

FOOD AND DRUG ADMINISTRATION

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TRANSMISSIBLE SPONGIFORM

ENCEPHALOPHATHIES

ADVISORY COMMITTEE

October 25, 2001

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Silver Spring, Maryland

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P R O C E E D I N G S

8:05 AM

DR. FREAS: Mr. Chairman, members of the Committee, invited guests, public participants, I would like to welcome you to this, our tenth meeting of the Transmissible Spongiform Encephalopathies Advisory Committee.

I am Bill Freas, the Executive Secretary for this Committee. Both days of this meeting will be open to the public with the exception of one short closed committee session around lunchtime today.

As stated in the Federal Register this session will be closed to the public in order for the manufacturers to present trade secret and confidential information to the Committee.

After this short closed presentation the rest of the meeting today and all of tomorrow will be open to the public.

At this time I would like to go around and introduce the members seated at the head table. Will the members please raise their hands as the name is called?

Starting on the right-hand side of the room, that is the audience's right, the first chair is occupied by Dr. Raymond Roos, Chairman, Department of Neurology, University of Chicago.

Next is a standing Committee member, Dr. Bruce

Ewenstein, Director, Boston Hemophilia Center, Brigham and Women's Hospital.

Next is a standing Committee member, Dr. Pedro Piccardo, associate professor, Indiana University School of Medicine.

Next is a temporary voting member, Dr. Lester Crawford, Executive Director, Association of American Veterinary Medical Colleges, Washington, D.C.

Next is a standing Committee member, Dr. Ermias Belay, medical epidemiologist, Centers for Disease Control and Prevention.

Next is a standing Committee member, Dr. Elizabeth Williams, professor, Department of Veterinary Service, University of Wyoming.

Next is a temporary voting member, Dr. George Nemo, Chief, Blood Resources Section, Division of Blood Diseases and Resources, National Heart, Lung and Blood Institute.

At the front of the table is a standing Committee member, Dr. Pierluigi Gambetti, Professor and Director, Division of Neuropathy, Case Western Reserve.

Next is an chair where we will soon be joined by Dr. William Blackwelder, biostatistical consultant, Biologics Consulting Group, Alexandria, Virginia.

Next is a temporary voting member and also a

representative from FDA's Blood Product Advisory Committee, Dr. David Stroncek, Chief, Laboratory Service Section, Department of Transfusion Medicine, NIH.

Next is the Chairman of this Committee, Dr. David Bolton, head of the Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

At the corner of the table is a standing Committee member, Dr. Peter Lurie, a medical researcher for Public Citizen's Health Research Group, Washington, D.C.

Around the corner is a standing Committee member, Dr. Stephen DeArmond, professor, Department of Pathology, University of California, San Francisco.

In the empty seat we will soon be joined by Shirley Walker, our consumer representative for today, Vice President of the Health and Human Services, Dallas Urban League.

The next occupied seat is a standing Committee member, Dr. Suzette Priola, investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories, and the next empty seat we should be joined later today by Dr. Paul Brown, Medical Director, Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Strokes.

Next is a standing Committee member, Dr. Jeffrey McCullough, professor, Department of Laboratory Medicine and

Pathology, University of Minnesota.

Next is a temporary voting member for today, Dr. Susan Leitman, Chief, Blood Services Section, Department of Transfusion Medicine, NIH.

Next is a standing Committee member, Dr. Dean Cliver, professor, School of Veterinary Medicine, University of California at Davis.

Next is a standing Committee member, Dr. Lisa Ferguson, Senior Staff Veterinarian, US Department of Agriculture.

Next is our industry representative, Dr. Stephen Petteway, Director of Pathogen Safety and Research, Bayer Corporation.

There were two Committee members who could not be with us today. They are Dr. Donald Burke and Dr. John Bailar.

I would like to thank everybody else for coming, and I would now like to read the conflict of interest statement into the public record.

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, Drs. Paul Brown,



William Blackwelder, Lester Crawford, Susan Leitman, George Nemo, Raymond Roos and David Stroncek as temporary voting members for this meeting.

Based on the agenda made available it has been determined that the agenda addresses general matters only.

General matters waivers have been approved by the agency for all members of the TSE Advisory Committee as well as consultants to this meeting.

The general nature of the matters to be discussed by the Committee will not have a unique and distinct effect on any of the matters, personal or imputed, financial interests.

Dr. Stephen Petteway is serving as a non-voting industry representative for this Committee. He is employed by Bayer and thus he has interests as employers and other regulated firms.

In addition, listed on the agenda are speakers making industry presentations. These speakers are employed by industry and thus have interests in their employers and other regulated firms.

The speakers for topic 1 were invited to present their comments on the implementation of new donor deferral policies and the speakers for topic 2 were invited to talk about their company's manufacturing or production processes.

All Committee discussions are general matters

discussions only.

In the event that discussions involve specific products or specific firms in which the FDA participants have a financial interest the participants are aware of the need to exclude themselves from these discussions, and their exclusion will be noted in the public record.

A copy of the waivers is available by written request under the Freedom of Information Act.

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

So ends the reading of the conflict of interest statement.

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

DR. BOLTON: Thank you, Dr. Freas. I have very few remarks this morning. I would like to thank all the Committee members for returning after our epic meeting in June. You are congratulated for surviving that ordeal, and I would, also, like to thank all the industry representatives and those members of the public who are at the meeting today.

We have a very relaxed schedule for this meeting as opposed to our last meeting and one clear indication of that is that Bill told me that he left the timer out. So, I

think we will be able to have free discussion and still be able to do a reasonable job of meeting our agenda targets.

With that I think we should begin. Our first topic today is the FDA's draft guidance on revised preventative measures to reduce the possible risk of transmission of Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease by blood and blood products as published in the Federal Register August 29, 2001, and our first speaker is Dr. Dorothy Scott who will give the topic overview.

Dorothy?

DR. SCOTT: Good morning. I think I will be presenting the results of all your hard work from the last long session that we had.

For the first topic I am going to review the FDA draft guidance entitled Revised Preventive Measures to Reduce the Possible Risk of Transmission of CJD and vCJD by blood and blood products.

This was issued on August 27, of this year. Just to very briefly let you know what the previous guidance said with regard to donor deferrals, the previous guidance recommended deferral of donor who had vCJD or CJD, risk factors for classical CJD as listed here and a geographic donor deferral for BSE exposure risk and this was for travel or residence in the United Kingdom for a cumulative period

of 6 months or more between 1980 and 1996, or injection of bovine insulin that may have been sourced in the UK.

Since the 1999 guidance there has been an increasing rate of the vCJD epidemic in the United Kingdom. This appears to continue statistically speaking. There has been an increased BSE epidemic detected in Europe. that is more countries have been identified with BSE and more cattle in some countries have been identified.

So, in some cases it is difficult to say that the epidemic is decreasing there. There was the often cited sheep transfusion transmission of BSE. So far we only know that one sheep had a transmission. However, the experiment is ongoing, and that particular report was a very preliminary report. so, we wait to see if more sheep come down with BSE, and finally there has been a continued scientific uncertainty as to whether variant CJD can be transmitted by human blood.

So, all of this triggered the question whether we needed additional donor deferrals if they can be tolerated for risk of vCJD.

This Committee considered increased donor deferrals for vCJD risk, that is BSE exposure at the last meeting as I am sure you remember. You weighed the risk of shortage of blood and the need for precautionary measures against each other, and I just wanted to point out some of

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the aspects of this that make the whole decision-making process for many donor deferrals so difficult.

The long incubation period of TSEs in general in humans and presumably vCJD although we don't know that, when we see epidemiological studies that are variable that might assure us that transmission with vCJD by human blood is unlikely, if transmission is possible, however, deferrals have current importance and it would be useful to implement them now instead of to wait for this evidence to come to light.

Studies on the infectivity of vCJD food are, also, quite limited to date. There are certainly a number of experiments ongoing, but we don't have those results.

Formerly as you saw in the last meeting blood shortages are considered possible if longstanding deferrals are recommended.

so, you considered options for donor deferrals at the last meeting, and the options that you voted for were incorporated into the FDA draft guidance that was issued.

The new donor deferrals which I will review in a minute decrease the total risk based upon exposure to BSE by about 90 percent and a 5 percent donor loss is anticipated for blood based on the web survey data that Alan Williams presented last time.

I just want to highlight a couple of aspects of

the guidance for you in addition to the donor deferrals. I will go through each of these, the first, implementation of the donor deferrals, pilot studies that are recommended for more stringent donor deferrals than the FDA recommended deferrals, the distinction that we are drawing between blood and plasma for the European donor deferral and finally a little bit about blood supply monitoring, but you are going to hear a lot more about that after I speak.

There are two phases recommended in the draft guidance for donor deferrals, Phase I and Phase II, and these will be implemented at different times.

Phase I, May 31, 2002 is the proposed date, and Phase II by October 31, 2002, and the purpose of this is to attempt to attenuate any impact of a sudden large deferral on the blood supply.

So, the first set of deferrals is for residents in the UK for 3 months and more between 1980 and 1996. I will talk about that 1996 time period next because the Committee had some questions about that last time.

France for 5 years or more between 1980 and the present, residence on a US military base for 6 months or more for these two different time periods here, and it is based on the British beef to Europe program. It is known for different portions or different locations in the military when British beef was actually sent to those bases and that

is why we see the two different dates and finally for recipients of transfusion in the United Kingdom.

Just to speak a little about this ending period of 1996, for the UK donor deferral this is based on our assurance of food chain controls which prevent entry of BSE animals into the human food chain.

This is quite well summarized in a recent report called BSE in Great Britain: A Progress Report. That is on the DEFA(?) web site. I have cited it here, but in particular by the end of 1996, the UK had implemented a specified risk material ban and this prevented more tissue and some of the tissue considered to be at risk for transmitting BSE. This specified the number of those materials from carcasses in a certain fashion. There was, also, a ban on mechanically recovered meat from vertebral columns because this meat can be cross contaminated with neural tissue, and they, also implemented the over 30 months scheme which means that cattle over 30 months would not be slaughtered for human consumption and cattle at 30 months and up are thought to have much higher infectious titers in them. They are all in other tissue, and that was the reason for that.

I don't have a slide about enforcement. However, this web site does outline quite nicely the level of enforcement which includes a number of inspections, and you

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can actually access the reports of the enforcement and prosecutions of slaughterhouses and people who are responsible in case any problems are detected.

There haven't been very many prosecutions, but they do appear to be careful to enforce these rules.

This is just so that you can see that other British endeavors have had an effect. Here we have the cases of BSE by year of report in the UK through June 30, 2001, and you can see that there is a decline in BSE epidemic indicating the effectiveness of their ban on feeding of meat and bone meal to ruminants.

You will see that the BSE epidemic peaked around 1992, and then continued to fall off considerably until we have 2001 here. Now, even though 311 BSE cows is a lot compared to most other European countries you need to remember that these cattle have been detected and that there is a specified risk material ban. So, theoretically even an infected cow which could enter the food chain would have its infectivity removed.

I, also, want to quickly mention non-European BSE. Just after the time when we issued the draft guidance a case was reported of BSE in Japan and this was confirmed and import ban was announced for ruminant materials from Japan.

I don't want to single out Japan, however. It is believed that the BSE in Japan is derived from meat and bone



meal from the UK **was** fed to Japanese cows, and we do know from UK export data which is, also, on the web that a fair amount of meat and bone meal went to other Asian countries.

So, this is something that we will probably have to address in the near future. However we feel the need to assimilate the current donor deferrals and then to consider additional deferrals for other countries and to bring that to the Committee to think about in a more comprehensive fashion.

Again, this emphasizes that food chain controls are important because it is quite possible that many other countries will have cases of BSE as time goes by.

This is the second phase of recommended deferrals for implementation in October 2002. This is deferral of blood donors who have lived in Europe for 5 years or more between 1980 and the present.

Donors of source fluids meant for plasma derivatives will remain eligible and that is what I want to talk about next. With regard to source fluids, we know that model TSE agents are partitioned and removed during plasma fractionation.

We, also, know from at least two different laboratories some unpublished data which shows that the variant CJD agent appears to behave like other TSE agents in these kinds of spiking and removal scale-down studies for

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plasma fractionation.

Also, it is interesting to consider that the magnitude of risk reduction achieved by plasma fractionation at a minimum is probably a couple of logs greater and in some cases -likely to be much more than that achievable by any donor deferral.

We, also, heard at the last meeting a lot of concerns about the effects of such a European donor deferral for donors of source plasma on nationwide and worldwide plasma supplies and therefore supplies of plasma products, some of which have been in shortage recently including plasma-derived Factor 8 or near shortage anyway.

There has been a tension in the market, and IGIV, a shortage which we experienced before in the setting of the classical CJD donor deferrals.

So, the effects, of course, are uncertain because we don't understand the elasticity of the source of plasma supply, but are potentially severe.

We hope to bring this issue in a more comprehensive fashion to the Committee in the near future.

I, also, want to point out that source and recovered plasma are differentiated here to prevent potential errors in the use of deferred non-plasma components.

We plan to re-evaluate this recommendation

frequently in light of additional epidemiologic evidence, transmission studies and advances in the validation of removal of TSE agents by manufacturing.

I just want to say a few things about supply of blood and blood components which is an issue that you all spent a lot of time on the last time. It is estimated that the current recommended donor deferrals would result in the loss of about 5 percent of donors by the blood study. We are aware that the Red Cross has, also, performed a donor survey, and they have different results for their deferrals but these two surveys were done in a different fashion and probably surveyed a somewhat different population.

We know that these donor losses are likely to be higher in coastal cities and we, also, know that even with the FDA deferral that about 35 percent of the New York blood center supply will be affected and this is a combination of the loss of Euro-blood which is 25 percent and US donor deferrals because a lot of people in New York travel.

The industry proposed deferrals or the other industry proposed deferral, the other deferral is for 3 months in the UK which we, also, have but 6 months in Europe and their study as I mentioned estimates a lower donor loss than ours did or the Red study did. They estimated 3 percent donor loss. and we estimated a 9 percent donor loss, and I suspect that the truth lies somewhere in between and will be

different for different blood establishments.

When we met before you all were sufficiently concerned about supply that you suggested to us with regard to implementation of the new donor deferrals that a national recruitment campaign and a system to monitor adequate blood supply be instituted and I wanted to mention that Dr. Nightingale will be talking about the monitoring of the national blood supply just after I speak.

Within the guidance we have added some things which we hope will attenuate the supply impact, the phased-in deferrals that I spoke of before, particularly making the European deferral later, and we feel that the Europeans compared with the people who at UK beef are at less risk and have had the least exposure to BSE. That was the rationale for making this particular deferral later than the others.

We are, also, recommending that pilot studies be done by blood establishments who wish to have more stringent deferrals. This includes implementation of a pilot program demonstrating donor recruitment, evaluation of potential donor loss and donor loss and an end point for the pilot study itself at which time a decision will be made either to have a new pilot study or to implement the deferral or a different deferral.

In addition, we have asked that recruitment efforts be monitored for their success and that fluctuations

in hospital demand for blood products be monitored.

As I mentioned, Dr. Nightingale will discuss national monitoring of the blood supply and demand. This is virtually in place. We do encourage enhanced donor recruitment, and we are aware that this is already occurring, and we have encouraged cooperation among blood establishments to provide each other with supplies in case of regional shortages.

In summary, the future of the draft guidance is collection and evaluation of comments to the docket, and this comment period is about to end.

To date we have received approximately 20 comments, and many of these have to do with the phased-in implementation with source versus recovered plasma and general streamlining of the guidance which if you read it you might, also, have similar comments.

We plan to issue the final guidance with revisions in a very short time frame. We, also, plan the monitoring of the blood supply as the recommendations are put into effect and we plan to continue the assessment with your assistance and advice of blood and plasma risk and benefits of these types of geographic donor-deferrals.

Thank you very much.

DR. BOLTON: Thank you, Dorothy.

We have time for some questions from the Committee

if there are any for Dorothy.

DR. LEITMAN: Dorothy, did you receive any comments on the difficulty of donor screening in determining if members of the military had been stationed north of the Alps or south of the Alps and is that part of the streamlining of that, sort of difficult donor questions that the guidance proposes?

DR. SCOTT: It does seem difficult, but actually we have a list of which countries are north and south of the Alps, which military bases were north and south and it really only amounts to, never mind the UK, because that deferral is more stringent, three countries north and I think five countries south, and I don't want to name them because I will miss one of those five, but we haven't heard from the military whether they find this difficult and from others we have a lot of general questions about streamlining the donor questions, and I think there might be a screening question that could be asked before going into all of these details and that may be true for some of the others, and I hope, I imagine, I think that we will be flexible enough to be able to allow streamlining of donor questions whenever possible.

DR. BOLTON: Other questions, Steve?

DR. DE ARMOND: I have a couple of questions but mostly for clarification in my own mind. The drafts of the

proposals that are sent to us and they were present at the last meeting it came up, there was an idea that there was a 5 percent risk of getting variant CJD in Europe versus compared to Great Britain, and it wasn't clear to me how those risk factors were actually derived because that ultimately led to a change in the time in Europe for deferrals from 10 years to 5 years.

These calculations are, at least I don't follow them.

DR. SCOTT: Right, and this is understandable. It seems to be a complex set, but basically the time spent in the UK which is just called a risk of one and everything else is compared to the UK. So, the French ate at worst approximately 20 percent British beef. The military ate at worst 35 percent British beef. The UK deferral that we are asking for is 3 months, and so if you calculate that up for eating only 20 percent British beef that becomes 5 years France, and the rest of Europe we are actually in a sense being conservative.

The BSE epidemic in Europe is probably about 1.5 percent that of the UK. So, we could make a European donor deferral longer but it seems simpler to keep France and Europe together and it seemed also, that we felt it was possible to tolerate by climbing the donor deferral. So, it is based on two things. One is the consumption of UK beef

and the other is female BSE worst case in other European countries which probably did not consume a great amount of UK beef. So, there are actually two different factors that go into calculating roughly the kinds of deferrals to have for these countries, and we tend to take the worst **case** and sort of, for Europe and have all the European countries be worst case even though we know that there are European countries with no BSE, no more likelihood of BSE according to the scientific steering committee on the geographical BSE risk, and they didn't get much British meat and bone meal.

DR. DE ARMOND: I understood the two parameters, but the numbers, how you mathematically got to these numbers was sort of not clear to me.

DR. BOLTON: The 5 percent comes from the importation of UK beef.

DR. DE ARMOND: Yes, I understand all of that, but still going from 10 years to 5 years --

DR. BOLTON: Just because the UK deferral went from 6 months to 3 months.

DR. DE ARMOND: Okay.

DR. SCOTT: So, that normalizes it to the UK deferral.

DR. DE ARMOND: The other question I had was regarding this. There is something I guess I missed at the last meeting regarding fractionation resulting in a



reduction of a 2-log greater reduction in CJD titer I guess than donor deferrals could generate. Is that right?

DR. SCOTT: You actually didn't miss that because it wasn't stated, and it is stated in a general way. What we have is a series of studies, different studies but mostly spiking studies of TSE agents into intermediates during plasma fractionation for different processes, and this is summarized in Peter Foster's paper that was included in your handout, but what is generally the case is that you have a number of logs of removal of these spiked TSE agents during plasma fractionations and during different processes. So, we were saying only in a very I would say broad sense not a, I don't want you to take this as a strictly numeric sense but many logs of infectivity can be removed in these kinds of studies.

You can argue about the details of the studies, perhaps and how relevant they are, but these are the kinds of studies that we, also, accepted as supporting evidence for stopping the withdrawal of derivatives for classical CJD risk.

What we would like to do though is bring this to the Committee for at least one-half day of discussion and actual presentation of data, probably at the next meeting so that you can feel more comfortable with these kinds of studies, but it wasn't possible to do it for this meeting.

DR. DE ARMOND: Right because the implication might be that deferrals are not that important or I am not sure that you are saying that, but the way that statement is read it implies that the techniques of fractionating are actually pretty good at eliminating infectivity, but I am sure you are not saying don't defer.

DR. SCOTT: I am not saying that. However, this point is being debated for plasma derivatives.

DR. BOLTON: Peter?

DR. LURIE: I have two questions. First is for those of us who get easily confused by the numerous categories and numerous recommendations, just clarify for me the way in which this draft guidance differs from the recommendation of this Committee because I think I am correct, am I not that there is a change with respect to the plasma and plasma derivatives? Can you just make that absolutely clear for us?

DR. SCOTT: Right. Well, you had some hesitations concerning the potential problems with the plasma derivative supply. First you have these donor deferrals from industry chiefly, and there was a considerable concern as you know that the plasma supply would be increasingly stretched especially if there were a European perception that their own plasma was not deemed, if you will, safe by the US, and I know that some Committee members actually said in the

second part of the first day of the last session, began to be concerned about the effect of this European donor deferral, and I wrote the donor deferrals on the plasma derivative supply. So, we have written that section into the guidance because we feel that there is some scientific evidence to support it as well as a supply concern.

Now, this probably needs to be explored at greater length with the Committee and I would point out that the European donor deferral planned implementation or suggested implementation time is next October. So, there is adequate time to continue this discussion if we feel it is important, and I think most of us do feel that that is important. Is that in answer to your question?

DR. LURIE: You are explaining the answer to my question without giving me the answer. It is a very simple question. I just want to know in exactly what ways the guidance differs from the advice of this Committee, just very concretely.

DR. SCOTT: We added the phased implementation.

DR. LURIE: Right, for sure.

DR. SCOTT: Right.

DR. LURIE: With regard to plasma, that is my question. I am clear in saying that there was no differentiation, right, between --

DR. SCOTT: Right.

DR. LURIE: I am trying to clarify this. You made no differentiation between --

DR. SCOTT: -- in the way that I have already described. I can't think of any other way.

DR. LURIE: Right. So, you made no differentiation between blood and plasma in UR; is that correct?

DR. SCOTT: That is correct.

DR. LURIE: That is what my question was. My second question, this may seem like a strange time to bring this up but anyway through this conversation about, going back for several years now, a lot has been made about the clinical or theoretical risk of this and so forth, and there have been a certain number of studies that are still ongoing, and again, in Britain it seems to be on the wane and hopefully one in Europe that will soon be on the wane as well and so my question is has the agency given any thought to the criteria that might be met which would result in your removing the deferral criteria that our Committee had suggested? Is there a set of, you know, a certain amount of time that might elapse with a certain number of cases, certain results of specific studies that it might actually say, "Okay, we have covered ourselves during this period in which much was unknown, but now enough data have accumulated and enough experience has accumulated, and we feel we can remove the restrictions"?

DR. SCOTT: That is a very useful question, and what we are thinking about is the possibility of removing some of these based upon the safety of the food chain and that was the rationale for making the UK deferral only until 1996, because we feel assured that people eating beef there after 1996 are at minimal if any exposure to BSE and so following that kind of logic you can imagine the possibility for re-entry as it were. However, the details of that sort of a plan have yet to be worked out, and again that is something I think the Committee would need to consider to have this lift.

DR. BOLTON: Additional questions? Pedro?

DR. PICCARDO: Do you know to which other Asian countries besides Japan was UK feed shipped to?

DR. SCOTT: I don't want to single out any countries, but I would say quite a few, and larger amounts that went to Japan, considerably larger.

Now, it is difficult to tell where UK meat and bone meal at the time of the peak BSE epidemic, how much of that went out that was made from pigs and how much was made from cattle. It is, also, hard to know for meat and bone meal when it is shipped out whether it is used for, even if it is labeled for use for chickens or fish whether it is actually used to feed beef.

So, there are lots of complexities when you look

at that, but a large number of Asian countries I would say 10 or 12 at least are in the UK export data. So, it is not a small or simple problem.

DR. BOLTON: Any more questions, from the public?

No. Okay, very good. Thank you very much, Dorothy.

Next we will receive an update on the current state of the blood monitoring project and plans to extend monitoring to the supply of plasma derivatives and their recombinant analogues from Dr. Stephen Nightingale.

Steve?

DR. NIGHTINGALE: Thank you very much.

We can possibly go to a slide show, but this is going to be a true multimedia presentation here, and I apologize for the delay. Give me just a minute.

I have two talks and 20 minutes to give the two talks in, and I will try to keep to my limit. The first talk is about monitoring of the supply of and demand for blood products and plasma derivatives, their current status.

I would like to begin by noting that we collectively, that is the blood community, has been monitoring plasma derivatives since October 1998. This program was initiated by what is now known as the PPTA through a contract through Georgetown Economic Services and that program continues. It is monthly and sometimes bimonthly reporting and the monitoring of blood products was

instituted in October 1999.

This was originally funded by the National Institutes of Health and for the last year by the Department of Health and Human Services with a contract to the National Blood Data Resource Center.

This is an example of the data that we have received from the plasma monitoring, and I have chosen it because it is the plasma derivative of immediate interest.

What you have here is the --

DR. BOLTON: May I interrupt you for a second?

DR. NIGHTINGALE: You certainly can, Mr. Chairman.

DR. BOLTON: There still seems to be some problem with the zoom on your slide. I don't know if that can be rectified. If not, you may have to do more explaining of each slide to let us know what that means.

DR. NIGHTINGALE: There is always something going on over your shoulder. What I can see and you can't is that the top of the slide here says, "Monthly ratio of inventory to release of recombinant Factor 8." That is not a good idea.

(Laughter.)

DR. NIGHTINGALE: I reiterate my previous statement. Let us leave it here, and maybe I can give 11 minutes of presentation.

The basic unit that we have used both with plasma

and in blood has been the ratio of inventory to release. In common parlance that is an analogy for number of days of inventory which you have in a commercial enterprise. For example, Ford has a 70, a 50 or a 30 day supply of cars that it has to sell.

What you are looking at here is the ratio. The blue is the months of inventory of human high-purity Factor 8 and what you are looking at in the turquoise is the months' inventory of recombinant Factor 8.

What you can see here there has been a lot more inventory of the red in September 2000, about 3.3 months' inventory, months' supply of human Factor 8 and not a whole lot, about a 3-week supply of recombinant Factor 8, and what you see over the past year and now right up to September is that the inventory of the manufacturers of recombinant factor 8 is low and getting lower and the supply of human factor 8 would appear to be substantial. At least it has a face value that is higher than for recombinant but now is approaching the levels of recombinant.

The fact is that we know from reports from the community that there are shortages of recombinant and the human Factor 8 is at very best tight right now. I have shown this slide, however, to show you that there are limitations to the data that we collect right now.

The limitations are first of all there is an



uncertain relationship in the data that I just presented you on supply and demand, and at what point was the supply of recombinant Factor 8 really truly short? Was it when one person couldn't get it? Was it when 100 persons couldn't get it? Was it when 3 percent of the population couldn't get it? That uncertain relationship to demand is the key intellectual question that we are still struggling with.

The second question is the timeliness of the reporting. When reports are gathered over a 1-month period, commented over the following month, and you get them 45 days after the trial reporting period that is really late in the game for just about anybody because you are going to hear reports of shortages before that time.

The lag time from a practical perspective in monthly data collection has proven not to be satisfactory for government, for industry or for consumers, and the third issue is the transparency of the process. I am not going to risk going back to the previous slide. I have had enough trouble so far, but there was one point in March 2001 where we didn't have a report on the supply of recombinant because there were only two manufacturers there and the rules of the game that were established were that you had to have three manufacturers to get a report. So there were times when we really would have wanted to know what the score was, and we did not get a score.

For the blood reporting contracted for a representative sample blood establishments producing the government did not know the identity of the blood establishments and that was not as problematic for us.

So, about the time that I spoke to you in June we had had a meeting of our Advisory Committee on Blood Safety and Availability, and we were in fact making plans to upgrade our data monitoring for both blood and plasma, and so we had a head start, and we surely needed it.

What we are doing right now is we are doing daily demand, daily monitoring of blood demand at the hospital level. The idea was that we were initially working with inventories on the producer side. We wanted to move down into the inventories on the consumer side, and the consumer in this particular case is the hospital. It is the factor if you will on behalf of the patient for providing the blood.

We have recruited 26 geographically distributed hospitals, two per city or per region and three regional blood banks. They are in the Northeast and within Brigham and Women's in Boston, Sinai, Columbia, Jamaica, Maimonides in New York, the Georgetown Hospital Center in DC; that is the northeast region, Brady and Emory in Atlanta, Mt. Sinai. In Miami we are going to have Jackson when they can come online. On the Gulf Coast we have Navy and Oxford Clinic.

In Dallas and the remainder of the South we have Baylor and Parker(?) Hospital.

In the Midwest we have University of Minnesota. I see Dr. McCullough there, Indiana University, University of Illinois, Central Campus and Northwestern and I keep remembering that I should mention that I have a conflict here. My wife is employed by Northwestern University Medical school.

We have University of Iowa and we have St. Alexis Hospital in Bismarck, North Dakota. We do plan to add another community hospital in the Midwest.

In the West we have Harbor and Cedars in LA. We have Denver General, not Denver General, I mean the University of Colorado and the University of Arizona at Tucson, and we plan to add another southwest border hospital to our group. We have the regional blood centers in Tampa, St. Pete, Pittsburgh and Seattle as well.

All of these sites, particularly the individual hospitals are intended to be set in their ways and representative. That was the original and that remains our purpose. It seems valuable to ask if 1 percent, 2 percent or 3 percent of hospitals are short of blood articles. If we get a report that a hospital is short on a particular day we want to know why that hospital is short, and particularly we want to know why that hospital is short and another sentinel

hospital nearby is not short.

We are trying to make this, if you will therapeutic rather than just descriptive, and we haven't gotten there yet.

The idea behind the study is to correlate the inventory, the days of inventory with occurrence of an actionable shortage. We ask all our sites to indicate in addition to their inventory data any actions that they took in response to finding that their supply was inadequate to meet demand, and we are monitoring them by ADA and Rh platelets, by random and apheresis(?) and by shortage reports.

On the first point I need to get out of here and go to my Excel files. What we do right now is generate a graph that looks like this. This is our data and I apologize. You cannot see the baseline that I can. The baseline here is the one that begins on August 1. We had several sites collecting in July but we really didn't have everybody up to speed until the first of August and we have retained the data. We paid for the data, but this is the point at which we started having the majority of our hospitals reporting.

The baseline, this is for inventory of all red cells combined and it is particularly unfortunate but right on the other side is the scale. We are going from August 1,

through October 15, and the scale here, this is 8.0 days' supply. We have on average, what I reported to my advisory committee on August 24, was an average of 7.4. It is pretty close to an 8-day average.

What you are looking at here at the top is the median. This is the 15th out of the 29 sites, and this is their inventory in days. That would be about 8.6.

You will see a periodic pattern. That pattern is a weekly pattern. I am sorry it didn't project here of the inventory throughout Sunday, Monday and Tuesday and they go down on Wednesday, Thursday, Friday and Saturday and they go back up again.

I point that out that we have sufficient number of sites, and we can reach in and we can measure the weekly variation in inventories, and you see this in individual sites, in most of the individual sites, certainly for A positive and 0 positive and for 0 negative it gets a little tricky. In the hope that this will come out a little clearer, well, it did not, but this is from our, this graph is from October 1, through October 23.

What we do on a daily basis is we get our updated Excel file and we run a program and we look sometimes briefly but we look at the data from every site and the aggregated data.

So far what we have seen is a pretty consistent

pattern. I think in the interests of time I will just go over, I will just show you the aggregated data. I had not been requested to show the individual sites which is some of, the individual site data confirmation but we do break this down by A positive, 0 positive and 0 negative and perhaps just for the record note. I am sorry but I don't have my baseline here and I am not going to get into it, but I have mailed this data out to the advisory committee mailing list, to our contractors and if anybody would like to review it with me I do have copies here, and I apologize for the technical difficulties.

Now, I am going to try to go back to the slide show, and continue and see what happens. This is just a summary of the data that I showed you days' inventory for all red cells. I did not mention but at the bottom we also graph out the two lowest of the 29 sites and you can see here where they are and those two with a couple of exceptions have been 2 days' inventory.

So, from the several sites there has been what appears to be an adequate collection, amount of blood but I want to qualify that with the following statement which is where are we going. This is clearly from the time thing a work in progress.

A very conscious decision has been to make the progress of that work accessible to the public so that we

can recruit comments, not all which have been failure to perform, but many have been, but one is appreciated more than the other but those are needed and that is the idea behind it.

We are about halfway through the process of going to direct web site entry. We have one full-time person, Virginia Wannamaker who is the manager of the project. When she spends all day entering the data, she doesn't have time to analyze, to check the data. So, I think 15 sites are on. We expect to have the other 14 on by November 15, and when we get them we enter them directly into the web. We will be able to implement a real-time data study technique.

Somebody has say 100 units of A positive in inventory and somebody tells us that there are 10 units, and we are going to make a phone call at the time and afterwards to see if there was a data entry error there and that is the first and we have time to scramble between them.

The platelet data monitoring, the supply of platelets is a complex one. There you have perhaps 1 day inventory of platelets and the platelet market turns over a whole lot faster. One of our substantial concerns is for the adequacy of the platelet supply as well as the blood supply and that is going to take a serious round of consultations with our contractors and with our public to figure out how to do that one right, and once we have gone

there we want real time comments. Somebody sends in a letter that says that I was short for 4 hours, and we have a set of boxes right now that we are adding but we want to collect information.

If there is a shortage situation we want to collect it in real time, and that probably is the bottom line for monitoring. Then statistical analyses I would much rather give you box plots than give you medians and two letters. We need to get to cluster and discriminate analysis. For example, I think you see the weekly variation in our data. We need to get at, one of the variables is we have given the hospitals freedom to report their data anytime of the day that they want, but they are asked for a consistent time, but if you report at 4 o'clock in the afternoon you may or may not have more blood than you have at 8 o'clock in the morning. It kind of depends when the delivery truck comes around, how many times a day the delivery truck comes and what your sources are.

For that we are going to need some decent statistical techniques and we just have to get time to set this up. We are in discussions with the American Red Cross and America's Blood Centers. Let me state this very publicly. The problem is really not them. I have been busy, being very straightforward, and I want to make sure that that is on the record. I sent them an e-mail on Tuesday



saying, "Can we talk?" I got responses back in 30 minutes, and I am the one who didn't make the telephone call back. We will get there when we can.

We want public access to this data on the web site at the earliest possible time. The contracts were initially for 6 months because this a learning project. We need to rebuild those. That takes a 'fair amount of time and not just the possible expansion of sites, and finally, the expansion of the model of the plasma derivative supply and demand that was not on this last slide here, is to also get, is to decide how best we can make the utilization of data.

The current New England, the paper about mortality is and transfusion in patients with heart attacks has some very interesting data, HCFA data set that is complementary to the BURN(?) data. We have looked. Dr. Paul Ness has looked at the BURN data and there are lots and lots of problems with using BURN data as measures of utilization and one of the things that we would like to do and we cannot do everything at once is to try to monitor or at look at utilization as a factor influencing supply.

That is a summary of the monitoring project to date before I go to the September 24, meeting.

Dr. Bolton is it okay if I ask for comments and questions on this presentation?

DR. BOLTON: Sure. I think that would be useful.

Are there any questions from the Committee?

Dr.Lurie?

DR. LURIE; Steve, I hate to do this but can you go back to that first slide of the data in turquoise and blue and whatever else, turquoise and purple, I guess.

It is the first PowerPoint or the second PowerPoint.

DR. NIGHTINGALE: The PowerPoint, sure. I will be glad to. You never expect an easy question from Dr. Lurie.

DR. LURIE: I guess what strikes me about these data, aside from the apparent trend downward is that from month to month there are some fairly big fluctuations downward, and some of those look to me to exceed 1 month of decrease in inventory over 1 month, and if one assumes that the demand for these factors remains stable and that there is absolutely zero production of the factor in question that would lead to a 1 month decrease in inventory. So, how do we get decreases that sometimes exceed that?

DR. NIGHTINGALE: You picked up the limitation of using days of inventory, weeks of inventory, months of inventory as a measure of either supply or demand, and that is one number divided by the other number and there we are. That is a hyperbolic function, and that means it is not a linear function, and what that means is that these numbers are difficult to interpret literally. There really is an

intellectual question here. I suspect that Dr. Ewenstein wants to answer the question for me.

This is where we are to date with what I would like to call the science of measuring. We definitely have a way to go.

DR. EWENSTEIN: I am not sure if this is the answer but this is US distribution, but the inventory could be distributed worldwide.

So, if you had an increase in non-US distribution it would account for your greater than 1 month decline. I mean I think it is a real issue that we have to grapple with because you are not really comparing apples and apples.

DR. LURIE: Obviously something has to be done about that problem, but that is the explanation.

DR. NIGHTINGALE: Yes, and I think, also, that this is data from the manufacturers. In the blood business we have a simple economic model which is that there are manufacturers and that there are consumers and the manufacturers are at the Red Cross agency and to some extent the big three, Tampa, St. Pete, Pittsburgh and Seattle, the big community blood bank and the hospitals are consumers.

That actually works except the consumers are a very heterogeneous lot. In the plasma business there are intermediaries and the question is how to measure those intermediaries, and the second question is how to do that

without violating individual rights, trade secrets, confidentiality and that is a really important political question.

DR. BOLTON: Other questions from the Committee?

Yes, Ray?

DR. ROOS: Steve, my perception is that blood donors increased in September as a result of the World Trade Center events, and it wasn't obvious in my quick inspection of the Excel graph that you had.

DR. NIGHTINGALE: We did not see a substantial change in the inventories at the hospitals around the country consequent to the September 11, events.

There is, and Dr. Jones is on the front lines here, and so I am going to send you into his answer. In October, yes, there is a real average increase, at least 5 percent I think increase. What I would like to be able to get at is to be able to quantify that increase for you, but I have got the weekly jiggles and I have got the jiggles for the time of day, and I really need to get a SAS(?) program called X12 out to filter those things out before I could quantitate it. What we have through August is that our sites, and these are our 29 sites, not all the sites in the country, but 29 of them, we are running on average about a 7-to-8-day inventory of all products, and that did not change after September 11, but Dr. Jones is the expert on

September 11.

I think Dr. Jones has some additional comments.

DR. JONES: Yes, it is well known there is a real nationwide now worldwide blood gut after the eleventh and what you are seeing here I think on your Sunday is you are seeing the capacity of the blood banks. They cannot take any more. In fact, if you really want to get an idea of how much blood there is you measure the cubic inches left in the blood centers' refrigerators because it is really strange that you don't see that there but in blood centers I am sure if you were measuring those you would see a huge increase in the inventories.

DR. BOLTON: Dr. Stroncek?

DR. STRONCEK: Speaking from our center or centers that collect blood I think you have to make the distinction between transfusion services and blood collection centers. You know your model is just looking at transfusion services. Red cells have a short outdate you know 42 days. Platelets have 5 days. You are out of your mind if you have more than 7 days of blood at a hospital. You don't buy this stuff to have it outdate and eat the cost. So, I think the fact that this is not showing up is a huge flaw in this kind of data and I think it is a huge disservice to collect this kind of data and distribute it if it doesn't reflect such a dramatic thing.

For our experience blood centers really do have a lot of blood they are outdating. They have a huge amount and if you are going to collect the data it should reflect the situation. Otherwise, you should just forget it and not collect the data.

DR. MC CULLOUGH: I do think it is necessary to make a response to that. We do collect data on outdating as well as data on exporting as well as data on transfusing. We don't see a lot of outdating. I think that I would just say that perhaps I have become though I am a nephrologist, an expert in the management of blood centers because of the data that has come to me and that I am trying to give to you and there are certainly many perspectives than the one that Dr. Stroncek just articulated.

DR. NIGHTINGALE: I have it here. I have 29 of them, and we are going to hear about that in a little bit.

DR. BOLTON: Dr. McCullough has a question?

DR. MC CULLOUGH: It is more of the same. I think Steve has done a great job of getting this project up and running, and this is a good illustration of how it is at kind of Phase I. For the benefit of many to emphasize this does reflect what a hospital needs to have on the shelf in order to deal with the patients in that hospital. It doesn't reflect the availability of the nation's blood supply. It illustrates demand and nationwide we wouldn't have expected

to see any difference in this data because nationwide there wasn't a net increase that was that noticeable in the demand and actual use of blood as a response to September 11. So this is what we would have expected to see.

Hopefully, as Steve expands this activity, a separate parallel set of data about blood availability can also, total blood availability in the US can be developed. This is just what is available in these hospitals as a way of indicating whether they have an adequate supply on their shelves. It doesn't indicate what is available in their supplier's refrigerators.

DR. BOLTON: Let me briefly ask a question? Is this somewhat the fluctuation of the data smoothed out because your graph is showing the median data point? Is that right? You are not showing the extreme, either the highest or the lowest.

DR. MC CULLOUGH: In these 29 hospitals there wasn't a huge increase in the use of blood after September 11. That is what it is showing.

DR. NIGHTINGALE: The bottom two numbers for the 29 hospitals are shown on the bottom graph here, and you can see that there are a few circumstances where hospitals reported a net of less than 2 days' supply. There are in fact a couple of hospitals with good relationships with suppliers that have lower inventories than others. There are

variations in inventory practice which I think are less appreciated within the community than I might have anticipated there were. I guess I might say there is less conversation in the hallways than I had anticipated.

DR. BOLTON: Dr. Stroncek can correct me if I am wrong, but I think his point was that it did not show the glut of that he expected should be shown and I think that would only be reflected if you were showing the highest supply, in other words the center or hospital with the highest supply, and I take it that the purple graph is the medium number. So, in fact, those data may be there and if they were replotted you would have very high numbers in some areas. Is that correct?

DR. NIGHTINGALE: Yes. Oh, yes.

DR. MC CULLOUGH: I don't think so. The glut of blood as I think Dr. Jones could elaborate, the extra blood stays in the blood center if the hospital doesn't need it, and these are 29 hospitals. Our blood center had like 5000 extra units of blood. The amount of blood we had in the hospital didn't change because we didn't have any patients that were affected by September 11. So our numbers aren't going to change, and you see hospitals, most of them; there are a few in New York City but most of the 29 didn't have any difference in their medical practice. So, the number won't change.



DR. BOLTON: I guess then going back to Dr. Stroncek's question is it valuable to have that kind of fluctuation at the centers reflected in this data in some way?

DR. NIGHTINGALE: I don't understand the question. The data is the data.

DR. BOLTON: But it is apparently not reflecting the ebb and flow of collections at the centers as opposed to at the actual hospitals. In other words it may be more the supply and then the consumer now.

DR. NIGHTINGALE: Okay, what you are looking at here is the consumer, and we are using days of inventory in the hospital as our best approximation for measure of demand. As I said, we are in discussion with the Red Cross and with America's Blood Centers to identify and measure what we would all be comfortable with as a measure of supply and right now that data comes say in advertisements in the New York Times, and occasional, and it links around September 11. I think we all know that data, but that data is, also, data that I must emphasize is for very legitimate reasons confidential until released by those agencies. Perhaps the misunderstanding between Dr. Stroncek and myself was in my presentation for which I apologize but I didn't specifically emphasize that what we are looking at here that is new is the measure of demand. The measure of supply is of

interest and to be blunt if I am in a hospital and I need a blood transfusion I am not interested in supply. I am interested in the demand being met and that is where we made the transition to the system we are going to right now.

DR. BOLTON: Dr. Fitzpatrick, let us not keep you standing any longer.

DR. FITZPATRICK: That is okay. I stand all the time anyway, a lot more lately.

Just to go back to Dr. Stroncek's question and maybe to help Steve a little since September 11, we have been receiving reports of the supply in the nation for both military and civilian blood. The supply has at least doubled, perhaps tripled but to go back to the idea about expiration there is this perception that we are going to see this huge increase which has leveled out actually. We have been seeing the sustainment of the level of about 500,000 units of blood available in this country. It is taking a little dip now, but we are seeing a little fluctuation, but we are not seeing -- it is now 43 days past the event but you went from a 2-or-3-day or 4-or-5-day depending on however you want to parse out the days of supply to 7 to 10 days of supply of a 42-day dated product.

We should not, if we are managing that inventory anticipate a huge expiration because we should be transfusing and meeting the demand that Steve was showing

with this now increased supply of 7 to 10 days as opposed to now if we had a 45-day supply then I would expect to see a huge increase in expirations.

We are seeing some isolated increases in expirations. We, the DOD are seeing some increases in expirations because I don't have quite the flexibility in Uzbekistan, Oman, Saudi Arabia and other sites to rotate the inventory. So, once it goes it is pretty much gone, but within the country we don't anticipate, and I don't see from the figures we are gathering that there is going to be a huge wastage of blood because good inventory managers should be managing that inventory and now they have a bigger inventory to manage, but it is not so big that they have so much excess that there is going to be a huge outdate, I don't think. I just wanted to clarify that.

DR. NIGHTINGALE: I think there is a very important follow-up number that Colonel Fitzpatrick let out there and that is 500,000 units of inventory. If we just do very simple back-of-the-envelope math transfuse 13 million units a year that 500,000 is 1/26th of the year. That is a 2-week blood supply and that is reason for huge satisfaction right now.

I think the concern that all of us have is putting out a number like that and say, "Okay, everybody go home." That is the real danger in the project that I have

undertaken is that it gives a false sense of security. I am very acutely aware of that and that is really the basis of the discussions that I kind of abbreviated between Dr. Marthan(?) and myself is how to provide the information to the public in a way that will not distract them and let me just pick a number out of the air. Let us say 200,000 but what do I know, I am a nephrologist? We don't know what the right, I as a nephrologist don't know what the right number is but we all what we all know is if somebody needs blood and cannot get it, we have got a shortage.

DR. LURIE: I think what follows from David's earlier comment is that the aggregated media data could well be hiding either successes, if you will, or failures and I think you often said that spot shortages are the issue more necessarily than aggregate shortages and so I think that is just one element.

Second, you seem to depict the inventory data as the index of demand, right, if I can just say that and I am not sure that that is conceptually right. It strikes me that the inventory is not that. It has both a supply and a demand element to it. Indeed it is the balance between supply and demand that is reflected in the inventory. So, I am not sure that one should be looking at it quite that way.

The third point is following up on Dr. Jones' comment it strikes me that an additional measure with making

the percent of capacity, it seems that at least in New York they reached that capacity and these numbers, again, as you were saying there is in effect a limit to how much inventory one would want to accumulate and it would be useful to somehow include in the way the data are presented what that limit is.

One aspect of that is that one would never have inventory demand, whatever, say, 10 days for red blood cells or another way would be to say that this is the fraction of capacity that we are at, and I think that would be frankly reassuring to people.

DR. NIGHTINGALE: Yes, I can make two comments. First of all, demand for those of you who know economics, one is price and you can only measure demand by price if you have a perfect market and what we have here is anything but an economically perfect market.

So, what we have had to look for is an opportunity cost and that is the sort of thing if I had \$100,000 I would hire a sophisticated economist to write a paper on this subject. In fact, there is a good economist I would like to hire, Dr. Chevy at Boston University who has written some very intriguing work on this field, but we didn't have time for that in July. So, we picked this particular surrogate.

The other point I would like to make is that we are trying to correlate an objective measure of the

inventory switches that you have to take an action on a particular day. That is what I hoped we would report to you at the next meeting, but we have looked at objective actions. I didn't have enough platelets. I didn't have enough red cells. We had to put off a liver transplant for 4 hours while we had that blood shifted from somewhere else. Those are the things on which we will be able to improve our measure of demand, but the measure of demand as you rightly pointed out isn't a perfect blend and my response to you is that we are aware of that and trying to improve it.

DR. BOLTON: Speaking of opportunity costs we are falling behind. So, I am going to delay your question as to the Committee discussion after the next speakers and ask Stephen to move on to the update from the DHHS meeting of September 24, so we can proceed.

DR. NIGHTINGALE: This one I can, I promise, do on schedule. Bear with me. As I announced at the last TSE meeting there **was** scheduled in fact, occurred a meeting in the Office of the Secretary. It was on September 24, to address the question that is on the slide here. Can the department's BSE action plan, the plan that I described to you at the June meeting be expanded to capitalize on the human physical resources, the pharmaceutical and biotechnology industries?

The heading says that I am going to give you a

brief summary of the meeting but I believe Dr. Freas that copies of the summary of this meeting are available or not?

DR. FREAS: The summary should be in the blue folders of each Committee member.

DR. NIGHTINGALE: Then you have a summary. So, I can make this even briefer than I might otherwise have made it. The structure of the meeting was as follows: Dr. Richard Johnson who can't be here today did give an overview of the NIH support programs. He identified approximately 70 grants and about \$20 million that is currently funded by NIH.

After that I had asked Drs. David Asher, Linda Detwiler and Peter Lurie to address the questions of what we do not know about TSEs from the perspective of a regulator of fluid parts, of animal parts and from the perspective of a consumer and it is my pleasure to refer you to the summary not because of the summary but because of the thoughtfulness of the presentations. I worked hard to try to capture the essence of what they said, but if I failed the transcript is available on the department's web site.

I asked Mr. Jacklin and Dennis Berry to comment on the relationships of industry to government and Mr. Christopher Healy to comment on the willingness of the plasma therapeutics industry to participate in collaborative research and Mr. Healy has been very constructive in that

respect.

Then, also, Dr. Robert Wiler and Dr. Neil Constantine made specific invited presentations. Dr. Ray is for a core laboratory facility to permit broader participation in BSE research. Dr. Constantine is for a collaboration among academic clinical pathologists to work on the mechanics of test development.

The boss then spoke and this is a summary of his remarks. He said that the projections are there will be \$30 million in Fiscal Year 2003 for BSETSE research and I am quoting here, and it is important that I do quote him accurately. It is a scientific rather than a budgetary constraint and the actual amount depends on the science merit of proposals. He said that the scientific merit is judged by the independent peer review, said that more money could probably be spent, that he would do what he could to see that that was accomplished. He, also, said if the scientific proposals did not pass muster then we wouldn't spend the \$30 million. We wouldn't spend the \$30 million unless the government was getting its money's worth.

He then asked the question do we now know enough to thoroughly and rapidly review any regulatory document instrument to anticipate that we deal with BSETSE issues. I will return to this question later, but his immediate follow-up is if not is industry interested in working with



us to develop that aspect of scientific knowledge about BSE and TSE that both industry and government will need and finally, in response to a question, I believe this was from Dr. Drolpen the Secretary would consider suggestions to modify traditional grants programs particularly the time, the duration of those grants to meet the specific needs of BSE and TSE researchers.

After the Secretary's comments we had a panel of eight presenters. This is just the part that says, "Meeting summary No. 2, Dr. Sheath, Dr. Fells, Dr. Johan, Dr. Monser, Neyman, Aker, Grossman and Burke all gave presentations which the department once again thanks them for those efforts and after the presentation there was a period of discussion and I summarized that discussion in this slide.

First in response to a question Dr. Johnson reiterated a point that was made in the BSE action plan that the principal bottleneck in his view to progress in this field was a shortage of investigators.

Dr. Drohan gently but firmly challenged that position and he pointed out in the presentation at the meeting just his contention that in fact the bottleneck was not a shortage of investigators but a shortage of laboratory facilities for those investigators to work. I think it was fair to say on behalf of both that one of the question is not who do you count as an investigator but where do you

count them. Is there a shortage in academics? That is Dr. Johnson's expertise. Is there a shortage in industry? That is Dr. Drohan's expertise, and Dr. Drohan's comments at that time were very persuasive and they were followed by Dr. Rohwer who pointed out that there was a number of productive investigators in Europe as well. I think that Dr. Rohwer did recommend a recruitment effort, a brain drain. We are taking that consideration under advisement but we did take Dr. Rohwer's other statements very seriously.

It was also pointed out by Mr. Hayward of Q-RNA that at that moment there was a shortage of venture capital and that could be considered something of a bottleneck. Mr. Dennis Jackman who had spoken earlier pointed that it is in industry culture and it is there to focus as much of the efforts as possible on the single surest path to a goal and that one thing that could benefit all concerned would be for facilities so that ideas that might take longer to develop or might have a higher risk in the short run could receive those scientific risks. There was a very pointed comment by Dr. Lynch that I recommend to you. Dr. Lynch was for many years a very valued employee of the government and we miss him. His pungent comment was that there is a distinct data shortage of data for regulatory review and that is a comment that I think is very much worth repeating here, and an advantage of putting additional funds into research would be

that it could address that need which might not be felt today but will certainly be felt soon if it is not addressed and finally, Dr. Dodd stressed the need to spend some time on the societal impact of various CJD screening in blood donors. So, in my final slide here we are.

The proposal is on the table. Proceed with the NIH component and the action plan including the RFA but there has not been a lot of enthusiasm for the suggestion that specific prizes in this field be developed and that suggestion is not at this time under active consideration.

I have the core laboratory, Dr. Constantine's proposal is also under consideration as I understood the time frame on the 29th, and the small business innovation research grants for BSETSE research.

I would be glad to answer any questions.

DR. BOLTON: Thank you, Stephen. I think what we should do is to hold the questions on this particular topic and proceed through our next four speakers so that we can then entertain questions for all of these areas after the open public hearing.

So, at this time I would like to welcome Dr. Bianco who will begin the update on the anticipated implementation of the new donor deferral policies.

DR. BIANCO: Thank you, Dr. Bolton, and I hope that our statement that you all received this morning will

help answer some of the questions that were raised earlier.

America's Blood Centers as many of you know is a national network of locally controlled non-profit community blood centers that collect half of the blood supply from volunteer donors. Collectively we operate in 45 states and serve more than half of the nation's 6000 hospitals.

ABC's total collection exceeded 6.7 million pints in the year 2000, and we thank the FDA for the opportunity and the invitation to participate in this public meeting.

On June 28, 2001, exactly 4 months ago ABC expressed before this Committee its concerns about the impact that donor deferral policies designed to address the theoretical risk of transmission of CJD or variant CJD by transfusion could have on an already limited blood supply.

At the end of August FDA issued its draft guidance, recommending that individuals who lived 3 months or more in the UK and 5 years or more in the remainder of Europe be deferred from donating blood.

FDA, also, recommended the implementation in phases as Dr. Scott has presented to us and the estimate that 5 percent of our donor base would be lost on that.

We are submitting comments to the draft guidance and those comments address operational issues and they actually do not alter the spirit of the guidelines.

The most important issues that we are addressing

in our comments are we asked CBER to eliminate recommendations to retrieve/quarantine/destroy all in-date products from donors with classical or sporadic CJD because there was a lot of reasoning that has already been presented here that indicates that transmission of classical CJD by blood and blood products is unlikely.

We urged CBER to modify the proposed donor classes to assure simplicity, clarity and better donor comprehension and finally, we expressed major concerns about the complexity of two different implementation dates, and we actually asked for a single implementation date in October that would ensure that education for donors, blood center staff, training and literature, donor registration cards and standard operating procedures would not have to be revised twice in a short period of time.

Our position of our centers regarding the FDA draft guidance, ABC member centers strongly believe that FDA made a diligent effort to balance safety and availability. Seventy-three of the 74 member centers that are based in the United States plan to implement the FDA recommendations as written and as stated in the final guidance. Only one of ABC member center plans to follow the American Red Cross deferral strategy. Thus, and that is a relatively small center, over 99 percent of the almost 7 million units that ABC collects will be performed according to the FDA

recommended criteria.

ABC members want to reaffirm their support of the FDA as the agency responsible for setting national blood safety guidelines. We strongly disagree with the more restrictive approach adopted by the ARC because it may reduce the donor base by 8 to 9 percent or maybe less according to their data, 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 is an important difference is in the donor loss.

I would like to touch upon Tuesday, September 11. As we prepared ourselves for the potential major blood shortages associated with the precautionary deferrals our lives changed.

In less than an hour after three airplanes hijacked by terrorists crashed into the World Trade Center in New York City and the Pentagon, in Arlington, Virginia, thousands of Americans donated blood in anticipation of the needs of survivors. Blood centers soon were overwhelmed by the public response.

By late Wednesday blood center refrigerators were full, their staff exhausted and their hospitals supplied with all their needs for days to come, and I think the data show exactly that.

Within 24 hours of the attack concerns about the availability of blood and blood products turned into concerns about excess collection, outdated and potential shortages in the weeks ahead because many donors scheduled to give in the coming weeks had responded to the current crisis.

Tragically the need for blood was minuscule compared to the enormity of the attack. The New York Blood Center, a member of America's Blood Centers that provides most of the blood used in the Greater New York City distributed only 600 additional units of red cells in the 24 hours that followed the attack or an increase of 20 percent over their usual daily distribution.

Ultimately more than one-quarter million people and the exact number is 259,714 donated blood to ABC centers from Tuesday, September 11, through Sunday, September 16.

Overall this represents nearly three times more blood than these centers would have collected in the same time frame.

As a group ABC members collected a 10-day supply of blood in only 4 days. ABC has provided the Committee and the audience with reprints of a commentary that was published in the October issue of the Journal of Transfusion. It summarizes our experience in the weeks following the terrorist attack.

ABC worked closely with governmental agencies. FDA officials called us within hours of the attack to ask what was required to maintain an uninterrupted blood supply.

The Army Services Blood Program Office of the Department of Defense was in continuous contact to offer assistance.

On Friday, September 14, the Assistant Secretary for Health convened a meeting with officials from ABC, the American Association of Blood Banks, the American Red Cross and government branches involved in the emergency to evaluate the status of the blood supply and to provide the American public with a unified message about blood donations.

We all agreed that the blood supply was sufficient to meet all anticipated short-term needs and that the nation's focus must change to assure the long-term needs over the ensuing months.

Unfortunately, later that day ARC rejecting what we thought was consensus continued to issue calls for blood donations and the excess blood would be stored in a frozen blood reserve.

I would like to talk a little bit about variant CJD deferrals in the future. Blood services in the United States as I said before have changed with a single devastating event.



We knew that the American population was willing to donate blood in a moment of national crisis. We saw it with the earthquake in San Francisco, the Gulf War, the Oklahoma City bombing and now the terrorist attack.

We have documented that there is a strategic donor reserve ready to be mobilized in times of extraordinary need. What we don't know is whether we can sustain such a response as the urgency decreases but demand for blood increases.

Our past experience led us to conclude that only a small portion of individuals donating during catastrophic events become regular donors.

ABC members do not believe that frozen blood is an effective solution. Frozen blood is extremely valuable for maintenance of small rare blood repositories for patients with rare blood cell phenotypes like patients with sickle cell disease and thalassemia. The process is too slow and cumbersome for management of large inventories in national emergencies.

ABC agrees with Carl Fitzpatrick from ASPPO. The best place to store blood is in the donor. ABC members are working actively to transform this good will and motivation to donate blood into a sustainable continuous contribution to the lives of patients in need.

We are investing in extensive market research to

learn how these individuals can be persuaded to donate more often. We will launch a major member initiative, donor initiative campaign in a few weeks and continue through the introduction of variant CJD deferrals to assure that hospitals and patients served by ABC centers have an adequate blood supply.

We will, also, contribute to the HHS efforts in data collection for monitoring the adequacy of the blood supply. We can provide supply data. Our initial monitoring system will be implemented in the next few weeks, 2 weeks actually, and I would like to thank you very much for the opportunity to present our point of view, and I don't know if you want me to answer questions.

DR. BOLTON: No, I think we will hold questions until after all the speakers have had a chance to speak.

Thank you, Dr. Bianco.

Our next speaker is Ms. Jacquelyn Fredrick from the American Red Cross.

Ms. Fredrick?

MS. FREDRICK: Thank you. Mr. Chairman and members of the Advisory Committee, we are delighted to be able to share with you our experiences of the last 4 months in ensuring the availability of the blood supply and preparing for variant CJD deferrals.

The Red Cross is committed to developing a stable

and sustained blood supply to meet increasing patient needs and hospital demand for these life-saving products.

In June we briefed this Committee on our plans to make chronic cyclical shortages a thing of the past. We shared with you the new systems we were implementing to monitor the amount of blood collected, distributed and inventoried at all of our blood centers nationwide as well as the market research and outreach programs to reach our generous blood donors.

Even prior to the attacks on our country the summer campaign highlighted our ability to increase blood collections by using the right strategy and resources. Our goal is now to sustain this effort.

By expanding and refining strategies we are working to ensure that we will collect 9 million units of blood within 5 years.

I would like to share with you our ability to respond to the blood availability needs of these past months. First, let me address issues in New York.

The Red Cross is committed to meeting the patient needs throughout the country. In June the Committee heard from New York City hospitals, the New York Blood Center, the New York Health Commissioner, Dr. Novella about concerns related to the potential impact of an expanded donor deferral criteria for variant CJD.

It was estimated that the deferral would result in cancellation of over 7000 transfusions each month in the New York and New Jersey hospitals in the metropolitan area.

In August the Red Cross responded to this need by announcing plans to provide blood to the New York City area to avert any supply crisis during a transition away from the area's dependence on European blood.

In August in response to these concerns and after discussions with the FDA and the State of New York officials the American Red Cross committed to provide 180,000 units of blood in order to cover the loss of blood imported from Europe by the New York Blood Center as well as the potential loss of donors in the New York City area.

We communicated this pledge of assistance to the FDA, New York Blood Center, the New York State Public Health Commissioner, the Greater New York Hospital Association and to the New York Congressional Delegation.

As I said, back in January the first time we had presented to this Committee we believed it was the responsibility of all the blood providers to come to the aid of the patients in New York.

Turning to the events of September 11, the Red Cross was, also, able to immediately mobilize its unique national network to respond to the horrific attacks in New York City, Washington, DC and Pennsylvania.

The Red Cross moved more than 5000 blood donations within hours to the two Red Cross blood centers closest to the metropolitan area. This added to the already 5000 units already positioned around that metropolitan area in Washington, DC for a total of 10,000 units.

Unfortunately, only about 1000 donations were actually shipped into the New York and New Jersey areas.

I would now like to turn to the impact of the variant CJD deferral. The Committee has asked us to discuss the anticipated impact of an expanded donor deferral for variant CJD.

As you know, the Red Cross implemented its new deferral policy for variant CJD on October 15, of this month. The Red Cross will defer donors who have spent time in the United Kingdom for accumulation of 3 months since 1980 or donors who have spent time in any European country for 6 months or more since 1980 or donors who have received a blood transfusion in the United Kingdom.

In May to prepare for the expanded deferral the Red Cross commissioned Wirthlin Worldwide to perform a telephone survey of a nationally representative sample of Red Cross donors. Those were donors who had donated in the last 12 months to determine the number of individuals that would be deferred under the new Red Cross policy.

The findings of this survey indicated a total of 3

percent of our eligible donors will be deferred with a margin of error of 0.6 percent and potentially additionally an additional 1 percent will erroneously self-defer even though they are actually eligible to donate.

Taken together, the results of the survey indicate that within the Red Cross we could anticipate about 4 percent loss of our donors.

Since October 15, we have been monitoring the deferral rates on a daily basis across the nation to determine the impact of collection and make informed decisions about our collection goals.

It appears that through our efforts to educate our current donors we have sent out about 5 million letters to our blood donors informing them of the change in our policy and encouraging them to donate if they were eligible.

Education of our sponsors. The on-site deferral rates will be substantially lower than even 4 percent, and we had planned in our collection goals for an 8 percent loss.

We have, also, turned our attention to increased collections. Prior to September 11, the Red Cross had already seen a dramatic increase in collections resulting from our initiatives to grow collections and mitigate any losses anticipated from the expanded variant CJD deferral.

Presenting donors to the Red Cross surged to 7.5

million in our Fiscal Year 2001, which was a 6 percent increase over prior year.

We had, also, implemented finger sampling for hemoglobin. If you had looked at discounting that and just looked at gross increases in presenting donors we actually saw an 8-1/2 percent increase in productive units.

Our collections in July and August this year have increased 8 percent over the same months last year. The increased collections had a direct impact on our inventory.

Our total red cell inventory was 33 percent higher this August than the past year and our type 0 inventory was 83 percent increased over last August.

There has been a tremendous outpouring of Americans wishing to give blood in response to the attacks on our country. In this period of uncertainty the Red Cross has a responsibility to be prepared for any contingency such as additional terrorist attacks on American soil or the potential to support the US military program.

During the immediate aftermath of the September 11 attacks we expanded blood collection, storage and freezing capacity so that we would not have to turn away donors who were seeking comfort in donation with the Red Cross.

We are now continuing those activities so that we can build and maintain a large readily deployable liquid inventory of blood and grow the frozen blood supply.

The 2-to-3-day inventory of blood that was traditionally tolerated within this country is inherently inadequate. At present the Red Cross has at least a 10-day inventory and our goal will be to sustain that inventory between 7 and 10 days in a liquid form in addition to frozen blood reserves.

We continue to move forward with our long-term initiatives to build a stable and sustained blood supply. We have been forecasting collections for over a year and one-half and we continue to refine our projection and demand models.

In conclusion, on behalf of the Red Cross I would like to thank you for this opportunity to provide our views and strategies to increase blood collections. We are confident and optimistic that the goals of safety and availability can be achieved through dedicated resources, coherent strategies that we are implementing throughout the Red Cross system.

Thank you.

DR. BOLTON: Thank you, Ms. Fredrick.

Next is Dr. Robert Jones from the New York Blood Center.

DR. JONES: Good morning. I would like to first thank the Committee for the opportunity to address you again. It is getting to be a regular visit. If you will,



this is our report from ground zero.

September 11, certainly changed our world and at least temporarily it, also, altered the landscape of blood donor recruitment and blood supply.

Suddenly we went from suffering the perils of chronic blood shortages to dealing with the equally problematic issues of acute oversupply and system overload.

Relative to the rise in new blood donor deferrals released as draft guidance from the FDA we have experienced some setbacks in implementing the plan initiatives because we suddenly had other priorities related to the World Trade Center attack.

The setbacks are related to delays dealing with our European partners for planning the phase-out of Euro-blood, postponements of meetings with the military and delays in dealing with alternative US suppliers in addition to putting off some of our initiatives that we had implemented prior to September 11.

As a review I would just like to remind you we stand to lose approximately 210,000 red cell units from the New York City affected blood supply which is a combination of Euro-blood, 180,000 units which counts the type mix effect and 30,000 units of our own collection, so a total of over 25 percent of the area supply.

Now, pending further discussions with **Europeans in**

publishing a final guidance we now see phasing out approximately half of the European supply at the end of May and the remainder at the end of October 2002.

Our own donor losses from pan-European deferrals will be absorbed in October as well. These supply gaps will be made up by a combination of increasing our own collections and purchase of red cells from ABC centers BCA, Blood Centers of America and the American Red Cross.

These purchasing arrangements are being finalized as we speak. We expect that the relative contributions from collections and purchases will be about equal through the end of October.. After October 2002, the contributions from NYBC collections will continue to rise as a percentage of the total supply.

We are very hopeful as others that the surge of new blood donors as a result of September 11, attacks will add to the overall donor base of our collections. We now have active programs in place to engage the thousands of donors who were asked to defer donation during the disaster or who were first-time donors that we actually collected.

However, with optimism and with the current oversupply there are warnings that the supply may be less stable than when we were dealing only with chronic shortages.

Consistently surges of massive appeals are

followed by proportional troughs of donations that can lead to shortages.

Furthermore, and this is a point I will expand upon after Colonel Fitzpatrick's remarks, massive outdateding and disposal of red cells from the overcollections following the attack will become public. It is not a day that goes by now that I don't have two or three reporters who are inquiring about our supply and what our plans are to do with oversupply.

We really won't have any precise or accurate ideas of what outdateding might look like until probably about 2 weeks.

Now, the reaction of the donor base to these public events is unpredictable, and we feel must be carefully managed in order to recognize the educational opportunity regarding the perishable nature of blood.

The public, one of the things we consistently learn from the public as we have a lot of time to talk to them when they are standing around waiting to donate blood, they simply do not understand that this is a perishable product.

Whereas we would all like to believe that blood shortages will never recur after recent events realistically we feel the supply is now even less stable and more unpredictable than before September 11.

Upon reviewing the draft guidance we, also, have concerns about public implications and the management of public perception that should be addressed. Our donor groups, organizations as well as our hospital customers have expressed these concerns. They are related to the underlying principle of geographic deferrals. Specifically as BSE is identified in other parts of the world or in the US is there a plan to extend this principle and how far will this mechanism be extended?

Will the millions of US citizens who travel abroad be warned of the risk of transfusion in BSE countries, and finally, does the public health benefit warrant the exclusion of 15 million Americans approximately and over 550 million Europeans from US blood donor eligibility?

These questions and others are concerns from the public as well as the transfusion medicine community and certainly will not be answered easily or today.

However, we hope there are issues that will be integrated into the future thinking of this group and actions of this group and FDA as guardians of blood safety.

As a vanguard blood care organization we remain committed to blood safety and the efforts of the FDA and this group.

We assure you that we are working diligently to manage this new horizon. However, we hope you, also,

recognize the new dynamics introduced by the nation's war on terrorism and how the priorities of the public and the blood care system continue to evolve day to day.

Thank you.

DR. BOLTON: Thank you, Dr. Jones and finally Colonel Fitzpatrick from the Armed Services Blood Program Office.

DR. FITZPATRICK: Good morning. Thank you for the opportunity to speak. Since we took a turn toward the blood supply, I am going to preface my presentation on vCJD if it is okay. I will stay within my time period.

We have had questions and discussions with Dr. Nightingale's presentations and the others about the blood supply. I just want to make a couple of comments.

Our responsibility is to judiciously recruit, safeguard and guarantee availability of blood, while we are frank and honest with our donors about the need and what happens to the blood we collect from them.

After September 11, there has been a huge outpouring of blood donations. As Dr. Jones said, we really don't know what is going to happen in the future. World War II and Korea created a core of lifetime blood donors. Vietnam did not. Most of the blood supplied in Vietnam, actually 95 percent was provided by the military, not by civilian collection agencies and Desert Shield, Desert Storm

because of it being a short war did not create a lifetime group of blood donors.

We now have a different situation. We have a situation in which our homeland has been attacked. We see constant notifications in the press about anthrax and homeland defense, and I will go back to my first statement.

It is our job as blood suppliers to judiciously recruit and safeguard the blood supply and guarantee availability while being honest with our donors.

So, that is the challenge that is ahead of us, the blood suppliers. The challenge ahead of you is to not become preoccupied with the availability of the blood supply, the impact on the donors but to provide us, the blood suppliers, the scientific information that the FDA, Health and Human Services, the Red Cross, ABC and ourselves at DOD need to determine who to collect the blood from and what the risk to the blood supply is from this agent, and I would ask that that be what you focus on because we need good valid information to make our determinations.

I was quoted as saying that the best place to keep blood is in your veins, and I did make that statement at an NCHS meeting, but I would like to, also, say that we, DOD, do maintain a mixed inventory of liquid and frozen blood, and we are in the process of replacing that inventory with new technology which makes it more available and will

provide us 14-day dating after we thaw and deglycerolize it because we have to supply blood in places that most people don't. We have to deal with the fact that there have been spot shortages in this country in the past, and we don't always have the influence of an attack on our country to recruit donors, and we have ships at sea and other things that most people don't have to deal with.

So, in light of that and if we judiciously recruit the best place for the donor to keep the blood until we recruit them and tell them to donate is in their veins, but we want them to respond when we ask them to donate.

We had a glut of donors in September, and we have continued to have donors. What Dr. Jones was alluding to was that in November and December we don't really know what will happen.

It is our job and our goal to maintain that supply and be able to deal with that.

So, with that I will go on to the next slide here and tell you what we are going to do with CJD. You may heard in the press that we limited access to some of our bases for civilian collection agencies. That was not in response to variant CJD. That was in response to the need to be able to respond quickly and immediately to an increased surge or requirement for blood from our own donor supply. We operate 21 blood donor centers. We collect about 105,000 units a

year, 1 percent of the nation's blood supply, not a lot, but we by maintaining our own program are not subject to those troughs and peaks that Dr. Jones alluded to. We do have our own troughs and peaks, but we try to maintain the ability to respond.

So, if that comes up I just wanted to clarify why we did that. It was not in response to implementing the variant CJD policy.

Monday we will implement our guidance which is based on the FDA guidance document that we have worked with the Red Cross, FDA, ABC and HHS over the past, I don't know, 18 months, however, long it has been to come to some conclusion as to where we would be drawing blood within this nation under about the same guidelines for everyone. That was our goal.

Our goal was to have a blood supply that was collected under the same guidelines. The difference in our implementation between what we have done and what the guidance document for FDA says is that it would, and there was a question previously about how hard is it to differentiate between north and south of the Alps and the years 1980 to 1990 and 1980 to 1996. We operate three blood collection programs, each service, the Army, Navy and Air Force operate their own programs under, their own FDA license. They have their own QA officers and QA program.



Their QA officers came to us and said, "We think this is going to be hard to do." There is a lot of travel between north of the Alps and south of the Alps. People sometimes rotate between north and south of the Alps. We go on what is called temporary duty. An Air Force individual who is stationed at Ramsdine(?) Air Base in Germany might be stationed temporarily in Italy for a period of time, sometimes 30, 60, 90 days at a time. What we would be asking those people to do is recall back through the years 1980 to 1996 when they were stationed where and how long they spent in those locales, and they try to be honest with us. They really want to be honest with us. What we anticipate would happen is that they would go home, talk to their wife who would say, "You know, honey, you were TDY down in Italy a lot," and that might have added up to 6 months. In order to alleviate those post-donation callbacks and the quote errors and variances that might result from them and to make it easier for our screening personnel who are not nurses; they are primarily enlisted personnel with medical technician training, a 2-year program of training and a special training in blood banking. They are certainly not novices and they are not untrained.

We wanted to keep it as simple as possible for them. Some of you may recall the military tries to keep the KISS principle. So, we combined those two categories and we

are deferring anyone who was stationed in Europe from 1980 to 1996 for 6 months or more for simplification in the donor screening process.

Everything else that we have done conforms with the FDA guidance. We reduced time in the UK from 6 months to 3 months. There is some question about the 5-year policy. If I was a college student on exchange in France for 4 years, I wasn't a DOD person who spent 6 months. Well, the 5-year thing applies to you, sorry. If you spent 5 years in Europe as a non-DOD affiliated person then you will be deferred, and then after 1996, for those people currently stationed in Europe the 5-year deferral applies to them and that is our policy. If you had been there from January 1, 1997, to January 1, 2002, then you will come under the 5-year deferral program.

The anticipated loss prior to September 11, was 18 percent. That is still the loss. We know 18 percent of our personnel that are currently on active duty spent at least 6 months or more stationed in Europe.

Just as the Red Cross we had a pre-information campaign. We have educated our groups. We have tried to educate our donors. I cannot tell you what the loss will be at the door Monday when they present and how many of them will actually come and present. I know that we have already had complaints from long-time donors as to well I can donate

this week, but I won't be able to next week.

My answer to them is relatively simple. I am one of that group, too. I have spent 6 months in Europe as most of us old colonels have, and my family is the most upset including my daughters who won't be able to donate until you as an august scientific body can present us with the right information to reinstate them as donors or tell us when we might be able to do that.

What are our concerns? Japan is a concern to us because we have a large group of Navy personnel stationed in Japan, Marines and Air Force, not so many Army. Those other nameless Asian countries that might have received bone meal products that we haven't been told about yet are of concern, also, because the Army has a large group of people stationed in Korea.

Our problem is that once a country comes out on the USDA list as a BSE country our veterinary agency takes action to deal with the food products that are purchased and consumed within that country locally and that raises the question to me as the head of the blood program, well, we cannot use the food anymore; what are you going to do about the blood, and I need some help to do that.

I need a time frame to work with. So, I would ask that this not be delayed until the next meeting but there be some sort of action taken to help address what time frame we

are concerned about here in the importation of bone meal from the UK; what is the risk of BSE transmission to individuals who may have consumed beef in Japan and how do we as a blood collection community deal with those donors?

So, that is really what I am asking you today about Japan.

In closing, which I may have gone a minute over, and I apologize, I would like to just reconfirm that what I would appreciate from my standpoint from this Committee is that you assist us in interpreting the data, however minimal that data may be and that you assist us in applying the precautionary principle that Dr. Epstein talks about so frequently in taking the data available at the moment, applying it to the donor population, allowing us to help interpret that so that we provide a safe blood supply, as safe as possible and ameliorate whatever hypothetical or real risk there may be for the transmission of TSE to a transfusion recipient.

Thank you.

DR. BOLTON: Thank you, Colonel Fitzpatrick.

I would, also, like to thank you on behalf of the Committee for all of your service and all those in the Armed Forces.

We now will move to the open public hearing, and I understand we have one person who signed up or requested to

speaking, that is Kay Gregory, Director of Regulatory Affairs from the American Association of Blood Banks. Is Kay here?

Very good, Ms. Gregory, you have the floor.

MS. GREGORY: Thank you very much for the opportunity to speak. I want to clarify that we have actually provided for the Committee three different sets of comments on this guidance document. They relate to different issues and the one that I am specifically going to discuss today is construction of donor questions that should be printed on the questionnaire to decide whether donors should be deferred or not.

The American Association of Blood Banks is the professional society for over 8000 individuals in blood banking and transfusion medicine. We are the professional association for 2200 institutional members who are involved in all aspects of blood collection and in transfusion services.

Our members are responsible for virtually all of the blood collected, and more than 80 percent of the blood that is transfused in the United States and in the last 50 years the AABB has maintained an adherence to safety and availability of the nation's blood supply as our primary concern.

Today I want to speak on behalf of the AABB interorganizational task force for redesigning the uniform

donor history questionnaire and this group is rather widespread. It consists of many different individuals. There are representatives from the blood bank organization. There are liaisons from both the FDA and CDC and the Canadian blood services and we, also, have survey design experts, statisticians and an ethicist who is representing the public on this particular group, and this task force is engaged in an extensive process to redesign and simplify donor questions.

By way of background the initial step of this project, of this task force was to evaluate the current questions and suggest new wording.

The new wording would help in focus groups of experienced donors as well as non-donors, and based on that input we made additional changes.

We are currently in the process of further evaluation of questions utilizing one-on-one cognitive interviews that are being conducted by the National Center for Health Statistics.

These questions are on the AABB web site to solicit input from the public as well as from our own members. Blood collection personnel will, also, be asked to review the final document and based on effective feedback from all those sources we may be able to make significant changes, and we view this to be the final product to FDA for

their approval.

I tell you this by way of background because I think many people think that donor questions are very simple to design. All you have to do is figure out what you want to ask them, and I am trying to make the point that that is not the case and particularly not if the questions are going to be validated and donors are going to understand what it is we are trying to ask them with these questions.

In terms of questionnaire format our simplified questionnaire will have time periods of concern. So, for example, we will probably have one heading of "Have you ever?" because there are a whole bunch of questions we want to know about, "Have you ever done this?"

All the questions that we want to know about "Have you ever?" would then fall under that heading. Another example, the time period that might be used then would be 1980 to 1996. So, from 1980 to 1996, there would be a series of questions that would apply to that time frame.

This type format is supported by the survey design specialist and was also proposed and discussed at the October 2000 joint FDA, AABB workshop to redesign the donor history questionnaire, and we want to take this opportunity to comment on this aspect of the draft guidance that we are discussing today.

During that 18 months we have conducted focus

groups to, as I said, evaluate the current questions that were already approved by the FDA. We then modified the questions based on this focus group feedback. The alternative wording that we are now proposing for this particular guidance on CJD and vCJD is based almost exclusively on these previously obtained focus group data.

When focus group data were not available for a specific question the survey design specialist on the task force provided the requisite expertise for developing some new wording.

The task force has now conducted focus groups to compare the questions that were proposed by the FDA in the guidance with the wording that the task force proposals in our comments to the guidance.

Unfortunately, we have just completed those focus groups. So, all we have is a very quick look at raw data, and I cannot provide you any details on what the focus groups said other than it is very clear that the focus groups preferred the more simplified language that the task force has suggested.

However, there are some concerns even with our simplified language and they have made some suggestions which we will be looking at and we will be submitting a second set of comments to the FDA as quickly as possible that we now would like to change the wording that we have



even proposed.

It is important that in these focus groups that we did we did include military personnel. Thanks to some help from our military representative on this particular task force we were able to find military personnel to try these questions out on, and to say that they were confused is being, I would be understating completely.

By way of example I just want to review one question. You have in your comments all of the questions and our suggestions, and I just want to take one as an example, and it isn't even one that is related to variant CJD. It is one that is related to CJD, but the proposed question and actually the one we have been using all along is have you or any of your blood relatives had Creutzfeldt-Jakob disease or have you ever been told that your family is at an increased risk for Creutzfeldt-Jakob disease.

Now, think about their hearing this because that is the way many donor interviews are going and if they don't hear it, they, are reading it. So, they are reading Creutzfeldt-Jakob disease and missing perhaps some of what we are really after.

So, the proposal from the task force is to make a very simple question. Have any of your relatives had Creutzfeldt-Jakob disease? The rationale for this is that we know from our focus groups that they do not like compound

questions. They don't want to be asked two or three things in the same question. They don't care if you have to increase the number of questions that we ask just so throw out the four things in the same questions because by the time I get to the end I have forgotten what the first thing was that you asked me.

The crux of this question if you think about it is really family history or risk of CJD, and we think that the simplified language will elicit that information. Eliminating the part of the question that asks whether the donor has CJD will reduce the number of false-positive responses that would ultimately defer a donor unnecessarily.

If the donor had undiagnosed CJD they would answer no because they wouldn't know about it. Further if they did have diagnosed CJD they would be extremely unlikely to appear as a prospective donor and would most certainly be symptomatic and deferred on that basis even if they did happen to come in.

In closing what I would like you to understand is that designing donor questions is not a simple matter of getting a couple of people and sitting around the table and saying, "Why don't we ask this and ask everything we need to ask about all in one question?"

Donors must understand the questions so that they can answer appropriately and the questions will clearly

distinguish and accurately distinguish those who should be deferred from those who are merely confused by the question.

The wording of these questions, particularly the ~~CDJ~~, vCJD questions must be carefully considered because they may have significant impact on the kind of donor deferrals that we see.

Thank you.

DR. BOLTON: Thank you, Ms. Gregory. I am sure that the FDA values your assistance in clarifying the construction of these questions.

Is there anyone in the audience who would like to make a presentation during the open public hearing?

Okay, I see no volunteers. So, at this time I think we will move on to the Committee discussion. What is our time frame? Well, we have 2 minutes for discussion. So, everybody speak quickly. We will run on a little bit longer and delay the break a bit, but I think we should open the Committee discussion now to address the issues presented by our four speakers on the update as well as the last part of Dr. Nightingale's presentation on the DHHS meeting.

Questions or comments?

Dr. Belay?

DR. BELAY: I would like to have some clarifications. So, I have several questions. The first question is to Colonel Fitzpatrick. It is not clear to me

whether or not your deferral policy regarding variant CJD is different from the recommendations of the FDA. Do you have any differences in the deferral policy?

DR. FITZPATRICK: The only difference we have is that we did not make the differentiation between north and south of the Alps and so an individual, right now an individual per FDA guidance if you were stationed in Germany after 1990, you could donate blood because we know very factually that the defense commissary agency who purchased beef from the United Kingdom quit purchasing beef at the end of 1990, and that was actually congressional legislation, totally unrelated to BSE, but it required the importation of US beef only to military installations north of the Alps.

South of the Alps beef purchases from the United Kingdom continued, and individuals stationed south of the Alps up until 1996, could have been consuming beef purchased from the UK. So, that is why the FDA came up with in their guidance the differentiation between people stationed north of the Alps and south of the Alps and the two different time periods.

Based on the input from our quality assurance officers in the three services we extended the period north of the Alps essentially rather than stopping at 1990 for that deferral period. We extended it to 1996 so that anyone stationed in Europe during the period 1980 to 1996, is

deferred not because they were consuming beef from the UK in Germany after that but because of the issues I raised about postdonation information, the fact that Kay brought up that the questions are very confusing. Trying to differentiate that is difficult and we have a good bit of travel between people stationed north of the Alps and south of the Alps back and forth during those time periods, and it would require them to try to accumulate from memory the time they spent in each geographic area and we just felt that was too difficult.

So, we are in complete compliance with the guidance and we are more conservative during that time frame 1990 to 1996 for people that were stationed north of the Alps.

DR. CRAWFORD: Actually with respect to the Japan question as I am sure the colonel knows the Government of Japan issued a statement early this week saying that the herd in question that produced the positive BSE case did not receive any meat and bone meal of European, of British origin and rather that the meat and bone meal came from Taiwan and perhaps some other Asian nations.

I suspect this does nothing more than complicate your risk assessment that has to be done because I would suspect that there is a trans-shipment problem so that meat and bone meal was shipped first to Taiwan or somewhere else

and then shipped to Japan, but it is a very, very complicated issue. It is going to require some kind of free-wheeling risk assessment, and in the current of the decision I would like to talk to you a little more about that.

DR. DE ARMOND: Kind of following up on that how much does the military in the Pacific buy beef from Japan? It seems like beef in Japan is very expensive. I am sure you wouldn't do that or do you get your beef from Korea or from Southeast Asia to feed the troops and when would the troops actually come in contact with a very small number of cattle that are infected so far? We don't even know if it is the variant CJD or the variant strain of BSE in Great Britain. There is a natural BSE in cattle to begin with.

DR. FITZPATRICK: I am not the best person to answer specifics. I can give you generalities. The commissary agency is actually run by the veterinary department because they do the food inspection, but as far as purchasing local product most of our consumers prefer just as you, fresh beef or fresh product and the commissary agency tries to meet the consumer's request. So, there are agreements with most of the host nations that we have bases at to procure fresh vegetables, fresh meat, those sorts of things for purchase by our personnel so that they have them available to eat. So as far as specifics in Japan as to how

many pounds and all that we had that information for your -- we can find that information for Japan.

There is, also, eating on the economy, having been an old colonel and stationed most everywhere in the world by now, I was stationed in Korea. I visited Japan frequently. I can tell you that most of the focal points of our, most of our people are stationed on Okinawa. Beef consumption in Okinawa is different from beef consumption in mainland Japan, and the Kobe beef steakhouses are the favorite place for people to go out to eat. So, they were eating it even if they didn't buy it from the commissary, they were eating beef on the local economy while they were stationed there.

So, that is about the most specifics I can give you on that right now.

DR. DE ARMOND: It seems like Kobe beef or certainly Kobe steak should not be infected and again we don't even know the extent of the disease of BSE in the country to even begin to assess the effects on the individual. Certainly 35 percent of their consumption of beef probably didn't come from the local area as it did in Europe from Great Britain.

DR. FITZPATRICK: Right, and again I don't know. It could actually be higher because to ship beef from the US overseas it has to be flash frozen. It is shipped as either a quarter or whole carcasses. I have been doing a lot of

work with the vets lately. So, I know a lot of this stuff, and it is expensive to ship and maintain and provide. So, in many cases it is actually cheaper to buy the product locally than to ship it there.

DR. BOLTON: Dr. Cliver and then Dr. McCullough.

DR. CLIVER: By chance I spent last week in Japan, and was aghast to learn that on 3 or 4 days' notice it was implemented that every slaughtered animal, bovine from veal calves on up has to have its brain tested before the carcass can be released for human consumption.

One, I think that is not a particularly wise use of resources but second, I think the flash implementation was probably ill advised because my own laboratory is getting involved with some of this stuff, and getting the laboratory to do valid tests entails some training and some phasing in, that time has not permitted there.

Having said that though one thing I didn't ask that I should have is until now what were the carcass fabrication regulations that were in place in Japan, were there rigorous efforts to exclude CNS tissue from what got sold as edible carcass. I have a fair idea of how we are going at that in the United States but whether anything comparable has been in place in Japan I cannot say.

I do think that there is a distinct possibility that that animal was a sporadic case even though some of my



colleagues mightn't agree that such would even exist. Beyond that it is important that we know whether this is a critical control point in the sense of our hazard analysis, critical control point safety system. Can we keep CNS tissue out of beef there or here and finally, if we are going to be testing how much safety does that actually impart from the consumer's point of view because the amount of resources given the Japanese economy is in trouble, the amount of resources that are being devoted to that probably are canceling most other food safety things that they have had in place in recent times, and those other food safety measures I submit will probably save more lives than 100 percent BSE testing, but then back to the concerns of the military, I think the key question is how have the Japanese been processing carcasses ever since we recognized the BSE threat earlier in the nineties. Have they been taking rigorous steps to exclude central nervous system tissue from the portions that are sold or not?

DR. BOLTON: Dr. McCullough?

DR. MC CULLOUGH: This is a question for either Dr. Bianco, Ms. Fredrick or Dr. Jones.

When this group originally recommended the BSE deferrals and voted in favor of the FDA's proposal there was and there has always been a great concern about the impact on blood donors. The events of the last 6 weeks have created

a wholly different environment and on the one hand there are enormous numbers of donors that have appeared. On the other hand we are hearing that the history of this sort of thing is that these don't necessarily turn out to be good long-term donors and that there may be other reasons, public image and things that this may backfire to some extent.

So, are there specific steps that you all are thinking about that might address the responses of the last 6 weeks and how that may impact the loss of donors that will occur from these new criteria?

DR. JONES: I mentioned in my brief comments that we have engaged new initiatives to contact these donors, the ones who were either first-time donors who came and were collected or donors who were turned away because we obviously knew the medical need was not going to be that great and this has gone through telemarketing and letters and focus groups and all kinds of things that we can come up with from a marketing point of view to try to make sure we maintain as many of those donors as possible.

My understanding though this has sort of been, as this has happened before, a lot of these efforts have not been so successful. We are confident that it will be successful, of course, but we will have to see what happens.

MS. FREDRICK: Likewise, I think. We have had almost 1.3 million people contact us within the first 4

weeks of this. Those are donors as well as potential donors, and we are now in the process of literally contacting every one of the individuals who contacted us, either through our 800 number or Internet or showed up at a blood drive and putting all those people in the database and we have now an active program that will go out 2 years in terms of telemarketing and direct mail to bring these donors back in.

I would, also, say that we are not anticipating a collapse in the blood supply in November and December and January. Essentially we have fully booked our calendar at least through January. We know that the blood supply today will carry us through the Christmas holidays at the very least.

I would, also, say, Jeff because of our planning we are not seeing the loss of donors that we anticipated. Either the initial numbers of the FDA 8 to 9 percent, our own survey said, "Three percent, maybe another 1 percent," I mean we are seeing very, very low numbers of people showing up that we have to defer on site.

DR. BIANCO: My comments for America's Blood Centers are similar to Dr. Jones and Jackie. Certainly the outpouring of blood donors was very important. What we are trying to do is we have created what we call a member donation initiative. We have hired consultants. We have run

focus groups and we are trying to reach the segment, the part of those numbers to focus on them, those that are more likely to donate again and become repeat donors, and we are putting a tremendous effort into that.

The other point was very important. I should just tell you as a matter of curiosity, Jackie, we received 1.2 million calls to the 800 number. ABC, each member center has their own local numbers and 800 numbers but the national number had 1 million calls and we paid \$56,000 in our phone bill for September just for that 800 number. So, I think that our challenge is to focus on these donors and maybe recreate what we had with World War II as a continuing set of donors that will keep our blood supply as we need it, and I hope we will be able to do it even in the face of the deferrals. Certainly the outpouring of donations gave us relief and gave us a new opportunity, a new donor base or a new potential donor base that we can try to draw upon.

Thank you.

DR. JONES: Why don't I just make one last comment? Relative to what Jackie said we, also, have very strong bookings for our blood drives going out into January, but what is really key is what we call the efficiencies, and that is when the people actually show up for those drives, and unfortunately the last two or three days we are starting to see some erosion of our efficiencies which had been

riding very, very high, 100 to 110 percent and they are now starting to fall off. Whether that is the beginnings of something we don't know, but that is the parameter that is probably more important for the supply than the actual bookings.

DR. BOLTON: Just to make a comment from Colonel Fitzpatrick, with respect to the Japanese situation it is important I think for us to remember that in the UK there were approximately 180,000 confirmed cases of BSE and possibly 800,000 to 1,000,000 potentially infected animals. I forget what the number is that was estimated that may have been of the human food supply, but it was quite significant. So, while two cases of BSE in Japan is clearly a red flag and raises concern, it certainly should not be thought of as on the same level of magnitude as that in the UK. I, also, would hope that both the Japanese and the other Asian nations have learned by the mistakes that were made in the UK in terms of the sourcing of beef for the human food supply and other regulations. Of course, there is no guaranty that that will occur, but I think that we have not yet reached that sort of level of concern for Japan.

DR. FITZPATRICK: And if you will note from our implementation policy by implementing the FDA guidance we are trying to take into account and conform with what is the theoretical risk as identified by the Committee and the FDA.

So, the S-year deferral follows. We are implementing that same deferral ban criteria and I would hope that at most Japan would follow the same criteria if there is a recommendation for deferral. So, I am not suggesting that we would immediately defer for Japan although we have based our deferral policy in looking at how the FDA guidance was written on the USDA list, and we have the conflicting issue of once a country is on the FDA list now our personnel stationed in that country, our veterinary folks and our commissary agencies are now dealing with the fact that just as they cannot procure beef locally in Europe and Britain we have the same problem in Japan and now we have a precedent set which was okay, that happened in Europe, and you said that I cannot donate blood. Now, it is happening in Japan, how come I can still donate blood, and that is the difference we are going to have to grapple with and try to explain.

DR. BOLTON: I think there may be an educational issue there, but this is certainly a complicated issue and I think that we can look out into the future with some reasonable certainty that Japan will not be the only Asian country that will report a BSE case. I guess we could expect that probably Korea and many other countries will begin to report cases or will have cases perhaps that don't go reported, and as I have spoken with Dr. Asher in the FDA

about this, this presents somewhat of a moving target for this Committee in terms of evaluating information and also for the FDA in terms of devising guidance, and I guess all we can do is our best effort to evaluate the data as it accumulates and to make recommendations as best we can.

Dr. Roos?

DR. ROOS: I wondered whether the American Red Cross representative would just clarify for me the differences between their guidelines and the present guidelines of the FDA.

MS. FREDRICK: I might have to call on the FDA to clarify their guidelines. We are doing UK for 3 months from 1980 to present. We are not stopping in 1996. So, we are continuing forward. Probably the biggest difference is we are doing Europe for 6 months cumulative time from 1980 to present and I think FDA's guidance is France for 5 years by May and then all of Europe in October for 5 years.

The military piece isn't an issue for us because of our 6-month deferral. We don't have to deal with that, and so we have a very simple question. Have you traveled outside the United States since 1980?

DR. ROOS: I guess the reason I bring this up is that there must be some confusion I would guess and maybe tension in blood banks that have donors, donations from American Red Cross and donations that are non-American Red