY: Good morning. My name is Chris Healey, and I'm the Executive Director for PPTA North America.

PPTA is the trade association and standard setting organization for the producers of plasma derived and recombinant analog protein therapies. As you all are well aware, these therapies are used to teat hemophiliacs, persons with primary immune deficiency, individuals with genetic emphysema and the producers of albumin also are used to treat shock and trauma, and other related conditions such as that.

PPTA and members companies, PTTA is a global organization and our member companies include Alpha Therapeutic, Aventis Behring, Baxter Biscience, Bayer Corporation, Grupo Griffolds, Octofarma and ZOB.

We stood before you last June and

presented information, and we're here again today. Our mission once again, like in June, is to try and help inform your decision process or your thought process on these issues, not to advocate for any particular outcome.

I can tell you that our member companies take the issue of TSEs, BSEs and CJD very, very seriously and we're doing a number of things to address it.

First, we have long established a number of expert working group, both on scientific issues and in public policy issues designed to help foster sharing of information among companies where appropriate and to develop materials that will help educate all stakeholders about the true nature of TSEs.

Second, we have conducted and are in the process of conducting a series of workshops around the world where we bring together some of the leading researchers on CJD and have an open and frank exchange of research information and ideas about CJD. Our first workshop was held in the spring last year in Brussels. Most recently we held a workshop in Washington, D.C. in October. And our next is slated for March in Tokyo.

The third way we're addressing it is to maintain an ongoing dialogue with regulators around the world making sure that we provide all available and appropriate information to regulators and public health officials around the world, and to gain as much information as possible about the nature of this still theoretical risk.

Fourth, and most important, is of course the research that's conducted at our member companies. Our member companies are home to some of the world's leading prion researchers, and that's why we're here today is to hear from those individuals.

You'll hear from Dr. Doug Lee whose the Director of TSE research at Bayer Corporation. You'll also hear from Dr. Martin Vey, whose the head of the prion research laboratory at Aventis Behring. And finally, you'll hear from Dr. Thomas Kreil whose the Director of Global Pathogen Safety at Baxter.

I think once they get through their presentations you will see that despite varying research methodologies and research materials, all of the data points in one direction; and that is that the process of fractionation leads to robust clearance of prions.

So I'd like to turn the microphone over to

Dr. Lee first.

And if you'd indulge me, I'd like to ask the panel to please hold your questions to the end so that we can be sure you get the appropriate person responding to the questions you may have. Thank you.

DR. LEE: Thank you.

I'd like to thank the Committee for taking the time to listen to our research and what we've done a Bayer Corporation.

What we have currently on the screen are the list of researchers responsible for the work that you're going to see today that I will present. Myself, of course, Dr. Stephen Petteway and Dr. Chris Stenland and Dr. Jeannette Miller.

What I'd like to demonstrate or show to you today are pieces of data from our laboratories that demonstrate reproducible partitioning of rodent-adapted prions or PrP. We'd like to show that partitioning of PrP by either a process in a coupled series versus those performed independently are the same. Demonstrate, of course, the utilization of the in vitro assay for measuring removal of PrP compared to removal of TSE infectivity or actual infectivity are one in the same, an additive. That partitioning of rodent adapted PrP^{Sc} is predictive of partitioning

of different forms of human CJD as well.

This slide is to show you several different species that most of you are aware of of various TSEs. The ones, the humans, the rodents and the sheep TSEs are all model system that we have used or species model systems that we have used in our laboratory.

This is summary slide of our in vitro assay, the Western blot assay which we have published and is out in the public domain. It's a Western blot assay specific for hamster 263k. It uses the 3F4 antibody, which does cross react with human CJD prions, and it's allowed us to do our variant and sporadic CJD partitioning work with the human material.

The titrations of PrP^{RES} are linear, which are consistent with the bio assay, and this linearity is reproducible. The graphic on your right hand side just demonstrates the ability to measure one log differentials of using the Western blot assay.

It's very important when performing partitioning studies for CJD or any pathogen safety assay or clearance study that the simulation of the manufacturing process be accurately represented at the laboratory bench. And this is just a few notes here

to show we first take the manufacturing process, scale it down to an experimental step that can be performed in the laboratory scale.

We then take it and whatever the process is that we're looking at, spike the input solution and immediately remove what we call a prove sample, which is our reference point for all the other fractions that then will come out.

We perform the separation, and then remove samples from the resulting, in this case represented here, in effluent and precipitate.

By convention what I will be presenting today is clearance with respect to the effluent. In other words, the numbers that you see regarding clearance are the prove values minus the effluent values.

Finally I think it's important to note that we are very careful in our simulations. As I said, you have to accurately represent that manufacturing process. And what you see the bar chart on the far side, it's just one way that we do that. And that is we take several marker proteins, compare those to the manufacturing process, either historical data or we'll actually go and take samples directly off the floor and compare that to our laboratory

simulation.

This is one example of PrP^{Sc} partitioning as performed with the Western blot. Our proved sample in this particular case was spiked with PrP, and you can see that in the top Western blot panel. Remember, that represents one sample which has been diluted out, and that's how we make our measurements.

The effluent demonstrates no reactivity. And the effluent in this particular case is our target protein is located in that, and then the precipitate is at the bottom demonstrating recovery of our PrP.

The last slide demonstrated very effective and significant clearance. This slide represents a low level of clearance for the cryoseparation. Remember this is clearance relative to the effluent. And what you see here or the other demonstration here is besides that we're seeing about a one log clearance for the cryoseparation, we're also showing the ability to perform in vitro assays is so more readily available. We're able to get multiple replicates much easier than can be done with a bioassay. Once we have data with Western blot assay, we at Bayer typically follow that up with a bioassay in order to confirm the known.

Finally, this is a 3 percent polyethylene

glycol cut that we do for our factor 8 product. This is what we consider a midlevel or intermediate level removal of the prion protein. And in this particular case there was more variability, but the average was about 2½ logs clearance.

It's important or it was important during the course of our studies, which have now gone on for approximately 5 years, to look at how the measurements made with the Western blot correlated with those with infectivity. And what we basically did was spike with the hamster 263k. Remember that is our rodent model of choice. And directly into a process solution. Remove samples immediately and simultaneously measure the Western blot and then sent the other samples off for analysis with the bioassay. These analysis were done by both laboratories at BioReliance as well as those by Dr. Richard Rubenstein at Staten Island Laboratories.

This, again, is the 11.5 percent PEG step I showed you earlier which demonstrated significant clearance. The bar graph on your left represents the bioassay or infectivity and the bar graph on the right represents those data collected with the Western blot.

In both samples where the bioassay which was done in replicate, in no case did we detect

infectivity in that effluent; likewise, we did not detect PrP with the Western blot, and we did detect both infectivity and the prion protein the resulting case.

This is a summation of several slides. And remember, this is clearance that we're detecting with either the Western blot, which is shown in the dark bars, or the bioassay which is the lighter bars. And what we demonstrated or what we were hoping to show you here is a lot of data collected over a lot of years where we've seen that clearance as observed with Western blot is similar to or even equivalent to that as we observe with the bioassay or measuring clearance of infectivity.

These are several steps in the cone fractionation process, as well as other steps, actually, that are part of our plasma derived product scheme. And you see varying levels of clearance is process dependent. And we actually have done a lot of bioassays as well.

The next set of studies I'm going to show you addresses the questions of we performed a lot of these studies with the process steps done independently or outside of the box of if the box is defined as our processing or manufacturing processing.

What I want to show you now is a series of studies where we put all these processing steps together, linked them together as they would normally be performed, scaled them down quite a difficult task, but it was done in our laboratories, and then spiked in one place, that is the pooled plasma and monitored both either infectivity or the prion protein throughout the process. These are the process steps. We spiked, as I said earlier, at the pooled plasma step, performed the cryoseparation, fraction one step and the fraction three step you see at the bottom results in our immunoglobulin product and beyond fraction two plus three are the alpha, the protease inhibitor products, a couple of others as well as the albumin.

Once we spike, we perform it and we measure sequentially as these samples are obtained the resulting fractions for either the bioassay which were sent off to do or the Western blot use and measured the PrP partitioning.

In this particular example I'm showing you, you're seeing approximately 5.2 logs of PrP detection in the prove. Approximately one log clearance relative to the effluent. Now for your reference point fraction one now becomes or the

fraction one step the cryoeffluent becomes the spike or the input material for the next step.

Again, as we've seen in independent steps, we see approximately one log clearance.

These are all the numbers obtained for this Western blot study, and you can see by the time you get beyond effluent 2 plus 3 or faction 3 you wind up with essentially no detectable PrP.

The data I'm showing you now is work we did with the Western blot and clearances detected with that. We've done this study or this work also with infectivity and measuring of the bioassay with similar results.

So in summary, the PrP Western blot assay we've demonstrated can measure clearance of PrP^{Sc} over a 4 to 5 log dynamic range. There is a correlation between clearance of the protein and the clearance of infectivity in plasma and biotechnology processes. The material or the assay is reproducible in significant in terms of clearance for experimental TSEs or as in the result of these types of processes, and partitioning determined for independent steps is consistent with what we've seen when you perform these steps. They're normally done independently within the series.

I'd like to now move beyond the hamster 263k and look at some of our model relevant studies that we've done also in the laboratory.

Using human CJD both sporadic GSS -- it's not CJD but GSS material as well as variant CJD, we performed studies with using the Western blot to measure clearance. We've utilized three different steps, the cryoprecipitation, the three percent polyethylene glycol cut, as well as the 11.5 percent PEG step which demonstrate low, moderate and high clearance respectively.

We've also performed these same studies using sheet PrP^{Sc}.

The results are shown here. The process steps are shown on your far left and then the various models are shown across the table. In all cases, whether you're talking about human variant CJD, sporadic, human GSs, sheep or hamster you get approximately the same clearance for each of the steps.

In addition to the studies I've just shown there talking about the human material or the human condition, we've also completed several studies looking at spiking preparations. And we've taken different spiking preps, specifically the crude

scrapie brain homogenate, the microsomal preparation and the Bolton prep and performed these same studies; the cyro, the 3 percent and the 11.5 percent PEG pay step and the results basically demonstrate that the more purified forms of PrP^{Sc} resulted in greater clearance.

It's important to note we typically spiked with brain homogenate, which as it's shown to be is the worse case scenario.

So again, in conclusion, I'd like to say that what we've seen in our laboratories and others have shown is that partitioning of the rodent prion protein is predicted of partitioning of infectivity, and that partitioning of the pathogenic form of the prion protein determined with animal models is predictive of removal of human prions, whether they be from a classical source such as sporadic or variant sources.

Thank you.

MR. HEALEY: Next is Dr. Martin Vey from Aventis Behring.

DR. VEY: Good morning. I also would like to thank the Committee for listening to the data we obtained for prion proteins in our manufacturing processes.

As Dr. Lee already pointed out, purification of plasma proteins involves a series of purification steps all linked up in the Cohn fractionation backbone and in further downstream purification processes.

The Cohn fractionation background and the cryoprecipitation provide enriched fractions; cryoprecipitate, fraction 1, fraction 2 plus 3, fraction 4, fraction 5 in which the plasma proteins are already concentrated to a certain extent. From here further purification steps provide then concentrates, factor concentrates and immunoglobulin concentrates which can then be used for therapeutic applications.

In order to address prion removal, we also scaled down production steps and determined equivalency of this scaled down protocol with the large scale production. We then add prion preparations to an aliquot of the original production loss and we perform single or several combined scaled down production steps.

We determined the prion content of the spiked prior starting material and the resulting fractions such as precipitates and supernatants by an assay called conformation-dependent immunoassay which

was developed by Uri Safer and Stan Prusiner's lab. And for some steps we have started doing infectivity bioassays.

We determined reduction factors for the individual or combined production steps, which are usually expressed in log dimensions. And, again, similar to Dr. Lee, we compare or we relate our reduction to the petitioning away from supernatant and fractions.

So if one combines the reduction factors for all production steps involved in the purification of a single plasma protein, one can determine the total prion removal capacity of the whole production process for that particular protein.

So, there is a challenge for prion removal evaluation for plasma proteins, and this is the following.

Prions have never been transmitted from human to human by blood or blood products and yet normally for the prion protein, called PrP^{sc}, which is believed to be the infectious agent, has never been detected in blood or plasma. So the biophysical chemical nature of a theoretical prion contaminant is not known. Also a relevant spiking agent mimicking this theoretical prion contaminant in plasma is also

not known.

So we addressed this challenge in the following way. We prepared different prion preparations with different biophysical chemical properties and evaluated their partitioning in our processes. By this approach we tried to cover all possible or all logical presentations of a prion contaminant in plasma.

And if there is significant differences in the partitioning of these different spikes, our production steps that we'll analyze must be evaluated with these different spikes because we don't know which one is the more relevant or are their contaminants which present as one of this and one of this or both of these spiking agents.

And this will then lead to a greater assurance about the safety margins of our products with respect to the unknown theoretical prion contaminant. So we're used to following spiking agents. Crude brain homogenate, microsomal membranes, which is a fraction of brain, caveolae-like domains which are a submembrane compartment and yet we use cyro for purified PrP^{Sc}. They were all prepared from pre-infected hamster brain.

This is one example for the purity of this

pure type PrP^{Sc}, and this is a tribute to David Bolton who in the '80s developed this method to generate membrane-free pure PrP^{Sc}. And this one we use as an extreme example of a pure prion contaminant. And you see it still works.

So the rational for selecting these spiking agent was although brain homogenate may not resemble the theoretical prion contaminant, we choose it because we felt it was important to compare our data to already published data from others.

The microsomal membrane fraction we thought would be more relevant because they might mimic prion containing cell fragments which were not already removed by the plasmapheresis.

CLDs, these caveolae-like domains might stimulate membrane domains which could be shed into plasma by cells. And what if the prion contaminant is not associated with membrane fragments? There was evidence for some of the prion infectivity in rodent models. Infectivity in rodent models that some of the infectivity of the low infectivity which was found there might not be membrane associated. And for that purpose we used purified PrP^{Sc} to simulate those kinds of prions once they were in this kind of biophysical chemical entity.

So your initial experiments already indicated that this made good sense. Because if you compare side-by-side in the same process purified PrP^{Sc} and microsomes there's a completely different behavior for these two spiking agents. Microsomes were comparable to the Foster study, lower than one log removal. And they also differed a little bit with respect to the Lee study, but there was a major difference between purified and membrane-bound PrP^{Sc}. We now systematically analyzed the Cohn fractionation backbone with this rational.

So you can see here that for the cryoprecipitation the prion reduction of any membrane containing spiking agent is insignificant. It's less than one log. Whereas, PrP^{Sc}, as I already indicated, there we see a significant reduction, more than two log into the precipitate.

For the 8 percent precipitation, 8 percent ethanol precipitation, you can see that the reduction factors now are increased also for the membrane containing spikes, but still they do not match the partitioning behavior of a purified prion spiking agent.

We compared here, of course, the spiked starting material with the supernatant after -- which

comes out of the process step. And here you can see that. We not only can see the reduction away from the supernatant, but it also appears, reappears in the precipitate fractions. We have also a very good mass balance, so we know where the prions ended up.

In the 25 percent precipitation now the membrane containing prion spikes also show very significant reduction away from the supernatant, as is the case again for the PrP^{Sc}.

And for a step involving 38 percent ethanol precipitation, we see complete reduction of all these different spiking agents.

Taken together we can say that evaluation of four major steps of fractionation backbone reveals robust prion removal for certain production steps and for all spikes, but that they are also clearly shows that different spiking agents can partition differently at a certain production step. So in general we found that the three membrane associated spikes partitioned similarly whereas PrP^{Sc} the non-membrane associated molecular spike partitions differently at different steps from the other spiking agents. From now on our evaluations included one membrane associated spike which shows morosomal membranes and the purified molecular form PrP^{Sc}.

We come to the evaluation of the downstream purification processes for our product Humate P® which is a Factor VIII from von Willebrand. You can see a list of steps, of purification steps and modification steps which is used to make concentrated factor therapeutic products.

In the beginning you have many impurities and along this line you remove the impurities and you end up with a concentrated product. But you can see here that along with removing impurities you have also the chance of removing pathogens such a prions. So for a step called glycine precipitation we see from mircosomes a significant reduction resulting in a reduction factor of 1.7 logs and for PrP^{Sc} even better reduction, meaning 3.3 log.

We then asked the question whether combining steps in this evaluation gives the same results as looking at the steps independently. And here we can say that combining the centrifugation step and the filtration steps leads to the reduction factor as if one looked at those ones individually.

So at the moment we have analyzed several steps for the purification process of -- and we come to a total reduction factor at the moment of 4.8 for microsomal spikes and 5.5 logs for PrP^{Sc} purified

spike.

We then asked the questions whether hamster prions partitioned singularly or identical to human prions. We tested two production steps, the glycine precipitation and the 25 percent ethanol precipitation. We tested the removal of hamster scrapie side-by-side of variant CJD prions and sporadic CJD prions. And we again used two independent spikes, one the microsomal preparations and one the purified PrP^{Sc}.

And here's the result. We see completely similar behavior with regard to partitioning of variant CJD prions in comparison with sporadic CJD prions in comparison with Sc hamster prions, SC237 hamster prions. Efficient removal for purified PrP^{Sc} more than three logs in the glycine precipitation and significant reduction of microsomes also in the glycine precipitation.

The same holds true for the 25 percent ethanol precipitation step. We have significant reduction for both kinds of spiking agents, more than 3 logs in all these cases.

This leads us now to the conclusion that the data that I showed before, which indicates substantial removal of prions by plasma protein

purification obtained with these hamster prions should be considered as relevant for the safety of plasma direct products.

And in this, I would like to thank you for listening to my presentation. I want to thank the following persons for providing material; Dr. James Ironside, Professor Stanely Prusiner and Dr. Martin Groschup. And I would like to thank my colleagues, Dr. Henry Baron, Dr. Bruner and many others for setting up this research project.

Thank you very much.

MR. HEALEY: Next is Dr. Thomas Kreil from Baxter Bioscience who will be providing an industry overview of the research that's been done in this area.

DR. KREIL: Good morning. I would like to thank this Committee for giving me the opportunity to discuss with you a consolidated view of what we understand about prion partitioning during plasma fractionation.

Specifically what I would intend to do in the presentation is provide you summary of what we understand about prion infectivity in plasma both from natural prion diseases and then also compare that to what we know from experimental models of prion

infection.

Also I would like to briefly discuss precautionary measures that the plasma products industry has already implemented and the safety margins that these safety measures afford to the products.

And then I would like to summarize the prion partitioning capacity of manufacturing processes for you. This is results generated from a number of different studies performed by different laboratories using different spike preparations, different assay systems and also investigating different manufacturing procedures.

What I think at the conclusion of that presentation will show to you is that regardless of how the study has been performed, there is a substantial contribution by the manufacturing processes to the safety margins of these products.

Let's start with what we know about the levels or prion infectivity in plasma from natural prion diseases.

Well, for natural prion diseases it needs to be kept in mind that there is no substantiated demonstration so far of blood infectivity. This is now also supported for variant CJD by two more recent

results from two research groups in the UK.

We have used a mouse bioassay for the detection of infectivity or very sensitive Western blot for the detection of PrP scrapie as a surrogate marker and could demonstrate that both infectivity and PrP scrapie can be found in the brain, in the spleen and in the tonsils of variant CJD patients, but they also showed that neither infectivity nor the surrogate marker could be found in plasma of these patients. So this is probably the type of information which is reflected in the epidemiological evidence which will also point against a transmissibility of that type of diseases.

Now, in experimental prion infections there is one general consideration that I'd like to bring to the attention of this Committee, which is that in all of these experimental models typically animals are inoculated through the intercerebral route, which we know is more effective in transmitting prion infection but is also less relevant as to the administration or therapeutic products which we are talking about.

So now in experimental models using these intercerebrally inoculated rodents the maximum levels of infectivity that were found in plasma were around

20 infectious units per mL during the clinical phase of disease. These levels were only two infectious units per mL in the preclinical phase of disease which, if anything, would be the one more relevant to a potential plasma donor.

In relation to what we know about infectivity in plasma, I'd like to bring to the attention of the Committee that Baxter Bioscience has a couple of years ago initiated the study investigating the transmissibility of classical or variant CJD in a primate model. The study is being performed under the supervision of Dr. Paul Brown from the NIH and Dr. Christian Abee of the University of South Alabama in Mobile, which is also the location of the study.

The animal model that we used there is the squirrel monkey, and the study goals are to understand where the blood of primates which are intercerebrally infected with human classical or variant CJD brain material would be infectious during the extended incubation periods of these diseases in the primate model.

To address that what we've done is we have inoculated intracerebrally these primates with either variant or CJD brain material and then from these

infected animals quarterly blood is drawn and transfused into a body in what we call one-on-one design. And a second goal of the study is to understand what the relative levels of infectivity in human classical and variant CJD would be, and that in brain where we know it exists and should it really exist also investigated as buffy coat plasma.

I would like to conclude what we know about the levels of infectivity in plasma that currently I think it's important to reiterate that there is epidemiological evidence suggesting that prion diseases are not transmitted through blood or blood products.

And for the natural prion diseases, and that now includes also a demonstration for variant CJD, plasma infectivity has never been demonstrated. Now in the experimental models where we have seen low levels of prion infectivity in plasma, that needs to be set into perspective with what we know about the levels of infectivity in transfusion-relevant virus infections.

It's important to understand that these levels of infectivity that have been found in plasma of experimentally infected rodents, these levels are 100,000 fold to 10 billion fold lower than the ones

that we know occur for transfusion relevant viruses.

Still we think that already theoretical risk has been reduced. Plasma from the UK is currently not being used for the manufacture of plasma derivatives, which based on the exposure to BSE cases has already excluded to the 99 percent of the potential exposure and as it comes to variant CJD it has excluded 96 percent of the potential exposure.

Another measure which has also put in place is that all product which is derived from a plasma pool which contains a contribution from an individual where we subsequently find out that the person went on to develop variant CJD would, in accordance with regulatory guidance both from the FDA and the European competent authority be recalled.

Now another donor deferral criteria which you are very familiar with is the donor deferral criteria based on geographic BSE and variant CJD risk. The point that I would like to make here, and that is really values taken from the summary of the TSE Advisory Committee meeting that you had in June.

The summary here is that altogether these measures provided risk reduction in the order of one log step. And that one log step, I'd like you to keep in mind when we go into the reduction factors that we

obtained during our manufacturing process studies.

So now the safety margins through manufacturing processes of plasma derivatives. It needs to be kept in mind that a number of different species has so far been used as both the source for the spike material used for these studies as well as indicator animals for infectivity used in these studies.

Also a number of different spike preparations have been used, as you just heard from the two presenters before me, which are a brain homogenate, then detergent solubilized brain homogenate, microsomal preparations, caveolae-like domain preparations, purified PrP^{Sc}; so really a number of different aspects have been investigated here.

And then also these markers have been investigated using different assay systems, which are bioassays which really detect infectivity in vivo and then surrogate marker assays in vitro which have used Western blot or the confirmation dependent immunoassay.

To facilitate a summary of all the studies that have performed so far, what I have done is I have summarized the results available according to major

product categories. The product categories that I would like to present to you are Factor VIII, immunoglobulins, then albumin and proteinase inhibitors.

So this is now a pretty complicated slide and there is a lot of information on there, which I think is good for you to see that there is so much information out there. What I have done here is I have given all the different process steps during the manufacture of different Factor VIII preparations which have been validated. Also I've given you here the log 10 reduction factors that have been obtained for these specific steps together with a reference here to the source of the data.

It needs to be kept in mind that not for all the Factor VIII products that are manufactured, all of these manufacturing steps are being used. So underlying that, I have also given you a summary line here in bold which gives you the reduction factor for individual Factor VIII products throughout the entire manufacturing process as far as these steps have been validated.

So I think what the information is that is in this slide is that where there is steps such as cryoprecipitation or also aluminum-hydroxide

absorption where we get rather limited contributions to the safety margins of Factor VIII products, you can see here the precipitation steps by either polyethylene glycol or glycine provide rather nice safety margins, which is also true for ion exchange or size exclusion chromatography. And then also for infinity purification of Factor VIII products.

Altogether if you summarize that over the individual manufacturing processes the Factor VIII preparations that have been validated so far enjoy safety margins between 3.2 logs and up to 8 logs through the manufacturing procedures.

It needs to be kept in mind that this range can be explained because there is Factor VIII preparations in there which contain -- and then there is also immunifinity purified Factor VIII preparations. So the preparations investigated here have been very different. Still, they all enjoyed really substantial safety margins through their respective manufacturing processes.

This slide now summarizes what we know about the manufacturing procedures for immunoglobulins. Again, the same theme with cryoprecipitation and precipitation of fraction I, we have somewhat more limited contribution. But then

precipitation of Fraction III specifically and depth filtration steps where they are being used in the manufacturing process provide very, very substantial removal capacity for prion infectivity.

Again, demonstrated in a large number of different studies by different laboratories using different spike preparation, but resulting in safety margins for immunoglobulin processes that are beyond 4.6 logs or greater than a 1 million fold reduction through these manufacturing processes.

This now summarizes the information that we have about albumin. I don't want to go into much detail for cryoprecipitation and precipitation of Fraction I again. But as you can see precipitation of Fraction III and then also precipitation of Fraction IV provide very, very substantial contributions to the safety margin of these products, which is probably not a surprise because the manufacturing processes of albumin just contains more steps that it can add up to the safety margins which finally are shown here. So that albumin products enjoyed greater than 7.7 and up to 16 log removal through their manufacturing process.

This slide now summarizes what we know about proteinase inhibitors. Again, the theme is that there is specifically here precipitation steps which

are the major contributions to the safety margin of that product class. So that proteinase inhibitor safety margins are somewhere between 3.1 logs and greater than 12 logs ten reduction of any potential prion contamination here.

What I would like to say in summary is that the safety margins that plasma derivatives enjoy through their manufacturing processes are, indeed, very significant and they are well beyond those provided by donor deferral. I've shown to you before the data that show the donor deferral result in a one log reduction of risk and that compared to the very substantial reduction factors you've seen.

These safety margins do not vary widely regardless of the prion spike material used, the prion assay system used, the specifics of the manufacturing steps investigated and who did the study. And also these safety margins are very substantial as compared to the still theoretical level of risk.

Thank you.

CHAIRMAN BOLTON: Dr. Healey, do you have any closing comments before we move to questions? Do you have a summary?

MR. HEALEY: Only to say that I was flattered by the title of doctor, but indeed I'm not.

So thank you for that.

CHAIRMAN BOLTON: Well, we'll give you an honorary degree.

Okay. Well, I'll open this up to questions from the Committee. Yes.

DR. SIMON: It seemed to me that there's been very substantial sharing of data, so I think it's an impressive showing by industry. And it certainly reflects, I think, the FDA's differentiation between the source plasma donors and the other donors and the fact that there are these additional margins of safety in the partitioning through the production.

So, I believe that we have the data that would answer any concerns about the exemptions of source plasma donors. In fact, I would raise questions whether additional exemptions might be order. But it would certainly, I think, be supportive of the guidance document.

DR. BOYLE: I'd like to raise two questions. First with industry. The comment was made that there's very little variation in the clearance based on the manufacturing steps investigated. The question is we know manufacturing processes vary from company-to-company within the same product. The question is are there any reasons for us to be

concerned about variations in manufacturing processes between companies that might impact upon the clearance of the prions?

DR. KREIL: Well, I had hoped to convene my presentation that really it doesn't depend on who provides data on their manufacturing process. The common theme in all the validation studies that have been performed so far is that regardless of which manufacturing process you take a look at, there are steps in there which will serve to provide a reliable contribution to the safety margin of the product that comes out at the end.

Specifically I think Factor VIII is a very intriguing product to have a look at because the manufacturing processes there do absolutely vary widely. But still, you get these very substantial safety margins which come out at the end of all the manufacturing processes. So I don't think that we should be concerned about differences that different manufacturers use in their processes.

DR. BOYLE: Okay. The second question I would like to pose to the FDA, and that is over the past five years have there been errors or omissions in GMPs that relate to the very processes that we're depending upon to have those types of clearance

practice. I take that as a no?

CHAIRMAN BOLTON: I'm not sure that anybody would be prepared to answer that question from the FDA right now.

DR. SCOTT: Well, I think we don't have all the information here, but that is the kind of question that we would be able to answer as we go back through our processes and compare them to the study processes for each product.

DR. BOYLE: Thank you.

CHAIRMAN BOLTON: Dr. Cliver?

DR. CLIVER: I heard some incredulity voiced during the public hearing about the relevance of these studies. This is not a question, it's a couple of comments.

First of all, as I approach the 42nd anniversary of my Ph.D. I would like to say that a lot of research on which more lives depend on this is done exactly this way; scaling down processes, using surrogates of necessity and testing individual unit operations for effectiveness because then you can see how effective they are rather than work with naturally occurring contaminants which you may not be able to measure quantitatively.

I'm very comfortable with the idea of