DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

63RD MEETING

VOLUME I

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Statement of Conflict of Interest

DR. SMALLWOOD: Good morning and welcome to the 63rd Meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. At this time, I will read to you the statement of conflict of interest that will apply to all proceedings of this meetings.

This announcement is made a part of the record at this meeting of the Blood Products Advisory Meeting on June 17th and 18th, 1999. Pursuant to the authority granted under the Committee Charter, the Director of the FDA Center for Biologics Evaluation and Research has appointed Dr. Paul McCurdy as a temporary voting member for all committee discussions.

Based on the agenda made available and on relevant data reported by participating members and guests, it has been determined that all financial interest in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the committee discussions have been considered.

In regard to FDA's invited guests, the agency has determined that the services of these guests are essential. There are reported interests which are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants.

The interests are as follows. Dr. Michael Busch is employed by Blood Center and is a member of Abbott's Advisory Committee. Dr. Susan Stramer is employed by the American Red Cross, serves as a scientific adviser to Abbott Laboratories, and has financial interests in a firm that could be affected by the discussions.

In the event that the discuss involves specific products for firms not on the agenda, for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in the committee discussions. 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 products they wish to comment upon.

Are there any declarations to be made at this time?

[No response.]

DR. SMALLWOOD: Hearing none, I would like to introduce to you the members of the Blood Products Advisory Committee. As I call your name, would you please raise your hand.

Dr. Blaine Hollinger, Chairperson. Dr. Richard Kagan. Dr. Marion Koerper. Dr. John Boyle. Dr. Mary Chamberland, who is a consultant to our committee. Dr. Fitzpatrick, who is also a consultant. Ms. Katherine Knowles. Dr. Buchholz. Dr. Paul McCurdy. Dr. Joel Verter. Dr. Jeanne Linden. Dr. David Stroncek. Dr. Rima Khabbaz. Dr. Gail Macik.

There are other members that I anticipate will be here shortly. They would be Dr. Mark Mitchell, Dr. Kenrad Nelson, Dr. Ohene-Frempong, Mr. Corey Dubin.

May I ask, so that there will not be undue disruption of the deliberations, that all cell phones be cut off and if you must have them, have them very low, please.

Thank you.

At this time, I will turn over the proceedings of this meeting to our chairman, Dr. Hollinger.

Welcome and Opening Remarks

DR. HOLLINGER: Thank you, Dr. Smallwood.

Welcome to the summer session of BPAC. We have again as usual some most interesting topics today and tomorrow dealing with a variety of topics. There will be some committee updates.

I do want to ask that anyone who is going to speak from the public, that when you come up to the microphone that you state your name and the organization, so we have it

for the record.

With that in mind, I think we will try to keep on time today as usual, and we start with the committee updates on several topics.

The first one, Dr. Hewlett is going to tell us about where we are with nucleic acid testing implementation.

Dr. Hewlett.

Committee Updates

Nucleic Acid Testing Implementation

Indira Hewlett, Ph.D.

DR. HEWLETT: Thank you, Dr. Hollinger and good morning, everyone.

[Slide.]

I am going to be presenting an update on the implementation of NAT, or nucleic acid testing, for blood and plasma.

It is now well recognized that NAT is currently the most sensitive method for virus detection in the window period and that implementation of NAT could further reduce the window period for HCV, HIV, and HBV, resulting in enhanced viral safety of blood and blood products and in enhanced public health safety by providing early diagnosis and referral for medical treatment.

[Slide.]

Due to the complex and labor-intensive nature of

NAT, the approach of screening minipools or small pools of plasma rather than single donations has been considered to be more practical and feasible.

By 1997, some countries in Europe had initiated voluntary screening of donations by testing pooled donations of plasma using a nucleic acid-based test method, and also a directive was issued by the European Union that HCV-RNA testing would be required in Europe for all plasma for fractionation by July 1st, 1999, and that HIV-1 testing of such plasma would be require at some unspecified later date.

This move created an impetus in the U.S. to implement such testing for blood and plasma, and this was made feasible by support from the NHLBI through contracts for developing such tests here in the U.S.

[Slide.]

A number of measures were taken in the U.S. to implement nucleic acid testing. FDA viewed minipool testing as a form of donor screening, and this position was endorsed by the Blood Products Advisory Committee at the March 1997 meeting.

FDA developed guidance outlining regulatory approaches for implementing pool testing and discussed them briefly at the September 1997 BPAC meeting.

[Slide.]

FDA also developed and published draft guidance to

industry for validation of nucleic acid tests. In September 1998, we held a workshop to discuss NAT for HCV and other viruses. At the last BPAC meeting, we discussed the issue of NAT implementation for whole blood and transfusable components under the IND mechanism.

FDA plans to hold a workshop in December 1999 to assess the status of NAT implementation under IND.

[Slide.]

Screening of source plasma for HCV and HIV-1-RNA was initiated in early 1998. Pool sizes ranged from 96 to 1,200 donations. At this time, virtually all source plasma in the U.S. is being screened for HCV and HIV-1-RNA by a nucleic acid-based test.

A significant portion of the testing is performed by a central testing laboratory or testing service, and some manufacturers are also testing for HBV, although this is much more limited than HCV and HIV.

[Slide.]

Nationwide screening of whole blood donations was initiated under IND in early 1999. Pool sizes ranged from 24 to 128 units, although sizes as small as 16 units have been proposed for future testing.

The ARC data, which was kindly provided to us by Susan Stramer, indicate actually that 2 out of 825,984--and that is an update that I got from Sue yesterday, so this

number is actually outdated at this point--2 out of 825,984 donations tested were confirmed positive for HCV-RNA in the absence of detectable antibody.

The ABC centers have reported that 3 out of 275,000 donations have been confirmed to be HCV-RNA positive in the absence of antibody. These are very recent numbers and apparently they have been reported or will be reported at the upcoming AABB meeting in November.

No confirmed HIV cases have been reported so far. The false positive rate, interestingly, has been found to be similar to serologic tests. This is during the Phase I testing of NAT. At this time, more than 80 percent of donations are being tested by a NAT method, and it is anticipated that 100 percent testing will be achieved by the fall of this year.

[Slide.]

This slide just lists the IND PLA-BLA requirements for test validation to give the committee a sense for the types of studies that are ongoing under the IND. The test should be demonstrated to be manufactured consistently under GMP with appropriate quality assurance for components and kit performance.

The purity, identify, and functional activity of primers, probes, enzymes, and other components should be determined and specifications should be established.

Methods for collection of specimens, pooling, testing, et cetera, should be validated and conditions of specimen stability should be established.

There should be in place a validated mechanism for identification and retrieval of positive specimens in a pool, as well as the implicated donor.

[Slide.]

Instruments used in generating pools of to perform the tests and software used to calculate results should be appropriately validated, and the tests should meet the analytic sensitivity requirement of 100 copies per ml for the pool and 5,000 copies per ml for the original donation.

The clinical sensitivity, specificity, and reproducibility of the assay should be established through clinical and laboratory studies, and finally, the test would be subject to lot release requirements for licensing. Compliance with analytical sensitivity requirements would be monitored using reference materials and lot release panels developed by the FDA.

[Slide.]

FDA has developed panels for HCV and HIV-1 RNA.

At the present time, a WHO standard for HCV-RNA is available. It is a lyophilized antibody-positive specimen from a single donor. The CBER panel is an antibody-negative specimen, genotype 1B. One of the panel members has been

calibrated against the WHO standard, so that one international unit equals 4 genome equivalence per ml.

[Slide.]

The WHO standard for HIV-1 RNA, subtype B, is currently being established and the international unit is yet to be defined. There are two FDA panels that are available. One is an antibody-negative plasma specimen, and two, is a cultured virus specimen spiked into HIV-negative human plasma. FDA will adopt the international unit for HCV at this time and for HIV when it is defined.

[Slide.]

The general study design for NAT validation involves screening of 300,000 to more than one million donations from at least 10,000 donors. Screening for HCV is universal at this time, and a significant percent are also testing for HIV-1.

Informed consent is obtained from donors who are recruited into follow-up studies to confirm results and resolve status. A validated supplemental NAT, that is, the same or another technology, is being used to confirm results. This allows donors to be enrolled in early treatment studies and, of course, recipients, as well.

[Slide.]

Clinical sensitivity, analytical specificity, and reproducibility are also being evaluated under the IND.

Blood and plasma centers need IRB approval for NAT screening for donors.

Pre-transfusion recipient concern is being managed by local IRBs of hospitals and transfusion centers. Cost recovery has been permitted by the FDA under the IND due to the high cost of NAT testing and the national scale of studies.

[Slide.]

A number of issues have been identified regarding implementation under IND. For example, NAT requires several days more than conventional tests due to logistics, that is, testing by centralized laboratories, and technology limitations.

Consequently, certain blood products, for example, platelets and some red cells, are expected to be released on the basis of serology during the initial phase of study, that is, Phase I.

This is necessary to prevent product shortages and harm caused due to lack of blood products. This phase, however, which is expected to be of short duration, will be followed by a phase where all components are released on the basis of both NAT and serology, and this would be in Phase II.

[Slide.]

Other issues are that no product labeling or

enhanced safety claims are permitted during the study phase, therefore, NAT screened and unscreened units would coexist during Phase I. Other issues are that donors are counseled on the basis of confirmed investigational test results and deferred until status is resolved. They are also indefinitely deferred from donating after they have undergone seroconversion.

In addition, lookback notification is required for recipients who receive NAT-positive units prior to test results being obtained.

[Slide.]

Again, informed consent and IRB approvals are required for these studies. Recipients are notified and counseled on the basis of serology during Phase I, and finally, there has been increasing concern about costs imposed on hospitals in particular by cost recovery.

[Slide.]

So, in summary, NAT is being implemented under the IND and at this time, more than 80 percent of whole blood and nearly all source plasma are being screened by a NAT method.

There are several implementation issues relating to donor, recipient, and product management that need to be monitored in the coming months and could be addressed in the workshop planned for December.

[Slide.]

At this time, there is universal product release based on NAT and serology, and is actually expected to occur in the very near future, so there is universal release based on serology, but release based on both NAT and serology is expected to occur in the very near future, and we have heard dates as immediate as July 1st, 1999, however, of course, we do have to watch the situation and see when this actually happens.

Other issues that are anticipated in the future are NAT for other viruses, for example, HBV, and the potential replacement of existing tests, such as HIV-1 p24 antigen. This last issue was actually discussed at the Blood Products Advisory Committee meeting last month, at the last meeting, which was in March of this year.

So, with that, I will conclude and thank you for your attention.

DR. HOLLINGER: Thank you, Dr. Hewlett. Any questions of Dr. Hewlett? Yes, Dr. Stroncek.

DR. STRONCEK: This NAT testing is progressing very quickly. This is an unconventional way to introduce a new test for testing for blood. In the past, they have all been licensed tests which have been readily available to all blood manufacturers and at low cost.

On the contrary, it is my understanding that this

testing is expensive and available only at a handful of sites around the country. Some of these centers have been very collaborative in that they have collaborated with other blood centers throughout the country. Yet, because of the IND mechanism, each of these sites has to be very inflexible in how they collaborate with the other centers.

This has created a number of practical problems for both blood manufacturers all over the country and for transfusion services. I guess I have a question as to the availability of the testing.

If this was available at a low cost and to all centers, then, I think it is reasonable to pursue the direction this is going, but the information I have is that this equipment and these reagents are just not widely available to all blood centers in the country.

Is there anyone from the manufacturers here that can address that issue?

DR. HOLLINGER: Dr. Tabor.

DR. TABOR: Ed Tabor from FDA. Your question makes me think that perhaps you are really Rip Van Winkle because we have discussed all the issues you have raised at multiple meetings of BPAC, as well as at a workshop held in September of '98.

It is certainly an unusual regulatory process. It has been driven by industry pressures that originate from

regulatory pressures in Europe, but the FDA has been very closely observing and controlling the types of studies that are being done, and that is why the testing is being done under the IND process.

Furthermore, the reason it is being done universally under IND instead of being held up until a test is approved is the scientific community and the blood bank community and the regulatory community are in universal agreement that this kind of testing with what we know now about the tests that are being used, despite the fact that they are not fully validated, can only make the blood safer in the interim.

DR. STRONCEK: I have no argument with any of that. I agree with the IND process. My question is, is do you all blood centers have access to the equipment and the reagents, so every blood center can apply for their own IND.

My information I have is that is not available and that is creating a number of competitive and practical problems for the collection and supply of blood in this nation.

I don't think it is appropriate for you to answer this question. I think this is appropriate for the manufacturers, and because if it is not available, then, what you are doing has many important practical implications providing care to patients and to donors.

DR. TABOR: As I said, the reason I am answering this question is because we have answered it and covered it many times before.

DR. STRONCEK: I specifically asked for manufacturers to come forward today and to talk about this issue, and it's not on the agenda, so I don't think you have addressed this issue in a forthright manner.

DR. TABOR: The last part of your question I think would be appropriate for the manufacturers to answer, and perhaps one of them would be glad to do that.

DR. HEWLETT: Yes, I think we are aware of the ramifications of testing under IND, but the issue of supply and availability of reagents, and so on, although we are in dialogue with industry, I think it would be--if there are members of the industry here, manufacturers of kits, perhaps we could hear from them, and if there are any comments about manufacturing and supply, this would be a good time for us t hear about. I think they were invited to speak.

Is there anyone from GenProbe or from Roche?

DR. STRONCEK: Frankly, I am appalled. We have on the agenda later on many issues about the availability of plasma, and while I agree that safety is paramount in the blood, and I commend the FDA for the job they are doing on moving this testing quickly into the field, you can't ignore the issues of availability and supply or availability that

is testing, and if you are not careful, it is going to impact, have important implications on the entire blood manufacturing.

I guess I have one more question for Dr. Alving. Dr. Alving is here from the NHLBI. You know, this testing would be helpful if it was available on an individual unit basis. You mentioned the NHLBI has funded some contracting for this testing. Are you funding more contracting to advance this testing, so we get beyond the fact where it is a very expensive assay and it's only available at a few places?

DR. HOLLINGER: Does anyone want to respond to that? Paul, do you have a comment about that in regards to the NHLBI? Perhaps you could, and then we will come back to Jay.

DR. McCURDY: I can't really speak officially at the present time since I am a consultant to the Institute and otherwise semi-retired, but I believe that the contractor has made available to a number of laboratories the technology and the equipment and supplies to do mini-pool testing and will ultimately be moving toward individual donation testing.

I think if an individual blood bank wishes to insist on doing it themselves, there could be problems. If blood banks are willing an interested in collaborating,

then, I think there is plenty of availability of equipment and supplies, so that it can get done.

There are some logistic problems if you are in a small, rural area with poor transportation. On the other hand, I learned of a small hospital blood bank that is arranging to get NAT testing done and is releasing products at the present time on the basis of NAT testing.

DR. HOLLINGER: Thank you, Paul.

Dr. Epstein.

DR. EPSTEIN: Well, I think, unfortunately, we are not prepared to answer Dr. Stroncek this morning, and that is the problem. I would say this, just a couple of things.

First of all, in the IND phase, although we approved large-scale studies, there was not the presumption that that led directly to 100 percent screening. Certainly, that is a goal, and I think that Dr. Stroncek has done us a service by pointing out that there may be some barriers to access to NAT testing for I presume small institutions, mainly hospital based, and I think that we simply need to look into that and discuss with the manufacturers how they will ensure 100 percent availability as soon as is feasible.

So, I think it is sort of fruitless for us to try to dispute the facts here this morning because we don't have the information, but we certainly will take on the challenge.

DR. HOLLINGER: Thank you. I have just a couple other questions. Dr. Chamberland.

DR. CHAMBERLAND: Yes. Has either the Red Cross or the ABC blood centers provided FDA with information about the results of no doubt early, but nonetheless, in-progress, lookback investigations for recipients who may have received products from these NAT-positive antibody-negative donations?

DR. HEWLETT: Not until the present, but obviously, that is something we would be asking them to provide us with. Those investigations are going on. It is my understanding that some of them are almost complete, but some of the others are still in progress. There are a total of five cases at this point.

DR. HOLLINGER: Dr. Fitzpatrick.

DR. FITZPATRICK: I just have two questions. The first one, you mentioned universal release as early as 1 July. What percentage of the blood supply and whom do you think will be doing that?

The other one is on the statement that there is no product labeling or enhanced safety claims, is there any effort by the FDA to enforce that issue?

DR. HEWLETT: In regard to the first question, it is an informal response, and I think I would like for Sue, who is in the audience, to comment about it.

We have heard statements being made that there is going to be a good-faith effort to try to bring this on-line even as soon as the 1st of July, and I will ask Sue to comment about it.

In regard to product labeling, there has been effort made at the FDA to enforce that. We have, in fact, sent letters to manufacturers addressing that very specific issue, and it has been brought to our notice by several people in the field, and, yes, we are making an effort to pursue that in the form of correspondence back to the manufacturers who are engaged, if, at this point they are, in fact, engaged in promotion labeling, that has been addressed in terms of correspondence being sent back to them.

DR. HOLLINGER: Dr. Stramer.

DR. STRAMER: Sue Stramer from American Red Cross.

Firstly, I would like to comment on Mary Chamberland's question regarding efforts regarding lookback.

Two of the five cases of NAT, only serological negative units that were reported by Dr. Hewlett, we were able to control all products from those two units, so there were no products issued from those.

Regarding lookback, both were repeat donors whose previous donation was greater than 12 months prior to the NAT-positive donation that we retrieved. So, per our IND,

we are only doing a 12-month lookback for HCV according to current guidelines for HCV antibody.

Regarding the implementation phases, I can speak to the ARC issues and how we are moving forward. We implemented NAT on 3-3-99, and in order to bring up 45 percent of the blood in the United States collected at 37 regions, it took us some time, because we wanted to do this carefully and not compromise availability, as Dr. Hewlett referenced, and compromise cGMP efforts to do this properly and within the context of the IND, we brought up our regions in phases, in five groups.

So, the final group of regions just began testing on June 7th, so now we are at 100 percent of Red Cross collections and any collections that Red Cross tests for are tested by NAT, but we do release under Phase I based on serology.

We are aggressively moving beginning in the July time frame, not necessarily corresponding with July 1st, although we would like that date to be true, but we are moving as aggressively as possible to now test very small pools, pools of 16, simultaneously with serology, such that all products may be released on the basis of NAT.

We are not there yet, but in the July, hopefully, not too much later into the August time frame, we will be at that point.

DR. FITZPATRICK: So, that statement refers only to the Red Cross?

DR. HEWLETT: Yes.

DR. FITZPATRICK: Thank you.

DR. HEWLETT: But I think the general anticipation is to move towards full implementation in July or by the fall of this year.

DR. STRAMER: Today, at this meeting, I also represent the AABB, and the AABB has put together a NAT advisory task force to discuss the issues relevant to the implementation of NAT nationwide, and all blood centers involved in the nationwide INDs, who are part of the AABB task force, including Dr. Stroncek, have discussed actively rapid movement to Phase II, such that all products are released on the basis of NAT.

Many of the ABC centers are already doing that, so much of the blood and probably greater than 50 percent of the blood released by the ABC centers is already released on the basis of NAT, and those that are not are moving coincident with the ARC timeline, so by the end of the summer, latest early fall, we anticipate all ABC centers and all ARC centers to be releasing all products on the basis of serology and NAT, unless emergency conditions force release just based on serology, for example, for emergency platelets or fresh red cells, or whatever the need be, but it would

only be based on emergency release.

DR. HOLLINGER: Thank you, Dr. Stramer. Thank you, Dr. Hewlett.

The next topic, Dr. Lynch is going to tell us about the human parvovirus B19 transmission in solvent detergent treated plasma.

Human Parvovirus B19 Transmission from SD Plasma

Thomas Lynch, Ph.D.

DR. LYNCH: Thank you, Dr. Hollinger. Good morning.

[Slide.]

B19, as you recall, is a common non-enveloped human virus about which you have some background information I think you should have received in the packets. In the interests of time, I only want to make two points about human parvovirus.

First, in the majority of infections, the patient is asymptomatic or very mildly symptomatic, however, there are certain populations of patients who are at risk for significant clinical consequences of B19.

These are principally pregnant women, individuals suffering from hemolytic anemia, and immune-compromised individuals. In those cases, there can be serious consequences of the infection and therefore B19 is not to be

taken overly lightly.

The second point I want to make is that in the ordinary course, an individual, once he or she is infected with B19, mounts a rapid and effective immune response, the antibodies neutralize the virus, and the individual is then immune from future infections with B19.

Most individuals, most adult individuals in this country and elsewhere in the world have been exposed to B19 at one time or another, and are resistant to it, and most individuals would test seropositive for anti-B19 antibodies.

[Slide.]

Pooled plasma, solvent detergent treated, is a product that was licensed here in the U.S. a little over a year ago, and it has been in use in several countries in Europe for some time longer than that.

It is manufactured by taking units of recovered plasma from whole blood donations, pooling together as many as 2,500 donations, treating the pool with a mixture of a solvent and detergent to inactivate lipid envelope viruses. This technique has proved highly effective at inactivating hepatitis B, hepatitis C, and HIV. The solvent detergent is then removed from the plasma and the plasma is redistributed into individual units.

The purpose for this procedure is to reduce the residual risk associated with hepatitis B, C, and HIV that

remains associated with single donations of FFP. However, one of the considerations during the licensing review phase for this product was the question of whether the pooling process would increase the risk of exposing patients to non-envelope viruses which would not be inactivated by the solvent detergent treatment. Principally, hepatitis A and B19 were the viruses of concern.

Because the majority of people are, in fact, seropositive for anti-B19 and hepatitis A, it was felt that the presence of neutralizing antibodies in these pools would be (a) consistent, and (b) effective at preventing transmission of these viruses to the recipients of this product.

This issue, as you recall, was taken up by this committee on at least two occasions in the past. In the end, the decision was made to move forward with licensure, however, the sponsor of the product was asked to perform a Phase IV safety study, examining specifically the risk, if any, associated with the transmission of non-envelope viruses, hepatitis A and B19.

[Slide.]

The study did not have to be terribly extensive in scope. We calculate that the risk of viremia donation for B19 is anywhere from 1 in 3,000 to 1 in just under 40,000. Therefore, given the size of the pools by which solvent

detergent plasma is manufactured, the risk of an individual lot containing B19 would range anywhere from just under 10 percent to approximately 75 percent.

Therefore, if this virus was transmitted, it should be readily detected in a modest clinical trial. Such a trial was designed and was initiated last year, and earlier this year, FDA received an interim report on the results of this trial.

[Slide.]

Jumping to the end, to date we have had 50 healthy normal volunteers who were initially seronegative for both hepatitis A and B19 enrolled in this trial. There has been to date no evidence for hepatitis A transmission by the product, just to get that issue off the table.

However, initially, the sponsor reported that 9 out of, at the time, 41 individuals had shown evidence of seroconversion either via IgG or IgM assays, seroconversion to B19. This phenomena was investigated by the use of PCR testing of the individual patient's plasma, which confirmed the presence in the seroconverting individuals of high titers of B19, suggesting that an active infection had in fact taken place.

[Slide.]

PCR testing was also applied to the lots of SD plasma that had been used in the trial. All of the

seroconversions had been associated with 2, the use of 2 of a total of 9 lots that had been used in the trial, and both of those lots had high titers of B19 DNA, approximately 10^7 genome equivalence per ml.

The 7 lots that did not exhibit any evidence of seroconversion for transmission of the virus had titers below 10^4 equivalence per ml. In all, the lots that were tested, a very uniform level of anti-B19 antibody was found, approximately 20 international units per ml.

At this point, the sponsor was asked to withdraw all lots that contained greater than or equal to 10^4 genome equivalence per ml of B19, and to test all lots manufactured to date by PCR for B19 DNA.

The upshot of this was recall in 3 separate cycles of 37 lots of SD plasma in April and May of this year, which is equivalent to approximately 25 percent of the production of this product.

[Slide.]

To address the observations made during this trial, the manufacturer has developed a release test for B19 DNA that will be applied to future releases of all lots of SD plasma, therefore, no future lots will be released if they have high titers of B19.

The sponsor is also developing a screening test for the incoming plasma in order to eliminate viremic units,

high-titered units before they are manufactured into SD plasma, and with suitable modifications, the clinical trial will resume using only low-titered lots of SD plasma to confirm that the threshold that has been set for B19 DNA is in fact appropriate and will assure against future transmissions of the virus to recipients of this product.

Thank you.

DR. HOLLINGER: Any questions of Dr. Lynch? Yes, Dr. Stroncek.

DR. STRONCEK: First of all, I heard about the recall via the FDA web page, and that is a nice service. I have yet to appear about it through the manufacturer or our distributor of the product. Maybe you could look into that to see if that has been recall appropriately.

Second, from what you have said, it is my understanding that this was a concern, parvovirus infection, about this blood product. You know, we were told the neutralizing antibodies would take care of any parvovirus in the product and it shouldn't be an issue.

The product was released. We have now found that that was wrong, that there was a problem with the product and some lots are released. I am not an infectious disease expert, but from my point of view, it looks like there is still some concern whether or not the steps taken will ensure complete safety of this product.

You have listed three groups of people where this might be a concern. Parvovirus infection, it doesn't sound like a lot, but quite honestly, immune-compromised patients do represent a significant portion of people that currently get transfused.

I guess my question is why is this product still on the market, and shouldn't this be withdrawn from the market until it has been proved to be completely safe, and then be put back on the market.

DR. LYNCH: Well, complete safety is an admirable ideal, and I think we all strive for it. It is, in fact, difficult to achieve. The concern over the individuals that you mentioned, the at-risk populations, is considerable, significant, and is recognized, and the labeling for this product points out the risks to these patients, the potential risk resulting from a B19 infection.

Because the product offers alternative benefits with regard to transmitting envelope viruses, it was felt reasonable to leave the decision to treat a specific individual up to the discretion of the physician and to make the product available to those who wished to minimize the alternative risks that the solvent detergent procedure addresses.

We feel that the precautionary measures that have been implemented since this information came to light will,

in fact, address the safety of this product adequately. Are we absolutely sure of that? No, that is why the Phase IV study will continue, and it will be scrutinized very carefully both by the participating investigators and by FDA.

In terms of the effectiveness of the recall, your point is well taken. We did go through the exercise of recalling the product, but, in fact, although this procedure is not visible to the general public, our Office of Compliance has worked very closely with the manufacturer and the consignees of the product to assure the effectiveness of this withdrawal.

DR. STRONCEK: I spoke with a medical director of one of the blood distribution centers handling this product, and this information that you have presented today was not being made available to them. They informed me that their calls to the manufacturer are not being returned to them.

So, while I think there needs to be some--if this product is going to stay on the market, the manufacturing distributor had better do a better job of communicating the benefits and risks of this product.

DR. LYNCH: Thank you.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: I note in your slides you point out that there is well-documented transmission by clotting

factor concentrates, but no confirmed reports of transmission by IG, albumin, and so on.

Is there a part in the manufacturing process that you would identify as likely to be removing these non-enveloped viruses like parvovirus?

DR. LYNCH: Yes, the situation for the manufactured products, the plasma derivatives, is complex. Parvovirus is physically very small, so it is difficult to filter out, and it is resistant to physical and chemical methods of inactivation that are commonly used.

However, it can be separated or partitioned away from one or another product, and it is somewhat sensitive to heat treatment. So, for example, I would speculate that albumin, the absence of transmission by albumin might result from a combination of the partitioning during the fractionation of that product, and perhaps inactivation of some small residual virus during pasteurization of the product.

For immune globulin, the IGIV products all have different viral inactivation methods. If it is solvent detergent, it wouldn't address the risk, nonetheless, these products don't transmit either, and I think my guess would be that this is an example of immune neutralization of the virus by the IgG itself.

IGIV, if you will recall, is the principal

treatment for an acute or chronic B19 infection, and has proved highly effective in that regard.

DR. HOLLINGER: Dr. Chamberland.

DR. CHAMBERLAND: Although reporting of adverse events is really a passive system and hence subject to a lot of limitations, is FDA aware of any adverse events that could potentially be representative of infection with B19, acute infection among actual recipients of the product outside of these Phase IV trials?

DR. LYNCH: Actually, yes. I was informed this morning that the manufacturer had received one report. It is the first report to my knowledge that an individual outside of the clinical trial had apparently seroconverted after using SD plasma.

The individual infected was a recipient of several of the lots of SD plasma that had been recalled, but I have no further particulars on that incident, and it hasn't been formally filed with our Medwatch system.

As you know, Mary, that is under a fairly tight timeline, so we should be getting a full report on that shortly.

DR. HOLLINGER: But other than seroconversion, any clinical problem?

DR. LYNCH: Not to my knowledge, no. There is certainly nothing in Medwatch that is suggestive, and during

the clinical trial, there was no evidence of seroconversions or certainly symptomatic infections.

DR. HOLLINGER: Thank you, Dr. Lynch.

The next topic, Dr. Nightingale is going to give us a summary from the Blood Safety and Availability Advisory Committee meeting.

Blood Safety and Availability Advisory Committee Meeting Summary

Stephen Nightingale, M.D.

DR. NIGHTINGALE: In the interests of time, let me get started. I can do this without the overheads if I have to.

Dr. Hollinger and Committee members: the Advisory Committee on Blood Safety and Availability met on April 29th and 30th of this year to examine the reserve capacity of the United States blood supply and to recommend how it might be strengthened.

[Slide.]

By way of very brief introduction, as I believe the BPAC members know, the Advisory Committee was chartered on October 6th, 1995, to advise the Secretary and the Assistant Secretary for Health on a range of issues to include one of three: the implications of blood safety and availability of various economic factors affecting blood product cost and supply; number two, definition of public

health parameters around safety and availability of the blood supply; number three, broad public health ethical and legal issues related to blood safety, and our meeting was conducted under this rather broad mandate.

[Slide.]

I am sorry, I had shown this merely to show that Dr. Busch, Dr. Chamberland, Dr. Epstein, and Dr. McCurdy are members of the committee here in the room, and Major Fitzpatrick will be joining the committee on the 1st of July.

The second, which is up there, the charge to the Advisory Committee is listed up here, and I will read it because it is brief for the record, that it may be necessary at sometime in the future to defer at least temporarily some portion of the donor pool in order to maintain the integrity of the blood supply; that this action should be done in a way that would minimize the impact on those who depend on blood transfusions for their health and even for their lives, and finally, plans to utilize the reserve capacity of the blood supply should be established before and not after circumstances require use of this reserve.

Dr. Satcher further charged the Advisory Committee to do so before and not after circumstances might require use of this reserve capacity. He concluded his charge by reminding the Advisory Committee that we should never be in

the position, as some have suggested we may have been in the past, where we would feel obligated to release a unit of blood if we had any doubt whatever about its safety.

[Slide.]

Regarding the availability of blood supply, Ms. Marian Sullivan of the National Blood Data Resource Center, which is an affiliate of the American Association of Blood Banks, then described for us the current availability of our blood supply.

She stated that in 1997, about 12.6 million units of blood were collected and about 11.5 million units of red cells were transfused, 93 percent of the allogeneic units were transfused, 2 percent were discarded because of screening test results, 4 percent became outdated, and 1 percent were unaccounted for.

However, as shown on this slide, total blood collections decreased by 5.5 percent between 1994 and 1997, while the total number of whole blood and red cell transfusions increased by 3.7 percent during the same period.

Extrapolating from these current trends, Ms. Sullivan estimated an available blood supply in the year 2000 of 11.7 million units, and a total demand of 11.9 million units.

Three substantive comments were made in the

discussion that followed this presentation. First, most outdated units are group AB blood donations, which as everybody I believe in the room knows can only be transfused into group AB recipients.

Second, the fact that overall supply exceeded overall demand during 1997 does not mean that there were no local shortages during that year, as in fact there were.

Third, one factor contributing to the trend Ms. Sullivan described is the aging of the population since about half of all transfusion recipients are over 65. As a result, as the population ages, there will be proportionately fewer donors and proportionately more recipients.

Dr. George Schreiber of Westat, Inc., and the National Heart, Lung, and Blood Institute sponsored a retroviral epidemiology donor study, then discussed how donor retention might influence the reserve capacity of the blood supply.

He began by noting that while almost half the adult population in the United States donated blood at sometime, only about 5 percent donate in a given year. In 1995, about 32 percent of the roughly 8 million blood donors were first time donors. Half of these new donors never returned, and two-thirds of those that did, returned during the first year after the donation.

Dr. Schreiber estimated that if the rate at which first-time donors returned for a second donation within one year could be increased by 15 percent, the blood supply could be increased by 10 percent.

The discussion that followed focused on the suitability of these donors that might be induced to return. Dr. Schreiber had found that individuals who had donated only twice had no greater incident of HIV or hepatitis C than individuals who had donated more than twice.

A similar observation has been made about paid plasma donors. Those who return only once regardless of the interval after their original donation appeared to be just as suitable as those who returned more often and more frequently.

Dr. Michael Busch of the Blood Centers of the Pacific then discuss differences in risk factors among blood donor groups. Dr. Busch and others have found that the prevalence of deferable risk is 1.5 to 2 times higher for just about any given risk in first-time donors than in repeat donors.

As a result, he concluded that a donor referral strategy that would increase the fraction of new donors in a donor pool would increase the risk of that pool, however, Dr. Busch did notice there was less difference between the incidence--that means the new onset of deferrable risks--in

new and repeat donor population.

The consensus of the Advisory Committee emerged that the retention of more first-time donors, as Dr. Schreiber suggested, was the strategy most likely to increase the capacity of the United States blood supply and least likely to increase its risk.

There was also consensus that it would cost a substantial amount of money and incentives, direct or indirect, to retain these first-time donors, and that blood banks could not fund these additional costs from current revenues, however, no conclusions could be reached on what, if any, incentives up to and including paid donation would be effective, how much they would cost, or who would pay for them.

With this in mind, the Advisory Committee then addressed the issues of what, if anything, individuals with hemochromatosis or the blood substitute industry could contribute to the reserve capacity of the blood supply.

[Slide.]

After considering this issue, the Advisory Committee concluded the statement that I have, the third here, which is a complementary strategy in addition to increasing the retention of first-time donors, would be to eliminated undue financial incentives for blood donation by individuals with hemochromatosis, and that such undue

incentives are removed to create policies that eliminate barriers to the use of this resource.

The potential contribution of this resource is substantial, but uncertain, but again, there is no guarantee that this potential would be realized.

I would be glad to answer any questions. I hope I have kept within my allotted time.

DR. HOLLINGER: Any questions? Ohene.

DR. OHENE-FREMPONG: Would you care to elaborate a little bit on the issue with those with hemochromatosis?

DR. NIGHTINGALE: Yes. What I think I would like to do by way of elaboration would be to read the exact statement that was passed unanimously by the Advisory Committee. I think that that would probably be sufficient elaboration for purposes of opening the discussion.

That recommendation reads incompletely as follows. The Advisory Committee recognizes that blood products obtained from persons with hemochromatosis carry no known increased risk to recipients attributable to hemochromatosis per se and therefore may be a valuable resource to augment the diminishing blood supply.

The Advisory Committee also recognizes that the obligate need for phlebotomy can constitute an undue incentive for blood donation due primarily to financial considerations.

For this reason, the Department of Health and Human Services should create policies that eliminate incentives to seek donation for purposes of phlebotomy. As such undue incentives are removed, the Department should create policies that eliminate barriers to using this resource.

Would you like to ask a follow-up question or was that sufficient?

DR. OHENE-FREMPONG: What is the rough estimate of how much phlebotomy from patients with hemochromatosis would add to the blood supply?

DR. NIGHTINGALE: The doctor asked the question why I glossed over it in my initial presentation. Let me give you the slightly less short answer.

The estimates given to the Advisory Committee ranged from 300,000 units to 3 million units of whole blood and red cells that could be added to the blood supply. There is some concern at least at the staff level, which I guess would be me, that the lower estimate might, in fact, be high.

Clearly, the frequency of the gene is known. There would be roughly a million people in the United States with the gene. At the same time, a quarter of those million people are under 21. Half of those million people are female who, while they do express the gene, I think it is 88

percent, if I have got the right number, of the diagnosed cases of hemochromatosis are male.

We have the issue of expression of the gene even though it is a C282, the nucleotide is the same. People are more complicated than that. So, exactly how many people would come in is the first question.

The second question is how many of those people would meet the current AABB standards, for example, for hematocrit. Clearly, because the phlebotomies are being done for therapeutic purposes, during the induction phase, the individual would be bled down below a hematocrit of 38. I think they are bled down to I believe 31 is the number that is used at least in some centers.

So, how many of these units would be useful is a second question. I think what folks came to would be a certain number we would like to think 180,000 seems like a reasonable estimate of how many units it would be. That would be the number we would expect to see for new people entering the system.

The second even less well characterized part of the answer to your question is how many people with hemochromatosis are currently donating blood, and I don't think anybody has a good answer on that one. I certainly don't.

DR. HOLLINGER: But they are a continuous source

since they are asked to donate at least three or four times a year after the iron had been removed from their system.

DR. NIGHTINGALE: Yes.

DR. HOLLINGER: Any other questions? Yes, Dr. Stroncek.

DR. STRONCEK: I would comment that I would be careful about assumptions about blood shortages because I think if a shortage occurs, many people will step forward and donate, so I am not sure that we will have a shortage and that we do need to change the policy on people with hemochromatosis.

The other comment is that it seems kind of schizophrenic to be recommending that one group here we have people with hemochromatosis donate, which I agree are probably no risk, on the other hand, we are going to talk, I think the next agenda item, on people traveling to England can't donate. They don't seem consistent.

DR. NIGHTINGALE: We would probably want to discuss privately the use of the term schizophrenic.

DR. HOLLINGER: The next topic is going to be a summary of the Transmissible Spongiform Encephalopathies Advisory Committee, which was held June 2nd, in regard to new variant CJD.

Dr. Jacobs.

Transmissible Spongiform Encephalopathies Advisory

Committee Meeting Summary

Mary Elizabeth Jacobs, Ph.D.

DR. JACOBS: Thank you, Dr. Hollinger. Good morning, members of the Committee, ladies and gentlemen.

[Slide.]

At your March meeting you received an update on the December 1998 meeting of FDA's Transmissible Spongiform Encephalopathies Advisory Committee meeting, and that is an advisory committee which advises all parts of the FDA on TSE-related questions.

We had brought to them the question of considering deferral of blood donors based on their foodborne exposure to the BSE agent through travel to BSE countries or residents there in order to reduce the theoretical risk of transmission of new variant CJD through blood.

At that December meeting, the Committee voted to recommend deferral, but asked for a survey of travel times in order better to estimate the impact on the blood supply.

In the June meeting, they took up that question again with the survey results, and again in order to have continuity with this committee, Dr. Hollinger served as a temporary voting member, as did Dr. Nelson, and we had other members who were there including Dr. Sayers and Dr. Leitman representing the blood banking community.

That transcript will soon be on our web site.

[Slide.]

In the agenda, we had first a consideration of the survey results by Dr. Williams, which I will give you in a second. We then had two speakers on scientific aspects related to the time of the BSE epidemic and modeling of new variant epidemic--excuse me, I shouldn't use new variant epidemic--it's the BSE epidemic.

Dr. Donnelly is the head of the Statistics Unit at the University of Oxford, which has done all the modeling of the BSE epidemic, and they also have done modeling for new variant.

You can see her discussion on the web site, but in brief, the conclusions were that at the current time we cannot say how many cases of new variant CJD will occur. The estimates go from under 500 to as high as 500,000, and the primary unknown is the time of incubation of new variant CJD.

The highest number, 500,000 cases, comes from using 40 years for the time of incubation. It is possible that if the cases go down over the next two years, that better estimates will be available for that, but right now there are no estimates beyond this frame of under 500 to as high as 500,000.

Next, we had Mr. Philip Comer speak. He was the primary person responsible for a risk assessment which was

done under contract to the Department of Health in the UK, and they asked Det Norsk Veritas, which is a consulting firm, to look at estimates for infectivity and to potential transmission through blood.

That risk assessment has been peer reviewed and is now publicly available. Again, although no definite scientific or good scientific data are available, in brief, we can state that there are more concerns with new variant, and these concerns include higher amounts of abnormal prions in the brain and also the potential role of B lymphocytes.

Next, we turned to questions of shortages because we asked the Committee to consider this in the light of potential shortages, and Dr. Nightingale, who just spoke, gave us a somewhat more detailed discussion of the BSE meeting.

Finally, we had a brief summary of Canadian discussions. There was a meeting of their National Blood Safety Council, and they have had parallel discussions, because they also have fair numbers of their blood donors who travel to BSE countries, yet, they have had no indigenous cases of BSE. They had one case in an imported animal.

[Slide.]

We at FDA feel very grateful to Dr. Williams, who is the principal investigator, and all those involved in

this survey which was so quickly done between the meeting in December and having results available in June.

It was done through the American Red Cross ARCNET program with support from National Health, Lung, and Blood Institute REDS program, and in cooperation with the American Association of Blood Banks and America's Blood Centers.

It was a random sample, anonymous mail survey. They had approximately 49 percent response at the time of the June 2nd meeting, and Dr. Williams presented data on 8,666 responses from a total of 19,067 that had been sent out.

Let me give you two of their results before we go to the main ones on which the decisions were made. They found that there were a total of 22.6 percent of all blood donors who responded had been in either the United Kingdom or the Republic of Ireland between 1980 and 1996.

Just for those of us who have forgotten our sixth grade geography, the United Kingdom includes Great Britain, which is England, Scotland, and Wales, and then going into the United Kingdom, Northern Ireland, the Channel Islands, which are Guernsey and Jersey, and the Isle of Mann. In addition, the Republic of Ireland was included.

So, in total, 22.6 percent had gone there, and as expected, more donors in older age groups had traveled there.

[Slide.]

Dr. Williams has given his okay to show his data today, and these are I think the heart of the matter. They show, in the first column, the deferral criterion, in other words, greater than or equal to 5 years cumulative in the UK or Republic of Ireland between 1980 and 1996 and then following down greater than or equal to 1 year, 6 months, et cetera.

The next column shows you the percent of the U.S. blood supply which this travel represent, and the last one shows you the cumulative person-days.

Now, one of the difficulties here is modeling the exposure which took place between 1980 and 1996, and the exposure method that was used here was linear exposure, in other words, to say 1 person who was there for 1 day is one person-day, 1 person who was there for 100 days is 100.

So, if we look at this, you can see what percentage in the righthand column, what percentage of the risk, if it is modeled in a linear way, would be removed if we used the deferral criteria on the left side and what percentage of the U.S. blood supply would then be removed.

Let's go to the decision that was made by the PHS Committee. We will then next go to the Committee vote, but then to focus on 6 months or greater residence would give a loss of 2.2 percent of the U.S. blood supply given our

current donor profiles as represented in the survey, and would remove about 80 percent of the risk if it is calculated linearly.

[Slide.]

Following the deliberations of the Committee and the presentations, they voted, and for the record I will read in what the questions were and what their vote was.

Should FDA recommend new deferral criteria for donors of transfusible components to reduce the theoretical risk of transmitting nvCJD from transfusions based on donor exposure to BSE in the UK?

Their vote was 12 yes, 9 no, 0 abstained.

[Slide.]

Next, we asked the question, if so, what deferral criteria should FDA recommend, that is, time period, nature and length of exposure.

Rather than take a vote on one time period, the Committee took a poll, and the poll showed that 5 years or more was recommended by 3 members, 3 years or more by 1 member, 1 year or more by 5 members, 6 months or more by 7 members, and 4 months or more by 4 members.

[Slide.]

We did only one thing differently in asking the questions this time compared to December, and that was separating out the question of plasma donors compared to

blood donors.

The second question asked the question for plasma donors. Should FDA recommend new deferral criteria for donors of source plasma and recovered plasma for further manufacture into injectable products to reduce the theoretical risk of transmitting new variant CJD from plasma derivatives based on foodborne exposure to BSE in the UK?

Here, the vote was 12 yes, 8 no, 0 abstention.

[Slide.]

The next one. Again, we asked, if so, what deferral criteria should FDA recommend, that is, time period, nature and length of exposure? The Committee did not vote on this question as written, but voted on keeping the criteria for question for 1b the same as the criteria for 2b. 19 yes, 0 no, 0 abstained.

[Slide.]

Now, what has been our follow-up? The Public Health Service has a committee called the Blood Safety Committee. This is chaired by Dr. Satcher, who is both Surgeon General and Assistant Secretary for Health.

That committee, which includes FDA, CDC, NIH, HCFA, and the Department, met one week later. There was a unanimous vote by the committee to Dr. Satcher to endorse the recommendations for deferral, and they recommended that the criteria be six months or more cumulative months of

residence or travel.

They also recommended that FDA review the scientific data every six months, which underpin this decision, and here I will add that FDA has a standing committee across all of its centers and also one within CBER, which follows the scientific information on a routine basis.

This committee assigned to FDA for implementation through revised guidance, and Dr. Scott will talk about the guidance, and also the committee and Dr. Satcher pledged to work on donor recruitment and retention, and to monitor the impact on supply.

[Slide.]

This shows our proposed implementation plan. FDA will call for blood establishments to implement this deferral as soon as feasible, but within 6 months of issuance of the guidance.

The FDA guidance will call for indefinite deferral from donations of blood or plasma of persons who lived in or traveled to the United Kingdom, England, Scotland, Wales, et cetera, for a cumulative time of 6 months or more between January 1980 and December 1996.

Thank you.

DR. HOLLINGER: Any questions of Dr. Jacobs? Yes, Dr. Buchholz.

DR. BUCHHOLZ: I am sorry, I may have missed your very last statement. What was the ending date?

DR. JACOBS: 1996.

DR. BUCHHOLZ: And why was that taken as opposed to continuing for the foreseeable future?

DR. JACOBS: I think the primary reason for that, although the committee did not explicitly vote on this, was the effect of the food bans and the displays of these which we seen in Dr. Donnelly's talk.

The remainder seems to be maternal-to-calf transmission within the UK, and therefore it is thought that these food bans are effective.

DR. HOLLINGER: Dr. Mitchell.

DR. MITCHELL: I guess I have more of a comment than a question. I think that people have been hearing that travel to England is a deferrable criteria, and I am afraid that people will not go for blood donation because of that.

I was wondering if they considered saying that living in England instead of travel to may be from a perception point of view more accurate to define what the committee has planned to do.

Have they talked about saying living in the United Kingdom during that period of time?

DR. JACOBS: I think that that is a very good question, and that has been discussed partially because

sometimes people interpret those terms differently, did they actually live there or did they only travel there.

We are using the term "cumulative 6 months." It is possible that people who travel there regularly for 2 or 3 weeks could possibly accumulate that amount of time there. So, I think Dr. Scott will be discussing the questions that are being considered, and we are trying to incorporate that aspect of it.

DR. MITCHELL: I think the issue is one of semantics and what is getting out to the public. If you say to the public, they lived, then, you can explain what lived actually means 6 months.

DR. JACOBS: Yes. Thank you.

DR. MITCHELL: Thank you.

DR. HOLLINGER: I think we will have Dr. Scott then tell us about the revised guidance for CJD and nvCJD.

Revised Guidance: CJD and nvCJD

Dorothy Scott, M.D.

DR. SCOTT: Good morning. I am going to summarize the proposed revised guidance to reduce the possible risk of transmission of CJD and new variant CJD in blood and blood products.

[Slide.]

I believe you got a copy of this, this morning, but I am sure you haven't had time to read it in great

detail. What I would like to do is just summarize some of the main points in that new guidance for your consideration.

[Slide.]

Since December of 1996, we had a memorandum which did address deferral of donors and withdrawal of products for CJD. Since that time, there have been a lot of ongoing advisory committee discussions, as well as new data that have come out, so as a result of all of these discussions and new data, which were taken into consideration, a recommendation was announced by Dr. Satcher late in the summer of 1998, and this was published on the internet by FDA.

That changed the previous recommendations, and I have put in bold the changes. The changes were no longer to retrieve, quarantine or destroy plasma derivatives if the donor had CJD risk factors, and I will list those for you, or CJD, and this was based on evaluation of a large body of epidemiologic and laboratory evidence, which is summarized in the new document.

It was still recommended to defer donors that had CJD risk factors or CJD. In addition, another new recommendation was made to retrieve, quarantine, and destroy materials if the donor had new variant CJD, and I am going to go into some of the details of that.

The TSE Advisory Committee on June 2, 1999, made

the recommendations that Dr. Jacobs has summarized for you, and that was to defer donors based on exposure to bovine spongiform encephalopathy in the United Kingdom.

This recommendation was actually made in December of 1998 and reaffirmed in 1999, but with the time period criteria that you have seen, the majority did vote to defer donors who traveled to or lived in the United Kingdom for greater than or equal to six months, but as you saw, there was a spread of opinions for exactly what this time period should be.

This was endorsed by the PHS Blood Safety Committee on June 9th of 1999.

[Slide.]

So, the three points of the new proposed guidance that I am going to expand upon a little bit are the incorporation of new donor deferral criteria for the United Kingdom. It also includes recommendations for products from donors with new variant CJD and suspicion of new variant CJD. It also incorporates labeling recommendations for non-implicated products which mention CJD as a theoretical risk.

First, I will just talk about the donor deferral recommendations which are still to defer all donors, of course, with CJD or new variant CJD, and also to defer donors with risk factors including family history of CJD in greater than or equal to one family member, and this has not

changed.

In addition, we are asking for deferral of pituitary hormone recipients. That is a slight change because before, we had specified human pituitary-derived growth hormone. Now, we are just saying pituitary growth hormone and gonadotropins since there are a few reports, mostly from Australia, that old gonadotropin preparations also transmitted CJD.

In addition, donors who have received dura mater grafts will be deferred as before.

The other new deferral is to defer donors with risk of exposure to new variant CJD, which you have just heard of. I have written the wording of that which you have also essentially just heard, but this would be precisely the kinds of donors that we would recommend deferral for, donors who have spent greater than or equal to six months in the United Kingdom, Great Britain, Scotland, Northern Ireland, Isle of Mann, Channel Islands, cumulatively between January 1st, 1980, and December 31st, 1996, for the reasons that Dr. Jacobs has explained.

This, or course, encompasses the years when the BSE epidemic had peaked.

[Slide.]

I am going to move on to how new variant CJD is diagnosed. Some of you have probably seen this before. It

became important to us because we realized that there could be cases of new variant CJD in the U.S. eventually if we are unlucky, and we need to certainly have a criteria for knowing that a patient has new variant CJD since this is going to result perhaps in large withdrawals if that person was a donor.

So, neuropathology is still currently required to make a definite diagnosis of new variant CJD, and I have listed for you the three neuropathological correlates that have been described by the United Kingdom groups. These are the things they believe can give you a diagnosis of new variant CJD.

One is the presence of florid plaques, which is unusual in regular or classical CJD. Spongiform change, particularly in certain places, the basal ganglia and the thalamus, but not the cerebral cortex, as well as immunohistochemistry, which shows a high-density prion protein accumulation again which is unusual in regular CJD.

Potential new diagnostic indicators are being developed, but none of these have been validated, and those include tonsillar biopsy with immunohistochemical staining for prion proteins. These are prion protein glycoforms which appear to be different for new variant CJD than for classical CJD, and also there may be an MRI criteria, which will be published soon by the United Kingdom group, which

suggest that bilateral posterior thalamic signal of high intensity may be diagnostic for new variant cases.

However, it also seems possible that one could have a new variant case that doesn't have adequate neuropathology. In fact, you can tell from those criteria for definite that you may actually want to look at a whole brain to determine the distribution of lesions.

So, it may be necessary to make the diagnosis of new variant CJD by clinical criteria.

[Slide.]

The CDC has a case definition for clinical criteria for new variant CJD in the United States, and we considered using this actually as a criteria for withdrawal in addition to neuropathological correlates of new variant CJD, but this CDC definition has to include all of the nine following qualities, and these again are mostly things that would distinguish a new variant CJD case from a classical CJD case.

First of all, the patients are typically young, age less than 55. They present with painful sensory symptoms or psychiatric symptoms rather than movement disorders or even cognitive dysfunction.

They have a delayed development of neurologic symptoms after their initial presentation. In most cases, this is for more than four months, but there have been

exceptions. They may have a normal or abnormal EEG, but not the EEG changes which are pseudoperiodic sharp waves that are seen in classical CJD, and they typically have a long duration of illness that is very drawn out compared to most, but not all, CJD cases.

It would be important for routine investigations to not suggest alternative non-CJD diagnoses. In the CDC criteria, they specify travel to a BSE country, which is the United Kingdom, but there are also other countries with low rates of BSE.

[Slide.]

We realized when we went over these criteria that it was quite possible that there would be cases which actually had new variant CJD which wouldn't meet all nine of these criteria, at least not right away.

For example, two of these criteria are based on the time course of the disease, either how prolonged it is or the development of symptoms in a certain order, and that time may not have elapsed to meet those criteria.

Furthermore, travel history and symptom history might not be available, and you can think of a few other cases in which all of those nine criteria have not been met, and that would actually be true of some of the UK patients who didn't have precise development of delayed neurologic symptoms by four months, and so forth. So, we needed a

lower threshold actually to be looking at cases which might have new variant CJD in the U.S.

[Slide.]

So, we proposed a threshold for investigation and consideration of quarantine and withdrawal of blood product for new variant CJD concerns, and that would be if the donor was less than 55 years old and if the donor had a physician's either clinical or pathological diagnosis of CJD, and because it's a young person, we would be concerned that this was actually a new variant case.

In the guidance, we are asking for immediate notification of FDA and CDC, and telephone numbers are provided. It would then be planned to perform a rapid investigation of the case with CDC and FDA both involved and to make decisions about blood products on a case-by-case basis, and in fact, if it was ambiguous as to whether the donor had new variant CJD, if it couldn't be ruled out, then, it is likely that precautionary withdrawals would be recommended.

[Slide.]

I want to go on then to the proposed disposition of materials for all of these kinds of cases that I have discussed both for deferral and for new variant CJD case. For CJD, CJD risk factors or new variant CJD exposure risk--by that I mean travel to the United Kingdom for greater than

or equal to six months, we would recommend withdrawal of components and unpooled plasma, but not withdrawal of derivatives.

If some of these components were to be used in non-injectable products, we would suggest some labeling for those. In the case of new variant CJD or precautionary withdrawals for cases that were suspicious might have new variant CJD, we would ask for withdrawal of components, derivatives, and that this material not be used for non-injectable products, but we would permit it not to be destroyed but rather to be used in research on new variant CJD with appropriate labeling, which is also suggested in the document.

[Slide.]

Finally, on the last topic, I want to go to proposed labeling of non-implicated products, which has been discussed extensively within the FDA, and this is the statement that we have come up with in collaboration with the Office of Vaccines.

First of all, I just want to read out the statement that is also contained in the guidance, that no transmission of CJD or new variant CJD by human blood or plasma derivatives has ever been documented from human to human, however, as a precaution, FDA proposes that all blood component and plasma derived products include labeling to

address the theoretical risk.

Now, this statement obviously covers more than CJD, but the statement is as follows. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Cretzfeldt-Jakob disease agent.

Thank you very much.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: I have two questions. One of the things, if I understood you correctly, is that some of the characteristics on biopsy or autopsy for new CJD are unusual, but sometimes present in classic CJD in the sense that you can't absolutely definitively tell between the two, is that correct?

DR. SCOTT: Well, that is correct if you look at any one of those autopsy criteria alone, but taken together, the United Kingdom group feels that they are quite characteristic. The other thing is, for example, in the case of some of these, the exceptions would be genetic cases which may have some of these feature, but, of course, those are easily ruled out with gene sequencing.

DR. BOYLE: But in cases, for instance, of very young CJD cases identified in the United States recently where there has been a statement that on biopsy, definitively, they are not new variant CJD, that we can

treat that as a definitive statement?

DR. SCOTT: Well, there are a couple of things that happened with that biopsy or a couple of qualities that it had which really did appear to rule out new variant CJD, which as you know, was a considerable concern, and it still led to precautionary withdrawals.

The first is that that biopsy did not have florid plaques, and the second is that the prion protein glycoform was looked at, and it was either a Type I or a Type II, I can't remember, but it was a classical CJD form, not the Type IV that has been seen in every new variant case.

So, those two characteristics led us all to feel much better about this case. It is my understanding now that the patient has died, but I don't really know where the brain got sent to.

DR. BOYLE: The second question is your nine criteria that you require basically for a case to be new CJD if you don't have definitive lab results. One of those criteria is under 55. Yet, we also heard from the travel survey that your likelihood of spending a long time in England is much higher for older persons.

I understand it in terms of looking at new cases, but are you setting up something where older travelers to England are people who, because of their age, are going to be non-CJD unless you have a lab diagnosis?

DR. SCOTT: Well, I think there are a couple of answers to that question. I think you are absolutely right. Although no case has been seen greater than 55 years of age yet, including in the United Kingdom, it is entirely conceivable that such cases are going to occur.

I think that is why we decided ultimately that we, FDA, would not require the meeting of all nine of these criteria in order to effect a precautionary withdrawal. So, we will use these qualities to help us evaluate that case, but we are not going to go ahead and do that. I guess that is the answer I would like to give.

DR. HOLLINGER: Dr. Koerper.

DR. KOERPER: Identifying someone who has already donated blood as subsequently someone with CJD or new variant CJD depends on, as I understand it, a voluntary reporting by the physician, and I wondered. It is my understanding that not every state right now lists CJD as a reportable disease.

DR. SCOTT: That is correct.

DR. KOERPER: What is the FDA working on in terms of trying to improve or increase the number of states that report CJD?

DR. SCOTT: It is my understanding that the CDC is actually working on that very subject, however, there are several different routes by which we might find this

information out. One is, of course, through the blood banks or plasma collection establishments which receive post-donation reports from relatives.

The second is, as you say, through the states to the CDC, as well. The third is through neurologists who are part of working groups that are involved in more or less surveillance for new variant CJD. But is the ascertainment perfect? I agree with you that it is not, and I think we all wish that it were better and there is work ongoing to try to make this reportable.

Even all reportable cases aren't reported, and so it still wouldn't be perfect once that is achieved.

DR. HOLLINGER: Dr. Epstein.

DR. EPSTEIN: Yes, I just wanted to make two comments. First, the draft guidance document that was provided to committee members is given to you confidentially and we are requesting your comments within the next two weeks. That is to assist us in finalizing it before it can be made public.

Second, one point I wanted to make about the FDA plan regarding implementing the deferral for residence or travel to the UK, it is our current thinking that when we issue the guidance, we would call for implementation of that deferral as soon as feasible by blood collection establishments and plasma collection establishments, but

within six months of issuance.

The reason that we are approaching it in that way or plan to is that we are highly mindful of the fact that the deferral may cause significant loss of blood or plasma in the supply, and we have a concurrent initiative to try to promote the retention and recruitment of donors to offset the losses that might be expected to occur.

We will try to monitor that situation very closely. So, again, our expectation would be that when we issue the guidance, we would call for implementation, but no later than six months.

DR. HOLLINGER: One of the issues I think, Jay, as you know, on the one chart that was spoken about earlier by Dr. Jacobs on the cumulative-person days, and the real issue is whether that is a good marker because it may be that one person spending 100 days in the United Kingdom may have far greater risk than hundreds of people spending one day, which still gives you 100 person-days, and that is an issue, and we don't know the confidence intervals around these numbers for choosing some sort of an exclusion.

Could you comment at all about that, Jay?

DR. EPSTEIN: Of course, you are right. That is one of the gaps in our knowledge, and there are some plans for animal experimentation to see what the cumulative effect is of subinfectious doses received multiply over time, one

of the questions being how fast you clear exogenous exposure to abnormal prions, and it may be that they accumulate and you can reach an infectious dose from multiple exposure.

But this was discussed at the TSE Advisory Committee and it was felt that the best that one could do was apply the assumption of linearity, that risk is simply proportional to time spent on the theory that that correlates to the risk to a single or discrete infectious exposure. No one knows if that is really true.

The other methodologic issue, which you didn't mention, is that there is some arbitrariness in assigning the exposure time as the midpoint of the interval that was queried in the history.

For example, if you were asked about exposure, say, between three and five years, exposure days were reckoned by calling that a four-year exposure if the answer is yes, and it becomes very difficult when you consider the prolonged exposures because if you then treat, say, all exposures over five years, you know, in theory, that runs out into lifetime exposure.

In practice, we reckoned it back to the earliest epidemic of 1980 and called it a 17-year interval, and then we chose the midpoint, but clearly, the contribution to capturing exposure time, if you apply those very long intervals, is disproportionate for the people who gave the

histories of prolonged exposure.

In other words, on the linear assumption, you are assuming that those people contribute the greatest risk, and that may not, in fact, be true. So, there are a lot of methodological limitations, and the bottom line is that we only had certain data available, and we had to make certain assumptions in order to deal with it, and that was the task that fell to the TSE Advisory Committee, and that was what they recommended that we do.

So, you know, you are right and I wish we had the data to answer that point, but we do not.

DR. HOLLINGER: Dr. Khabbaz.

DR. KHABBAZ: I have a couple of comments to make, to clarify for clarity, regarding the criteria for suspected new variant CJD, the CDC criteria. These criteria are for, and the definition of suspected new variant CJD, is for surveillance purposes, and including of the young age, less than 55, I mean they are carefully crafted based on what we know of the new variant CJD cases reported in UK.

These criteria are likely to change with time as more information accumulates. The age is not cast in stone. There is some criteria may drop, may be added, and they are carefully reviewed, and so it is an ongoing process. In no way did we think or suggest that these criteria ought to be the threshold for looking at it.

In fact, we encourage reporting of young cases. I mean we use the same threshold of just young CJD to initiate investigation, and the investigation is for the purpose of if you don't have a pathologic diagnosis, then, we use those criteria to classify cases suspect new variant CJD for counting.

With regard to the reporting, we work with the Council of State and Territorial Epidemiologists for decision on what disease to include or not, but just to clarify that with regard to surveillance--and there are some complicated issues--making a disease nationally notifiable does not by the large assure reporting and results in better surveillance, and we have ample examples of conditions where we have better surveillance through other systems.

DR. HOLLINGER: Thank you.

Thank you very much for this nice summary of that conference.

Dr. Smallwood wants to discuss the schedule of the OBRR Workshops coming up. There is a number of very good workshops.

Schedule of OBRR Workshops

Linda A. Smallwood, Ph.D.

DR. SMALLWOOD: In the interests of time, I am going to try to be very brief, however, on the table outside we have listed the proposed Office of Blood Research and

Review workshops for 1999. There are eight of them, and I will just read the titles briefly and give you the dates of those that have been scheduled.

The most imminent will be the Blood Donor Suitability Workshop - History of Hepatitis. That is scheduled for July 21st, 1999, and it will be held at the Natcher Auditorium located on the NIH campus.

The second is Bacterial Contamination of Platelets. That will be held on September 24, 1999, at the Jack Masur Auditorium on the NIH campus.

The Blood Substitute Workshop is scheduled for one and a half days, September 27th and 28th, 1999, at the Natcher Conference Center located on the NIH campus.

There will be a Workshop on Plasticizers: Safety Issues in Blood Collection and Storage scheduled for October 18th, 1999, at the Jack Masur Auditorium on the NIH campus.

A Workshop on Inactivation of Plasma Derivatives (Human Injectables) from Non-Human Sources, scheduled for October 25th, 1999, Jack Masur Auditorium, NIH campus.

The Nucleic Acid Testing Implementation Workshop has been mentioned earlier. It is scheduled for December the 7th, 1999, Jack Masur Auditorium.

A Donor Suitability Workshop is tentatively planned for October, the date subsequently, hopefully, to be determined.

Finally, a Workshop on Leukoreduction scheduled for December the 10th, 1999, at the Natcher Auditorium.

Information regarding these workshops may be found on the CBER web site page under What's New. The web site address is as follows: www.fda.gov/cber/whatsnew.htm.

DR. EPSTEIN: It has been brought to our attention that the December 7th workshop date for the NAT workshop is in conflict with the American Society of Hematology meeting, and we have a request that we try to find an alternate date. So, I think people shouldn't get too wedded to that date today. We may change it.

DR. SMALLWOOD: I would just like to follow up. If you would keep abreast with respect to our web site, you will be notified of alternate dates and times.

Thank you.

DR. HOLLINGER: We are going to move into the next session, actually, the first session for discussion. This is going to be on the post-donation information affecting plasma pools for fractionation (inadvertent contamination). We discussed this at some length last time with an algorithm. I made some suggestions which Dr. Tabor and their group have put together again for discussion. I hope you all have had a chance to look at that, so we can move through on that.

Dr. Tabor, could you give us an overview, then, of

the risk issues.

I. Post-Donation Information Affecting Plasma Pools for Fractionation (Inadvertent Contamination): Risk Issues Overview

Edward Tabor, M.D.

DR. TABOR: Good morning.

[Slide.]

Inadvertent contamination is a subject that is a term that has been in use for more than 20 years, and since our discussions are new about this subject beginning in 1997, there has been a lot of interest, and I think some of it came from members of the Blood Products Advisory Committee although I don't know whether they are current members who brought this up, that the term "inadvertent contamination" is really not a very good name for this.

Nevertheless, after wracking our brains for a substitute term and coming up with nothing suitable, and also realizing that everybody knew what inadvertent contamination was even if no one liked the term, we continued to use it for a while, but now we are going to be calling post-donation information.

As long as you recognize that these two terms are interchangeable, you should have no trouble following the discussion.

In June of 1997, we presented to BPAC information

on inactivation procedures that are applied to plasma derivatives, inactivation and removal procedures, and the amounts of the viruses hepatitis B, hepatitis C, and HIV that were removed by these procedures in comparison with the amount that could be present in any pool.

So, we discussed that type of inadvertent contamination and really presented raw data in June of 1997. In September of 1997, we discussed a different type of inadvertent contamination, which we were calling risk factor inadvertent contamination or now risk factor post-donation information.

Basically, what we were talking about then was those donors who answered negatively or appropriately to all donor questions, whose serum or plasma was tested negative for all of the licensed tests for hepatitis B, hepatitis C, and HIV, but who nonetheless, after donation at some point provided post-donation information that they, in fact, were a member of a risk group for one of those three viruses.

So, that was September of 1997. Then, in December of 1998, we presented you with a draft algorithm for test-positive cases of post-donation information, that is, where you discover after collection and perhaps after pooling, perhaps after manufacture, that one of the units that had been reported as testing negative, in fact, tested positive. That was in December of 1998.

At the last meeting, in March of 1999, we presented a revised algorithm which you voted to approve with some minor modifications, and a copy of that is in your information today, and it is not a subject for discussion unless you have something urgent to ask about it.

What we are going to talk about today is the algorithm for risk factor post-donation information. At the March 1999 BPAC, you were given a draft algorithm, and the committee had a number of concerns about the draft algorithm and asked us to go back and revise it.

I might add also that there were concerns raised from members of the audience regarding the large number of plasma pools and plasma derivatives that would be affected by post-donation information related to risk factors, and so today we are going to discuss the revised algorithm for risk factor post-donation information.

We are limiting our discussions in the BPAC meetings that I have listed for you and in this one to these three viruses: hepatitis B, hepatitis C, and HIV. We recognize that there are post-donation information issues related to other viruses. We recognize that there are post-donation information issues related to viruses that have not yet been discovered, and perhaps we will muster the courage to bring those to you at a future BPAC, but right now we are talking about HBV, HCV, and HIV.

These are viruses for which we have tests to detect the viruses, and there are viruses for which inactivation methods or inactivation removal methods are available. As I mentioned, there are test issues which we are not discussing today, and donor issues.

Donor issues or risk factor issues are really window period issues. Today, with the tests that we have to detect infected individuals, when you ask someone if they are a member of a risk group for one of these viruses, you are really asking could you be in the window phase when you are infectious, but not detectable.

[Slide.]

I would like to just briefly go over recommendations that were made by BPAC in September 1997 when we discussed risk factor issues in post-donation information. You do not have to stick by your previous recommendations, but I think they will give you an idea of what the committee at that time felt, and I think probably at least half of you were members of the committee at that time.

The committee recommended that in cases of inadvertent contamination or post-donation information of a pool consisting of units negative for HIV, HBV, and HCV markers containing a unit from a donor with a subsequently discovered risk factor, FDA should determine regulatory

action based on an assessment of product risk.

I think what the committee was saying was we should evaluate how much virus could be in the pool if a window period unit happened to be included under these circumstances and what the effect of the inactivation rule procedures would be.

[Slide.]

The committee further recommended an assessment of product risk should consider the maximum level of contamination that could occur and the capability for virus removal and inactivation.

[Slide.]

Finally, the committee recommended again with regard to risk factor issues quarantine of distributed product cannot be dispensed with even if there has been a record of GMP compliance by the company.

What the committee meant was just because the company has had good GMP inspections at every regular inspection over the past so many years, doesn't mean you can ignore the fact that a unit with post-donation information is in the pool, that is, that you have to look at GMPs again, and they recommended--and this is important for our discussion today--that a negative nucleic acid test on the donor or pool, or subsequent test-negative donations by the donor, can obviate the need to destroy the product.

[Slide.]

Now, let's talk about the algorithm. Let me just mention the algorithm has some footnotes. For some of the footnotes, I will flash this to the footnote slides, for others I will just read you the footnote. There are some footnotes in the footnote list that applied to the previous algorithm and may or may not appear here.

In the case of whole blood, which of course involves ultimately recovered plasma which can enter a pool, let's just say that a risk factor is discovered. If the unit has not yet been transfused, you would destroy the unit of blood and plasma, and notify the consignee to destroy it if it had been shipped.

You would defer the donor, and there is footnote g, which I will read to you, which is the donor must be deferred. In addition, if the donor can be located, all licensed tests for markers of HCV and HIV should be done on a newly obtained sample.

If any tests for HCV or HIV are positive or indeterminate, lookback should be conducted, and lookback here refers to both product retrieval and recipient notification, and prior collection should be quarantined. Consignees of recovered plasma should be notified.

If the blood unit has been transfused, the blood unit recipient should be notified, the donor should be

deferred with the provisions for possible lookback for HCV and HIV, as I just described.

Prior collections should be quarantined, and again the consignee of the recovered plasma should be notified.

[Slide.]

I recognize that this may be hard to read from a distance. One of the objections that the committee had at the last meeting was that we talked about recognizing risk factors as having been discovered after the fact, and the committee was concerned that some risk factors were not as important as others.

So, we have changed the algorithm to say listed risk factors discovered with a footnote i, and I will show you that footnote in a minute. The donor should be deferred with provisions for lookback if it involves HCV or HIV-positive donor, and quarantine of prior collections because many of these donors will have given many times before.

[Slide.]

This footnote i lists the risk factors for HBV, HCV, and HIV to be used for post-donation information algorithms. This list was compiled based on reports to FDA concerning post-donation information, and a little later you will hear a talk by Sharon O'Callaghan about those reports and the numbers we have received.

It was also modified based in part on scientific

information about the relative importance of these risks, but I will just go through it now, and we can discuss it later.

The risks that would trigger this algorithm are needlestick or a transfusion within the past 12 months, having been tattooed within the past 12 months unless it was conducted in a presumed sterile situation, body piercing other than ear piercing within the past 12 months, ear piercing being considered to be performed in most cases in sterile situations nowadays, I.V. drug use ever, male to male sex within the past 12 months, sex with an I.V. drug user within the past 12 months, a sex partner who tests positive for current HBV infection or HIV infection, having exchanged sex for drugs or money within the past 12 months, a history of incarceration greater than for a period of 72 hours within the past 12 months, AIDS-related signs or symptoms at the present time.

Some of these may seem a little unusual to be listing as risk factors, but you will hear from Sharon O'Callaghan that these are reports that we get in some numbers. A female who had sex within the past 12 months with a male who had had sex with a male, any sexually transmitted disease within the past 12 months, and travel to or immigration from HIV Group O areas, which mainly involve the countries of the Cameroon and those countries bordering

on the Cameroon.

Now, I will go back to the algorithm.

[Slide.]

One of the donors is discovered sometime after donation, despite having answered all the questions appropriately at the time of donation, to have one of these risk factors. Either they forgot and called up and said, gee, I forgot I had had a tattoo or something like that, or they may have come in to donate again and answered yes to one of the questions that they had answered no to before.

I want to clarify footnote k, which I will just do verbally. Footnote k is a post-donation information typically is found to apply to multiple collections from a single donor. So, we are talking here about any units from this donor that have not yet been pooled would be destroyed.

Any units that have been pooled, but not yet processed would be subject to quarantine of the pool, and we will discuss that further. Units that have been pooled and processed, but not yet shipped, the products would be quarantined. Any final products that had been shipped, you would notify the consignees to quarantine the products, and that is footnote j.

[Slide.]

I am going to turn to the footnote, so you can read it. Footnote j says that quarantine is not necessary

if additional testing is negative under a later part of the algorithm labeled point A--and we will come to that--or if comprehensive GMP evaluation is adequate under a later part of the algorithm labeled point B, and either of these is completed within 72 hours of the discovery that a unit in the pool came from a donor with a listed risk factor post-donation information.

The choice of 72 hours we can discuss later. It is somewhat arbitrary. It is hoped that this whole process listed under footnote j will encourage manufacturers to keep better records and better computerized records, so that a GMP evaluation can be done rapidly and effectively.

Dr. Lynch later will discuss some of the problems involved in that.

[Slide.]

Just to go quickly through the remainder of the algorithm, in this situation, a company has 72 hours in which to do one of two things. They can either take process a or process B. Process A involves NAT testing, and process B involves a comprehensive GMP evaluation.

Under process A, a validated NAT test--and, of course, right now we have no licensed NAT tests, but we are talking about a test that has been adequately validated under the INDs to the satisfaction of FDA, and we can discuss this further--a validated NAT test for HBV, HCV, and

HIV on the pool and the original sample would be done.

If the original sample is unavailable, all licensed tests, as well as a validated NAT for HBV, HCV, and HIV could be done on a subsequent sample from the donor. What we are trying to do here is make sure that the donor was not in the window period at the time of the original donation.

If all of these tests are negative, the pool or the product could be released. If any of these tests are positive, the pool obviously could be destroyed or the company could move to the GMP part of the algorithm, which they could have done in the first place if they wanted to avoid the testing, and a comprehensive GMP evaluation would be done.

[Slide.]

Under footnote d, a comprehensive GMP evaluation would be done by the fractionator to verify virus removal and inactivation. GMP inspection, an actual inspection by FDA would be done as needed. The fractionators would send reports to FDA listing all GMP evaluations conducted because of post-donation information.

[Slide.]

So, if this GMP evaluation by the fractionator is conducted within 72 hours, and is found to be adequate with regard to those parts of the GMPs related to virus removal

and inactivation. We are not talking necessarily about a complete GMP evaluation, but just relevant portions regarding virus inactivation and removal.

If these are adequate, the pool or product could be released. If they are not adequate, the fractionator would have to destroy the pool or product and issue a recall. There is one exception to that situation is under footnote f, which states that in some cases, pools or products can be reprocessed if done so under an approved protocol.

I think at this point I would be glad to answer any brief questions, but some of your questions may be clarified by subsequent speakers.

Dr. Hollinger, do you want to move on to the next speaker?

DR. HOLLINGER: Yes.

Post-Donation Information

Sharon O'Callaghan

MS. O'CALLAGHAN: Good morning. I am Sharon O'Callaghan from the Office of Compliance.

[Slide.]

What we have done is looked at the error and accident reports that we have received in FY '98 and compiled information related to the post-donation information report, so I am going to provide the background

of how we got to the list of the risk factors.

[Slide.]

We will start off with the definition that we have come up with for post-donation information, and that is, information that is provided by a donor or other source, and the other source could be either a donor spouse, friend, ex-girlfriend, could be physician, state health department. It could be even the police department given the information.

It is information that is provided at a subsequent donation or shortly after a donation. About 70 percent of the post-donation information is provided at a subsequent donation. This information would defer the donor if that information had been known at the time of the previous donation, and the information could affect the safety, purity, or potency of the product.

[Slide.]

So the types of post-donation information that we have seen reported to us have included "do not use my blood" where the donor calls back. This is usually within a day or two and just says, "don't use my blood," and gives no other information.

It includes post-donation illnesses that are not related to hepatitis or AIDS, such as measles, mumps, Lyme's disease is a big one lately. It also includes post-donation illnesses that are related to hepatitis and AIDS. History

of hepatitis or jaundice. Sexually transmitted diseases, syphilis, gonorrhea, chlamydia. Sex partner testing positive for hepatitis, AIDS, or sexually transmitted disease.

Male donor having sex with another male. Female donor having sex with a male who has had sex with another male within the last 12 months. I.V. drug users. People having sex with I.V. drug users. Travel or immigration to high-risk areas, specifically, the Group O HIV risk areas.

[Slide.]

Exchanging sex for drugs or money within the last 12 months. Receiving tattoo, body piercing, transfusion or needlestick within 12 months of the donation. Non-sexual exposure to hepatitis to AIDS. This mostly includes household type exposure.

Travel to malarial endemic areas. History of disease or cancer. History of CJD or associated risk factors. Either the donor had a family member that was diagnosed as CJD or received growth hormone.

Received vaccine or medication, such as Proscar or Tegison. Donor was incarcerated for more than 72 hours within the last 12 months. History of hepatitis A or exposure to hepatitis A.

High risk behavior that is not specified. Frequently, a donor will call up or come back the next time

and say, yeah, I am in one of these groups, one of these high risk groups, but not specify which group they are in or what type of behavior they have engaged in. Also, information not specifically related to hepatitis or AIDS, such as non-I.V. drug use.

Donors will frequently call up and ask for their test results. The blood centers will defer them because they are thinking that they are donating to be tested, so without giving them any additional information.

We have had a couple of reports related to donors being mentally retarded or giving some indication that their history may be unreliable. Also, we had one that the donor had a sex change operation, so the blood center decided to defer them for that.

[Slide.]

This table just gives you an idea of the number of reports that we have received. The column on the right is the total number of error and accident reports received, and this is separated by the type of establishment reporting, the blood establishments versus the source plasma establishments.

Sixty percent of the total error and accident reports that we receive are related to post-donation information, and that has been a consistent number for the last five to seven years.

The blood establishments, 59 percent of their reports are related to post-donation, and 80 percent of the source plasma centers reporting involve post-donation information.

[Slide.]

So, we took these types of post-donation information that we receive and we identified the actual risk factors that are associated with specifically HBV, HCV, and HIV.

This is the actual number of reports for each type of risk factor. I want to make a statement here that one report could represent multiple donations, just like Dr. Tabor had mentioned. We have donors who will come in, plasma donors who have donated for several years, and a frequent donor, every three to five days or something like that, for several years, all of a sudden now says, oh, yeah, I had sex with another man. Now, all of those donations could be affected.

So, the number of reports versus blood and plasma are depicted here, with the needlestick, transfusion, tattoos and body piercing all grouped as one category, 978 reports from the blood industry, and 183 from the plasma industry.

For I.V. drug use, the blood industry reported 274 and plasma was 114. Male to male sex, 216 reports from

blood, and 47 from plasma.

Sex with an I.V. drug user, 169 from blood, 25 from plasma. Sex partner testing positive for hepatitis B or HIV infection, 414 from the blood industry, and 52 from the plasma industry. Actually, when I looked at that this morning, I had to go back and double-check that number because that seemed awfully high, but that's what we have.

Exchange sex for drugs or money is 40 from blood, and 18 from plasma.

[Slide.]

History of incarceration, only 26 from blood. There is a lot more we get from the plasma industry, 161.

AIDS related signs or symptoms, blood reported 21, and plasma is 6.

Female having sex with a male who had sex with another male, 42 for blood, and 4 for plasma.

Sexually transmitted disease, 22 from blood, 2 from plasma.

Travel to or immigration from the HIV Group O risk area is 190 from blood, and 6 from plasma.

So, when you look at just these specific risk factors, that brings down the post-donation totals to about 34 percent of the post-donation reports fall into this group for blood establishments, and 70 percent, which is still a high number, for the source plasma industry fall into these

risk factors.

Are there any questions about any of these specific risk factors or post-donation? Yes.

DR. BOYLE: Of your first category, which merged transfusions and needlesticks and body piercing, what proportion does body piercing represent?

MS. O'CALLAGHAN: We haven't separated those out, but as a good guess, probably about 20 to 25 percent. It is a fair number. It is also difficult sometimes with the way that the reports are presented, the donor is deferred for body/ear piercing. So, it is difficult to tell whether it was one or the other.

DR. FITZPATRICK: Did you exclude high risk behavior - not specified, or is that included in some of those others?

MS. O'CALLAGHAN: We didn't include the high risk behavior - not specified only because we were trying to look at the things that we knew really did affect, were related to hepatitis B, C, or HIV.

It is very nonspecific information. I mean you could use the same argument with the "do not use my blood," you know, and the donors calling back, you know, for their test results. It is the same kind of unspecified risk, but it is not directly related to HBV, HCV, or HIV.

DR. HOLLINGER: Dr. Mitchell.

DR. MITCHELL: Can you talk about the risk of being in prison? Specifically, I am concerned, I want to know why 72 hours.

MS. O'CALLAGHAN: Well, that was one of our guidance documents, and I don't recall the actual date of that one. We had recommended deferral of donors that had been incarcerated for 72 hours because of potential high risk behaviors that could occur during that stay or any other kind of exposures that they may not know about.

DR. HOLLINGER: Mark, I think it is primarily because a lot of people may be placed into prison overnight or a few hours, and things like this, and they wanted to remove that large number from the situation, so they had to choose a point, and they chose the fact that if somebody was in there three days, then, they would probably be in there longer.

DR. RUTA: I am Martin Ruta. That was exactly the concern that we had, where for the overnight, the 72 hours to capture people who might have been incarcerated over the weekend, but most of the data on incarceration relates to prisons where people are held for a longer period of time. But you are right, Dr. Hollinger, that is the reason.

DR. MITCHELL: I guess I am concerned about shorter periods of time. It seems like a rather long--we know that people who are in prison, that a large percentage

of the rapes, for example, occur within the first 72 hours.

DR. TABOR: Let me clarify something before we discuss that further. First of all, I want to thank Sharon O'Callaghan for the really marvelous presentation of data that helps explain how we came up with this list in response to the committee's question at the last meeting.

What we tried to do, a group of us sat down and also I worked on it myself, as well, but a group of us sat down and tried to take the list that Compliance had of deferrable information and decide which of those factors would impact, as Sharon O'Callaghan said, on risk for HBV, HCV, and HIV. So, obviously, the receipt of a vaccine recently has no impact on that.

We had to make some choices. What we are dealing with here is a very low risk situation anyway. You are dealing with people who are test-negative, most of whom are not in the window period for any disease.

So, what you are trying to do is find the window period. Now, the clarification I wanted to make with regard to your question about incarceration is we have two lists here. The lists that Sharon O'Callaghan showed is a list based on guidance documents, such as the one Dr. Ruta was describing.

We are not in a position to change that list or the guidance documents, and they are really not a subject

for discussion. What is a subject for discussion is footnote i on the algorithm, and which should or should not be included there.

So, with regard to your question about incarceration, we said on footnote i, incarceration for greater than 72 hours. You raised the question whether 72 hours is appropriate. For footnote i, we can discuss should it be a shorter period of time.

Now, one of the problems we face is can we have criteria on footnote i for the use of this algorithm that is inconsistent with currently approved guidance documents. You may hear arguments on both sides of that, and I think there are probably arguments on both sides.

So, your question is a very good one, but it should only apply to footnote i.

DR. HOLLINGER: I think what I would like to do, if we could, I would like to maybe finish up the presentations, and then we will come back with me--unless it is a question that really needs to be--go ahead.

DR. OHENE-FREMPONG: It was just a quick question about what you define as "needlestick."

MS. O'CALLAGHAN: Most of those involve like hospital workers that have drawn blood from a patient, and then stuck themselves with a needle without knowing whether or not the patient was actually hepatitis or HIV positive.

DR. OHENE-FREMPONG: So, you mean accidental.

MS. O'CALLAGHAN: Accidental needlesticks, yes.

DR. OHENE-FREMPONG: I think it should be clarified.

MS. O'CALLAGHAN: Sorry, didn't have quite enough room on the slide.

DR. HOLLINGER: Thank you very much.

If we could then go to the final presentation in this section. Dr. Lynch is going to talk about GMP Investigations.

cGMP Investigations

Thomas Lynch, Ph.D.

DR. LYNCH: I should start out by saying that an investigation itself into adverse information regarding the manufacture of a product is part of GMPs itself. Information can be received from a variety of sources.

[Slide.]

We are here concentrating today on information regarding the status of a donor with respect to a risk factor, but what I am about to say also applies to the case where a positive donation may be identified or if the information relates to the use of a product and an adverse event or suspected transmission associated with that use.

Finally, you should bear in mind that information can also come from within the manufacturing operation

itself, such as where an audit reveals a heretofore undiscovered deviation in intended procedures or let's say a stability sample goes south at some point.

[Slide.]

In all cases, the information should flow into the part of the organization called Quality Assurance, and this component has several responsibilities in this process. It certainly does collect the information, and it initiates and coordinates the investigation intended to assess that information.

In the first instance, it has to determine what the appropriate scope of the investigation is, that is, what products might be affected by whatever information has been received, and then once the investigation is completed, some sort of risk assessment has to be performed or health hazard evaluation, if you will, that will determine what, if any, risk there is to the recipients of the products that have been affected, and then based on that risk, appropriate action is identified and taken, and, if possible, corrective actions to prevent a recurrence are implemented.

Throughout the course of this, where appropriate, the appropriate regulatory authority, such as FDA, are informed of the situation.

[Slide.]

In the course of fulfilling these

responsibilities, QA has to ask itself several threshold questions. The first, whether or not the information does impact the transfusion-associated risk is a given here. Risk factors associated with the donor or donation, and relating to transfusion transmittable viruses are certainly relevant to plasma derivatives.

The second question, of course, is whether the manufacturing process addresses that risk, and that depends on the nature of the virus in question and the types of viral clearance procedures that are incorporated into the manufacturing process.

Here, we are talking about hepatitis B, C, and HIV, all lipid envelope viruses, and as we reviewed in 1997, are viruses for which clearance procedures have been incorporated into the vast majority of all plasma derivative manufacturing processes.

Then, finally, given the nature of the virus and the type of clearance procedures that have been adopted, does an adequate safety margin remain with respect to that product.

Again, we reviewed the risk factors associated with, for example, a window donation, and the effectiveness of the clearance procedures that are incorporated into manufacturing, which suggests that an adequate safety margin in most cases should exist.

[Slide.]

The adequacy of viral clearance is, if you recall, determined by taking whatever the production process step is and scaling it down into a laboratory model, and assessing its ability to remove or inactivate high titers of virus, which gives you a measure of its viral clearance capacity.

[Slide.]

So, this is the theoretical capability of a clearance process, however, for that process to be reliable, it has to be performed on a daily basis according to good manufacturing practices, which are a set of standards that encompass all aspects of the manufacture of plasma derivatives and particular in biologics and drugs in general, and they are designed to assure that the quality of these products remains consistent and to prevent manufacturing errors and contamination of these products.

[Slide.]

Rather than try to enumerate all aspects of good manufacturing practices, it is useful I think instead to consider what events would constitute breaches of good manufacturing practices that would impact the viral safety of any of these products.

I have listed a few of those here, for example, deviations from your established written procedures would constitute one such deviation, the nonconformance of a

product with some predetermined specification that relates to viral clearance or the failure to properly maintain key equipment or to calibrate critical instruments that are used to control the process, or finally, anomalous laboratory results relevant to the clearance procedure that have not been adequately resolved.

All of these things could create uncertainty about the effectiveness of one or more viral clearance procedures in a manufacturing process.

[Slide.]

And because the risk that a recipient of a manufactured product confronts with respect to a donation that has a risk factor associated with it, that was used to manufacture that product, depends entirely, in my view, on the safety measures that are built into the manufacturing process, risk evaluation becomes largely a question of how closely good manufacturing practices have been adhered to during the production of that product.

[Slide.]

The effectiveness of a good manufacturing practice investigation in verifying that the products are safe from a viral perspective depends on four premises.

First of all, the manufacturing process is assumed to include effective clearance steps, and provided that those steps are properly performed, an adequate safety

margin with respect to the virus is effected.

[Slide.]

While the overall quality of the product is determined by a global adherence to good manufacturing practices, we can identify particular steps in that process that are particularly germane to viral safety. Those are the viral clearance steps themselves.

Therefore, the scope of a GMP investigation should focus on those particular steps. However, the complexity of a GMP investigation is influenced by more than just this one factor.

[Slide.]

For example, a single donor with a particular donation history reports post-donation information that feeds back into the collection center, for example, and thence to the manufacturer.

That donor may have contributed a number of donations over a span of relevant time, which have been incorporated into more than one manufacturing pool, each of which may have given rise to more than one product.

As you all know, a single plasma pool is the source material for multiple plasma derivatives. Furthermore, in the course of manufacturing those products, intermediates in the process may become pooled together to form a single lot of a product, which therefore can be