DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

64TH MEETING

VOLUME I

Thursday, September 16, 1999

8:00 a.m.

Bethesda Ramada Inn
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Bethesda, Maryland

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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. Welcome to the 64th Meeting of the Blood Products Advisory Committee of the Food and Drug Administration.

I am Linda Smallwood, the Executive Secretary. At this time, I will read to you the conflict of interest statement that will apply to both days of this meeting.

This announcement is made a part of the record at this meeting of the Blood Products Advisory Committee on September 16th and 17th. Pursuant to the authority granted under the Committee Charter, the Director of the FDA Center for Biologics Evaluation and Research has appointed Drs. Paul McCurdy, Mary Chamberland, and Michael Fitzpatrick as temporary voting members for all committee discussions.

In addition, the Senior Associate Commissioner for the Food and Drug Administration has appointed the following participants as temporary voting members for the discussions on the reclassification of HIV drug sensitivity assays: Dr. Paul Edelstein, Dr. Roy Gulick, and Dr. Carmelita Tuazon.

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. Richard D'Aquila is involved with a contract supported by Visible Genetics to perform HIV sequencing assays for subjects in a Visible Genetic clinical trial. Dr. Robert Gasser is a federal employee serving as the principal investigator for a Department of Defense study to evaluate candidates in a malaria diagnostic assay from firms that could be affected by the discussions of antigen antibody testing for malaria. Dr. Nguyen-Dinh is a CDC employee serving as a collaborator on a CDC grant for the detection of malaria using a product manufactured by firms that could be affected by the discussions of antigen and antibody testing for malaria. Dr. Neal Young, from the National Institutes of Health, NHLBI, has received consulting fees from Biotech.

In the event that the discussion involves specific products or 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.

At this time I would like to take the opportunity to introduce to you the members of the Blood Products Advisory Committee. As your names are called, would you please raise your hand.

Dr. Blaine Hollinger, Chairperson. Dr. Gail Macik. Dr. Richard Kagan. Dr. Mary Chamberland. Dr. John Boyle. Dr. Michael Fitzpatrick. Ms. Katherine Knowles. Dr. Buchholz. Dr. Paul McCurdy. Dr. Stroncek. Dr. Verter. Mr. Corey Dubin.

I would also like to acknowledge that some of our advisory committee members will be completing their terms, however, some of them will continue with us as consultants. At this time, I would just like to thank all of you that have served with us and hope that you will continue to support us in this effort. Dr. Mark Mitchell just arrived, as well.

On the table outside there was a list of pending workshops that the Office of Biologics Research and Review has proposed for this year 1999, and we hope that you would pick up a copy of that and govern yourselves accordingly. These workshops will be announced, and are announced, on the FDA CBER web site. All of the committee members have received a copy of the schedule of the workshops in their packets.

May I also encourage everyone who is speaking to please speak directly into the microphone, so that we may record your comments, and also please state your name, so that we will have that for the record, as well.

Some of you had expressed concerns about the storm. As you can see, we are here this morning and unless there is a drastic change we will proceed with this meeting as scheduled.

If there are no further declarations to be made, at this time I will turn over the meeting to our chairperson, Dr. Blaine Hollinger.

Welcome and Opening Remarks

DR. HOLLINGER: Thank you, Dr. Linda.

We have a full day today, so I think we will get started with the meeting because there are several, particularly in the updates, I think which are really important and with perhaps some potential questions or at least some comments.

We are going to start off with the first committee update. That will be Dr. Stephen Nightingale on a Summary of the PHS Advisory Committee Meeting which was held very recently.

Summary of PHS Advisory Committee Meeting

Stephen Nightingale, M.D.

DR. NIGHTINGALE: Thank you very much, Dr.

Hollinger.

Dr. Hollinger, Committee members, guests: The Advisory Committee on Blood Safety and Availability met on August 26th and 27th to consider four topics, the first of which was government policy in response to the FDA guidance regarding to deferral of donors who had resided or traveled in Britain for more than six months between January 1980 and December 1996.

The second was the current availability of plasma derivatives. The third was the status of the hepatitis C lookback effort, and a more general topic was the fourth agenda item, which was how federally mandated blood safety measures should be financed.

Regarding British donor deferrals, the first agenda item, that policy, as you will recall, was announced on June the 17th here at the BPAC, and Dr. Jacobs will be discussing that policy in much more detail in the next few minutes.

I would say briefly, only to cover what was discussed at the Advisory Committee, the government response was initiated at two meetings. The first was the prior meeting of the Advisory Committee on Blood Safety and Availability on April 28th and 29th.

That was the meeting at which Ms. Marian Sullivan, the National Blood Data Resource Center, presented her

projections of future supply and demand for red blood cells. In response to that projection and other information presented to the committee, the committee had recommended that the Food and Drug Administration reevaluate its policies in reference to blood donations by individuals with hemochromatosis.

As I believe you know, and will be discussed in more detail I believe by Dr. Gustafson, that reevaluation has in fact taken place.

The other locus at which government response to the British donor deferral policy was initiated was a Blood Safety Committee meeting on June 8th, at which Dr. Satcher appointed an interagency working group on blood safety and availability, and that also will be discussed later.

Dr. Satcher, in his opening remarks to the Advisory Committee, predicted the discussion would be lively and he hoped that it would be constructive. In the interests of time, I will simply say that both proved to be the case.

The second item on the agenda was the availability of blood products, and the industry reviewed progress that had been made since the April '98 advisory committee on blood safety meeting on this subject.

Specifically, they mentioned that the monthly production figures were now made available to all interested

parties, that there were emergency supply programs, the capacity of some of the manufacturers had been expanded in compliance with GMP by those manufacturers had been achieved, they were pursuing research and exploring importation, and Baxter subsequently announced successful completion of that initiative. All the recommendations of the Advisory Committee in April 1998 dealing with it had not been adopted, was one recommending constraint on exports of plasma derivatives, and that had gone to the Secretary and the government's action was based on the Secretary's decision.

The patient community responded that production, however, remained flat, at about 15 million grams a year, whereas, demand based on previous production had been at 17 million grams per year, and that there were estimates that demand was rising at the rate of about 10 percent per year.

These concerns were expressed both by the Immune Deficiency Foundation and the Alpha 1 Foundation. At that point, discussion turned to reimbursement policies and the reimbursement climate as a possible reason for the shortage of plasma derivatives, and there was much discussion of the proposed ambulatory procedure classification 906 and the proposed reimbursement for it.

At this point, the discussion, which had been of the shortage of plasma derivatives and was moving towards

discussion of reimbursement of blood products, as well, threatened to squash, for want of a better word, discussion of the third agenda item, which was progress with the hepatitis C lookback.

We suspended discussion of plasma derivatives to deal with the issue of hepatitis C lookback. Dr. Mied presented the Government guidance, the FDA's June 17th guidance on that policy, and he will discuss it later. I would say only at this time that our current policy, like all substantive blood policies, have been carefully reviewed and unequivocally endorsed at the highest levels of the department.

The discussion then returned to the subject of plasma derivatives. There was extensive discussion and presentations of the impact of the proposed outpatient prospective payment system, which has completed its comment period and is approaching the Department as a proposed Final Rule.

The discussion at the meeting paralleled the discussion yesterday at a subcommittee of the House Commerce Committee that is chaired by Mr. Bilirakis. The same concerns on a larger scale for the health industry were those that were presented to the Advisory Committee for Blood, and the formulation of the issue at the House Commerce Committee yesterday was that there certainly were

issues to be addressed, and the question was whether or not these issues were to be addressed through legislative remedy or administrative remedy, and at least at the time that I had to leave the hearing yesterday, there was no resolution of that, and that would appear to be the line of discussion and negotiation on this issue that will proceed for the rest of the year.

The discussion of the Balanced Budget Act of 1997 that took place at the Advisory Committee did include a presentation by the Health Care Financing Administration in which Ms. Nancy Edwards representing HCFA did make a statement that HCFA was aware of the potential impact of its proposed actions on the blood community, and did assert that HCFA was aware of these, and the word that she used was hope to ameliorate those concerns as best as possible. She did, however, state that HCFA was not, at the time she made the statement, favorably inclined -- again, I believe that was her precise word -- towards a passthrough for blood or blood products, although that does remain on the table.

There were a variety of motions that the Advisory Committee passed. I think the first of them that there was a motions that the Advisory Committee concurs with the guidelines that had been forth regarding variant CJD donor exclusion, that the vote on that was 5-4-3 against and 5 members abstaining. The committee did ask to be kept

advised about the status of that policy, and that will, in fact, occur.

There was a lengthy motion that was introduced by Mr. Walsh, which in the interest of time I will summarize it. The committee recommends that the Secretary of Health and Human Services use her existing authority to exclude therapies under APC 369 and elsewhere, also 906, from the Prospective Payment System for hospital outpatient services and reimburse them on a reasonable cost basis.

That was passed unanimously. In regards to the hepatitis C lookback, the committee recommended that the Secretary direct the FDA to construct the ACF lookback in accordance with the prior recommendations of that Advisory Committee, and there were 10 for that and 1 against and 1 abstention for that motion.

The final motions of the Advisory Committee were regarding prospective payment. The first was that the committee recommend that the Secretary work with Congress to seek additional resources as far as the introduction and maintenance of mandated blood safety measures. That was passed unanimously. The final motion -- I stand corrected -- it was a motion of Mr. Walsh's about the shortage of the plasma derivatives, and it read that the committee remains concerned about the continue shortage of intravenous immunoglobulin and alpha I antitrypsin despite laudable

efforts on the part of both industry and government, and the committee would support new, as well as continuing, efforts to alleviate these shortages. That motion passed unanimously.

I will be glad to answer any questions.

DR. HOLLINGER: Are there any questions in regards to this update?

[No response.]

DR. HOLLINGER: Thank you very much.

We are going to have a Summary of the Workshop on Donor Suitability: Blood Donor Deferral for History of Hepatitis.

Dr. Biswas.

Summary of Workshop on Donor Suitability: Blood Donor Deferral for History of Hepatitis

Robin Biswas, M.D.

DR. BISWAS: Good morning.

On July the 21st of this year, an FDA-sponsored workshop was held at NIH's Natcher Auditorium to discuss donor suitability as related to a donor history of viral hepatitis. This workshop was one of a series that have occurred and that will continue to occur to reexamine the scientific basis of current policies on donor suitability.

[Slide.]

Now, two current regulations, one for whole blood

and the other for source plasma, preclude persons with a history of hepatitis from donating whole blood or source plasma.

These regulations have been in place since the late 1950s and blood establishments have used the history of hepatitis or a jaundice criterion for determining donor suitability since the early 1950s.

The current regulations and the blood establishment questions regarding history of hepatitis were put in place before any tests were developed that detected hepatitis viruses and before much was known about the infections caused by these viruses, for example, did individuals who had clinical hepatitis remain infected after apparent clinical recovery.

Since that time, tests for several hepatitis viruses have been developed and, in particular, very sensitive and specific serologic tests for hepatitis B virus and hepatitis C virus, two bloodborne hepatitis viruses which cause diseases in recipients, have been licensed and implemented in blood establishments.

Testing technology continues to advance with the introduction of experimental nucleic acid tests for HCV on minipools under IND. These minipool format NAT tests were applied to all plasma donations in the U.S. by the end of 1998, and good proportion, almost all whole blood donations

within the past few months.

Because of the increasing testing of blood donations for viral hepatitis over the years using increasingly sensitive and specific tests, together with the reduction of risk for viral hepatitis in recipients to almost not detectable numbers, and because of the advancing knowledge about viral hepatitis, the need for these regulations has been questioned.

We were of the opinion that it was time to reconsider the regulations, and that is why we arranged the July workshop. Actually, the Blood Products Advisory Committee has discussed this issue in the past, in 1982, 1991, and 1992.

[Slide.]

Consistent with its recommendations, the regulations are currently interpreted by the FDA as follows: donor with a history of clinical hepatitis after age 11 years should be deferred. This was considered appropriate because CDC data presented at the 1991 BPAC meeting indicated that almost all viral hepatitis that occurs in children under age 11 years was hepatitis A.

At present, viral hepatitis is interpreted to be a clinical diagnosis of hepatitis which might include jaundice. This was in response to the committee's recommendation that for the purposes of the exclusionary

regulations, not to interpret test results alone as a history of hepatitis in the absence of clinical history or absence of a medical diagnosis.

Thirdly, in a donor with a history of jaundice, if it is not possible to rule out viral hepatitis as a cause of the jaundice, the donor is deferred.

[Slide.]

The goal of the July workshop was to discussing the following: is there sufficient information today to consider eliminating the exclusion of donors have a history of hepatitis.

The following is a summary of the most important points. In the past, markers for hepatitis A, B, and C, and elevations of ALT were more frequently found to a significant degree in most deferred donors with a history of hepatitis than in donors with no history of hepatitis.

This was shown by Dr. Tabor in a 1970 study and by Dr. Tegtmeier in a 1980s study. I should point out however, that there are no recent studies on this. The regulations, another point that was made, the regulations excluding donors with a history of hepatitis were probably effective in preventing post-transfusion hepatitis in the past.

The number of donors excluded in 1998 by the regulation was estimated to be about 13,000 by Dr. Celso Bianco. Residual risk for hepatitis B and C in blood

donations is extremely low and is in the process of being decreased further as a result of NAT testing, and according to the Schreiber paper, when NAT testing is fully implemented, about 9 per million donations are at risk for HBV and about 3 per million donations for HCV.

Another interesting point that was made was that the incidence of hepatitis B and C have declined dramatically in the general U.S. population in the past decade.

In the mid to late 1980s, there was about 400,000 cases per year versus 200,000 cases a year now. For hepatitis C, in the late 1980s, there were about 200,000 cases a year, and now there are about 40,000 cases a year.

Transfusion-associated hepatitis B and C, if they occur at all today, seem to be extraordinarily rare and their incidence is evidently very difficult to detect. At the present time, as far as is known, it appears that most, if not all, known viral hepatitis agents apart from hepatitis B and C do not cause significant health risks to blood recipients except in very rare situations, however at the workshop, CDC reported that 3 percent of reported cases of hepatitis in the U.S. is hepatitis non-A through E, for which there are not tests available except experimental ones presumably.

There have been preliminary reports mainly in the

nonscientific press of a virus referred to as Senv, which may be a candidate non-A to E agent, and Dr. Tabor will be talking about that very shortly.

My own questions regarding these reports are, are they are the same entities, this 3 percent that CDC found and Senv, do they cause clinical disease or not, do they cause chronicity or not, if so, in how many individuals and donors, is there a health risk to recipients.

It was felt by workshop participants that the effect of eliminating the exclusion would be very difficult to detect if there was a very slight change in the incidence of post-transfusion hepatitis in blood recipients because of the very low incidence of transfusion-associated hepatitis overall today.

What that means is to show no change versus very little change, a very large number of observations would be required, and you would need a very large study to do this.

As a result of the workshop, the FDA will consider the following options: entirely eliminating the exclusion for a history of hepatitis, keeping the exclusion as it is, exempting donors for exclusion who have a viral hepatitis that is not a significant risk for recipients, for example, proof of past hepatitis A infection, and/or perhaps instituting a specified deferral period e.g., one year after an individual has been just diagnosed with viral hepatitis.

Our recommendations regarding this regulation will be brought before the committee in the future.

Thank you very much.

DR. HOLLINGER: Mr. Dubin.

MR. DUBIN: Just a record clearing comment, an historical comment. The broad comment that donors with a history of viral hepatitis were excluded, I think we need to be careful with. That was not the case as we have learned in the 1980s, it is part of what went wrong, and so when a broad statement is made like that, I think we begin to kind of slightly revise history a bit, and I want to be on the record saying that today, obviously, we are doing a significantly better job, but that was not the case, and the documentary evidence is absolutely there and could be placed on the table, so I would like the record to reflect that.

DR. HOLLINGER: Any other comments?

DR. EPSTEIN: A point of clarification is needed. The issue that you raised pertains to whether there were permissible collections in people with a known anti-HBS-positive marker, and there has been a long-standing debate whether the proper interpretation of the reg should or should not have included laboratory test results as history, and this is why we clarified, as Dr. Biswas noted, that we were interpreting the reg to mean clinical evidence, and it was not determined by laboratory evidence.

So, what Mr. Dubin states is correct, but I think that it needs to be understand that the controversy had to do with laboratory markers versus clinical histories.

MR. DUBIN: As collection practices.

DR. EPSTEIN: What I am saying is that collections were permitted in people with known positive anti-HBS, because we were not interpreting the marker as the equivalent of the clinical history.

DR. HOLLINGER: Robin, just a question. I was at the meeting also and sort of walked away with not being sure of where things were going after the whole day.

Is there a timetable for the FDA to make some recommendations and bring this issue even further, do you have a thought about that?

DR. BISWAS: Well, I believe that the next Blood Products Advisory Committee is in March, so it is not going to be before March. Jay wants to add something to that.

DR. EPSTEIN: Well, in a more general way. We are in the process of updating all the regulations, and Dr. Ruta will be talking about some proposed rules that have recently published, but lying down the road is reconsideration of donor exclusion requirements, and we will need to address the history of hepatitis exclusion as part of a broader initiative to look at donor suitability criteria, so within the next year or two for sure, and it can be presumed that

this would be one of the issues that we vet prior to a rulemaking.

DR. HOLLINGER: Thank you, Jay. Thank you, Robin.

The next update is a Summary of the Guidance Document on Revised Precautionary Measures to Reduce the Possible Risk of Transmission of CJD and nvCJD by Blood and Blood Products. Dr. Jacobs is going to provide that update.

Summary of Guidance Document on Revised Precautionary Measures to Reduce the Possible Risk of Transmission of CJD and nvCJD by Blood and Blood Products

Mary Elizabeth Jacobs, Ph.D.

DR. JACOBS: Good morning, Dr. Hollinger, members of the Committee, and guests.

[Slide.]

Our guidance was issued on August the 17th, and its title is "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob disease and new variant Creutzfeldt-Jakob disease by blood and blood products."

It is available on our web site, which is www.fda.gov. Go to Biologics CBER and then go to Guidelines, so anyone can get it. It is extremely detailed and I am going to hit the major points this morning.

It was issued for immediate implementation with

full compliance for six months, and at the same time we are receiving comments on that, and I want to let people know that we are planning to issue in the near term interim comments on that addressing some of the most critical questions that have been brought to our attention, so you will be hearing on those relatively soon.

It supersedes our previous guidance which was issued December 11th, 1996, and which had a subsequent internet recommendation on September 8th, 1998.

[Slide.]

I want to cover these major points from the new guidance. These are all the new recommendations. They cover, first of all, deferral of donors who were in the U.K. for six months or more between 1980 and 1996.

At the June meeting, I updated you on the rationale behind that and the meetings of the advisory committees and the committees at the PHS level.

The second topic is on the non-withdrawal of plasma derivatives from donors with CJD or CJD risk factors, and withdrawal of plasma derivatives from donors with new variant CJD or likely new variant CJD, and the third major topic is on the labeling of non-implicated materials.

Each of these overheads will show you first the prior recommendations from guidance, secondly, the new recommendations, and then thirdly, the rationale for change.

[Slide.]

First, deferral of donors with possible increased risk for exposure to BSE, the probable agent of nvCJD. The prior recommendations from 1996 did not address BSE exposure. The new recommendations, first, for deferral of donors who have lived in the United Kingdom, which includes England, Northern Ireland, Scotland, Wales, Isle of Man, Channel Islands for six months or more between 1980 and 1996, and that was announced in June.

[Slide.]

The second one addresses a point which was brought to our attention subsequent to the meetings of the TSE Advisory Committee, and we thought that it was important to include it in this guidance and are getting comments back on this.

The point that was brought to our attention is that there are people who are importing for their own use beef insulin from the United Kingdom. Therefore, we included in our guidance deferral of donors who received injectable products made from cattle in BSE-endemic countries since 1980.

The rationale is until more is known about the number of people incubating nvCJD, and about the likelihood of transmission by blood, donors with potential risk of developing nvCJD through exposure to BSE are indefinitely

deferred as a precaution. This recommendation will be examined as new scientific information becomes available.

[Slide.]

We have already become aware that this deferral recommendation on the injectable products has caused questions. We did not have any prior recommendations in the previous guidance about this, however, we did have FDA policy in 1993 not to source materials for drugs or biologics or devices from BSE countries.

[Slide.]

The next question is on disposition of plasma derivatives when the donor has the donor has either CJD or CJD risk factors. The prior recommendation had been to withdraw plasma derivatives from donors with CJD or CJD risk factors, and those include human pituitary growth hormone, dura mater transplant, two or more family members with CJD.

Our new recommendation is do not withdraw plasma derivatives if the donor has CJD or CJD risk factors. The rationale for this is the epidemiological data indicates transmission of CJD by blood or derivatives is unlikely, and that is summarized in the guidance document, a short summary. We have also a longer one if available if you would like it.

Secondly, laboratory studies suggest removal of CJD agent by manufacturing processes. I want to mention as

a kind of sidebar on that point that there is tremendous interest in the removal of TSE agents by manufacturing processes, and FDA sponsored an international workshop on clearance of TSE agents from blood products and implanted tissues. This was held on Monday and Tuesday of this week, and we thought it was too early to give a summary today, but Dr. Epstein gave a summary of the issues related to blood and to tissues, and we will be planning to have a summary of that on our web site, so that will be probably be available in six weeks or so.

In addition, for your reference, because of the interest in TSE diagnostics, we are planning a workshop for Fiscal Year 2000 on diagnostics, and that will be across all of FDA and sponsored by other groups, as well. So, as soon as we have a date on that we will let you know.

Let me go back to the guidance now.

[Slide.]

Disposition of plasma derivatives when the donor has nvCJD. Just as an update again, we have had no cases reported in the U.S.

The prior recommendations from 1996 did not address nvCJD. The new recommendation recommends withdrawal of all material collected from a donor who develops nvCJD or a donor with clinical presentation highly suspicious for nvCJD in the absence of confirmatory neuropathology.

The rationale for this is that there is not any available data yet, either epidemiological or laboratory, to determine whether the nvCJD agent is transmitted by blood. nvCJD is biologically different from CJD, so that CJD data cannot be extrapolated to nvCJD.

[Slide.]

This, of course, raises the question of what do we mean of a donor be suspicious or likely having nvCJD, and this addresses disposition of plasma derivatives when the donor has features of nvCJD.

The new recommendation is that FDA and CDC be immediately notified in case of a donor with physician's clinical or pathological diagnosis of CJD and age less than 55.

The rationale for this is nvCJD has a median age of 29, classical CJD has a mean age of 65, investigation of young CJD donors is most likely to uncover nvCJD.

The actions that we expect are that expeditious CDC/FDA investigation and decision about blood products will follow, and I just want to point out here that we would like to be notified rather than having a blood establishment conduct its own investigation first. We will then be able to look at the question about blood products and be able to refer the determination to CDC about the individual patient.

[Slide.]

This is disposition of plasma derivatives when donor has features of nvCJD. This is in the case where definitive neuropathological confirmation of nvCJD in a donor may be unavailable.

The donor has clinical features suspicious for nvCJD and decisions about disposition of blood products cannot await confirmation.

Actually, this is a little out of order. It should have preceded the other one. We would like that to be reported to us.

[Slide.]

The prior guidance did not have considerations of labeling, and that has been addressed in the new guidance. It addresses labeling of non-implicated products for the theoretical risk of CJD transmission.

The new recommendation is to label all blood products including those used as additives or excipients for other products, to indicate theoretical risk of CJD transmission, and also to state potential risks of viral transmission.

[Slide.]

The rationale for this is although CJD transmission has never been documented by blood or blood products, labeling of non-implicated products will provide information to the public about potential risks.

[Slide.]

I would like to read for you the statements for the labeling.

The recommended labeling for all blood products except for albumin is: "Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent."

Then, I would like to read the labeling that is recommended for albumin. Albumin is of particular concern because it's used in vaccines.

"Albumin is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of CJD also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin."

Thank you.

DR. HOLLINGER: Any questions by the committee? Yes, Dr. Bianco. Almost a member of the committee.

DR. BIANCO: A friend of the committee.

It is just a clarification, Dr. Jacobs, if you could help us understand the new guidance, you did not discuss, despite making this very clear review of the lack of transmission of classical CJD, reverts to earlier

procedures in terms of recipient notification in which we would do lookback even for individuals that had a single family member, an indefinite lookback.

Could you clarify for us the reasons for that approach?

DR. JACOBS: Do you mean the approach in the labeling?

DR. BIANCO: No, in terms of notification of deferral of blood donors, not plasma, and notification of recipients of prior donations.

DR. JACOBS: I would like to defer to Dr. Epstein, if I can, because he knows the history of this issue a bit better than I do.

DR. EPSTEIN: As far as the lookback for purposes of recipient notification, that is not a change in policy. It is the same policy that has been there since 1995. What that refers to is the risk that potentially exists for blood components.

That is not to say that there is any new data suggesting a risk, all studies are still negative including case control studies and lookback studies, but the thinking is that physicians may want to make individual decisions.

So, we are not mandating notification, unless the HCV lookback regulation, for example, but we are saying that the consignees down to the level of the patient's physician

should be notified, so that individual decisions can be made about notification.

Now, the case for derivatives is different. There is no recipient-oriented lookback for derivatives, and the thought there is at two levels. First of all, it is impractical. The recipients of derivatives are hard to trace. There are many thousands from even individual product lots, and the thinking was that the relative risks and benefits were quite different in the two settings. When you administer a component, you administer a high volume of product, it is the highest risk setting for a transmission should it occur.

In the case of derivatives, we believe that there are mitigating factors including the dilution effect and also clearance in manufacturing, so that we made a decision based on the relative risk and benefit. It is not meaningful to have a lookback and notification program if there is also a product withdrawal.

So, basically, the situation is that for components, there is still a retrieval and destruction recommendation, a lookback tracing recommendation, and a voluntary notification recommendation.

In the case of derivatives, for cases of classic CJD or classic CJD risk, there is no longer a withdrawal policy and there really has never been a notification

policy.

DR. BIANCO: Where I am confused is that in the way I read the new guidance, I see a change back to a single family member as a definition, so that was not the intent.

DR. EPSTEIN: No. What was changed in December '96 was that the recommendation for derivative withdrawal, which had been originally triggered in the August '95 memo by a single family member, positive family history, was modified, so that derivative withdrawal was not indicated unless it was two or more documented blood relatives.

However, the recommendation for component withdrawal, lookback and notification remained the same, so a donor is still deferred based on a single family member with CJD unless exonerated on the basis that it is not a blood relative or that there is a normal gene PRP polymorphism in the donor.

So, we still do have a recommendation for donor deferral, product retrieval, quarantine destruction, and lookback to trace recipients based on a single family member positive history, and that has not changed since August '95.

So, the confusion, I think, of the change to two or more family members when it was made only applied to the derivative withdrawal policy. It never changed the component policy.

DR. BIANCO: Could you help us understand the

rationale based on all the evidence that classical CJD does not, for recipient notification, considering that classical CJD does not appear to be transmitted?

DR. EPSTEIN: Well, the basic rationale is that the absence of cases of transmission in the available data can only be stated as certain level of confidence statistically, and the studies have low power for many reasons, either low numbers studied, limited periods of follow up, et cetera, and so the concept is that some level of risk may still exist, however, we made determinations based on the relative risk and benefit of these policies as they operated in the two different settings.

In the setting of blood components, we are talking about retrieving a very small number of components to provide perhaps a very marginal added protection to a very small number of potential recipients.

In the area of derivatives, the problem that we ran into since the policy was put in place in '95, was that the policy was contributing in a major way to very serious shortages of derivatives, and we had to trade off the implications to supply against the theoretical risk, and there we felt that given the fact that the epidemiologic studies were negative, and the fact that there were emerging data showing clearance of the agent in manufacturing, that we had bad tradeoff going with a minimum expected benefit of

withdrawing products and very evident harm from creating shortage situations, so the decision was changed.

So, it is not that we have reached a final conclusion that there is no risk, nobody has ever said that, it is just that the risk-benefit doesn't appear to be the same in the two settings.

Now, in terms of notification, it has always been our position that the benefits of recipient notification are unclear because there is no good way to counsel the recipient. You know, you may or may not have been exposed to an agent that may or may not have infected you, which, you know, may or may not result in a disease over the course of 40 years, and we can't diagnose it and we can't intervene. Not a very good counseling message.

So, we have always left that part of it voluntary and discretionary.

I hope that helps, Celso. I understand the subliminal message here, which is that this is an arduous burden with not a clear benefit, but we felt that we could also not ignore those individual exposures. We simply left it up to medical decisions what to do about it.

DR. HOLLINGER: Thank you.

Dr. Jacobs, just a question on this bovine-derived injectable products like insulin, and so on.

DR. JACOBS: Yes.

DR. HOLLINGER: Is that a real problem? Would that be primarily people who receive these products because they lived in England or the United Kingdom, they needed insulin, and so they bought it there? Is that what you are really talking about since these are non-licensed -- I presume they are not really sold here in the United States anyway -- is that going to be an issue?

I know Dr. Gilcher from Oklahoma. I think he said that they don't transfuse diabetics anyway, but is that a problem? I mean it seems to be a potential problem.

DR. JACOBS: Well, we found interesting that some blood establishments do accept as donors people who are on insulin, who are stable, and some don't. So, that addresses that part of the question.

This could refer to people who received this when they were in the U.K., but we have also become aware that there are people who prefer to take beef insulin and have continued to import it even though it is not licensed within the U.S., and that was the first focus of this question.

In response to the comments that we have gotten, we are going to be clarifying this because it was hard to understand the question and people want to know exactly to how many numbers of products it applies.

DR. STRONCEK: Concerning the same question on bovine-derived injectable products, we were quite surprised

that that question came up in your recommendations because apparently it hasn't been discussed as other things have been at these meetings.

Would it be possible to implement the rest of the recommendations and hold this one out for further discussion and we may implement it at a later date?

DR. EPSTEIN: Well, first of all, why it didn't have antecedent discussion, we were notified essentially two days before the publication date of the memo by the Center for Drugs that the Lilly Corporation, which was the sole U.S. manufacturer of bovine insulin in the United States, was discontinuing that product, and we were informed that the Center for Drugs was aware of personal use importation of bovine insulin from the U.K.

We also were aware that there were potentially many other bovine-derived injectable products that could have been sourced in BSE countries, products like thrombin, aprotinin, surfactant, and others, and so we felt that the better part of valor was to put it in the memo.

We tried to limit the impact in such a way that the question is designed only if the donor knowingly used such an identifiable product would the deferral kick in. We were trying to avoid placing the burden on the blood centers to try to elicit information that the donor might now know. In other words, negative responses are okay or responses "I

don't know" were okay. It was only if the information was spontaneously elicited.

But we have received letters from parts of industry saying that the question is nonetheless cumbersome, asking us to clarify which products are at risk, and indicating that it's just impractical to do.

Our current thinking is to clarify the question, such that if the donor is asked whether they have used insulin in the last four months, which is in most donor questionnaires, that it would be sufficient to further inquire whether the donor has received a bovine insulin made in an BSE endemic country.

The concept there is that most or the vast majority of insulin-dependent diabetics don't go off insulin, so that if they are a current user, that is a sufficient enough screen to capture the users who might have been injected dating back to 1980.

We are also thinking that we will restrict the exclusion based on the questioning to just insulin without raising the question of other products because the deferrals incident to use of other products are likely to be very rare, whereas, the insulin-dependent diabetic population is a much larger population.

So, I guess the answer is that we would encourage blood centers to go ahead and implement, but we will show

flexibility on exactly how it is implemented.

DR. HOLLINGER: Thank you. Dr. Buchholz. This will be the last question.

DR. BUCHHOLZ: Jay, I wonder if we could go back to Dr. Bianco's question with respect to the kind of difference in policy between derivatives and the blood-derived components.

Correct me if I am wrong here, but if I understood the gist of your message, it is that there is a lot of data that says blood products do not transmit CJD, and you then went on to say there is a lot of derivatives, but we really don't have any data.

DR. EPSTEIN: No, no.

DR. BUCHHOLZ: Therefore, we seem to have something, as least as I understood what you said, that seems to me to be just a little confusing in terms of the product group that we have the data on, we are holding to a higher standard in terms of notification than a product group that we don't have data on.

Perhaps I misunderstood what you said, but could you clarify the thinking about that for me?

DR. EPSTEIN: The derivatives have been in use starting with albumin back to the 1940s, and there are no cases attributable to derivatives either. The available data set for any blood product is no evidence of

transmission, however, there are differences in the data sets.

In the case of components, there are the animal studies which have indicated two things - first, attempts to infect mainly rodents, but also primates with blood and blood concentrates, such as buffy coats from humans with CJD, have sometimes been positive for evidence of infectivity in blood. There are five such reports in the literature. Each individual study can be questioned methodologically, but that is what is there.

Additionally, animal model studies in which animals are experimentally infected with a TSE agent, which is a model for the human agent, it is not the human agent, it's usually a rodent-adapted strain of either scrapie or CJD or GSS, have consistently shown the presence of low level infectivity in the blood.

Now, some of that infectivity does carry over into fractionation albeit at lower titers. The difference, however, is that when you infuse a component, there is no processing to remove infectivity. You get whatever is there.

So, if there are, say, 10 infectious per milliliter, which is consistent with the conservative picture in the animal data -- it runs 10 to 20 in different studies -- then, you get 250 ml of, say, plasma, you are

getting 2,500 units of infectivity.

So, we believe that there is a theoretical risk even though there is no epidemiologic evidence for transmission.

In the case of derivatives, once again, there is no epidemiological evidence for transmission, but we also know from various studies that have been done on partition of infectivity in the process of fractionation, that there is significant clearance of TSE infectivity in the fractionation process.

So, we have an added safeguard, as it were, above and beyond whatever benefit may obtain from dilution.

So, I think the situations are not identical with respect to the scientific data, but the point of difference is not knowledge of transmission for derivatives. The epidemiologic data are also negative for derivatives.

For example, something like 26 million children were exposed to measles, mumps, rubella vaccine, and have already lived 10 or more years. There are zero cases of CJD attributable to a vaccination based on the lack of cases in ages 5 to 19, and those vaccines contained albumin.

So, there are negative data also for derivatives.

DR. BUCHHOLZ: Thank you.

DR. HOLLINGER: Thanks, Jay.

I think we will move then to the next update topic

on the SENV Virus. I think Dr. Tabor is going to provide us what information is available.

Update on SENV Virus

Edward Tabor, M.D.

DR. TABOR: Good morning. In recent months, considerable publicity has been given to a newly discovered virus known as SENV. This virus has been suggested as a possible cause of those cases of post-transfusion hepatitis that are not due to the hepatitis B or C viruses or to any other known hepatitis virus. This is often referred to as non-A-to-E hepatitis.

To date, there have been no scientific publications with data about this virus, however, preliminary release of research findings has occurred at some public discussions, such as FDA's recent Donor Suitability Workshop dealing with the exclusion of donors with a history of hepatitis, as well as at press briefings by the company that discovered the virus.

I am going to summarize the publicly available information about SENV. All of this should be taken as preliminary. None of it has been subjected to side scrutiny in the scientific community. Nevertheless, it is a potentially exciting area of study, and we at FDA want the members of BPAC to be fully aware of it.

At present, about 10 to 20 percent of all cases of

post-transfusion hepatitis are due to agents presumably viruses that cannot be identified or isolated. Although these cases represent a very small number nationwide, they represent a challenge to those who are trying to achieve a risk-free blood supply.

Diasorin, a company in Italy with research facilities in the United States, which is a subsidiary of American Standard that is well known for its plumbing manufacturing, announced to the press in February and in July that one of their scientists, Dr. Primi, had found a unique DNA, presumably a virus, in the serum of an IV drug using AIDS patient.

The patient was studied as part of a strategy to find new bloodborne agents in individuals who had had presumed exposure to many viruses, in this case through IV drug use, and who were immunosuppressed.

The DNA that was found, which was designated SENV virus, soon was found to be present in the serum of Italian patients with non-A-to-E hepatitis. So far, the only way the virus can be detected is by nucleic acid amplification methods, such as PCR.

No serologic tests have been developed. The virus has not been cultured. It has not been visualized by electron microscopy. It has not been transmitted to chimpanzees, an animal that is susceptible to most other

human hepatitis viruses, and it has not been sought in paired sera from donors and infected recipients.

Furthermore, the DNA sequence of the virus has not been made available for other scientists to try to duplicate the findings or to study the virus further. A panel of coded sera were provided to the company by Dr. Harvey Alter of the National Institutes of Health.

SENV nucleic acid was detected in 10 of 12 or 83 percent of sera from patients with non-A-to-E hepatitis, but in only 4 of 50, or 8 percent, of transfused patients without hepatitis in 1 of 49, or 2 percent, of non-transfused patients, and in less than 1 percent of normal blood donors.

In another study by Diasorin, 13 or 19, or 68 percent, of patients with chronic hepatitis of unknown etiology had SENV detectable. These data show promise for the identification of a non-A-to-E hepatitis virus associated with post-transfusion hepatitis, however, although they are a promising beginning, they remain very preliminary. Their greatest shortcoming is the absence of any scientific publications by which they can be properly evaluated by the scientific community.

Many experiments are needed before a reliable scientific assessment can be made and before it can be determined whether screening of blood and plasma donors for

this virus will have utility.

Diasorin should be encouraged to present its data to the rest of the scientific community, so that progress in this area can be expedited. Failure to make the data and sequence available will prolong the interval until lives can be saved using this knowledge if the findings are confirmed.

We will continue to keep BPAC updated about this subject as developments occur.

Thank you.

DR. HOLLINGER: Thank you, Ed.

Unless somebody has any other questions, I don't think -- is that all you know, Ed?

[Laughter.]

DR. TABOR: That is all that has been publicly presented so far. There are obviously studies ongoing particularly at the National Institutes of Health, but also elsewhere, but that is a summary of all the publicly presented information.

DR. BIANCO: Dr. Hollinger, can we assume that because hepatitis has disappeared from the population of clotting factor recipients, that the current inactivation methods would inactivate SENV?

DR. HOLLINGER: I would think that is a reasonable assumption, but as I said, I think you will just have to look to see it later on, but I mean that is a reasonable

assumption.

Dr. Nelson.

DR. NELSON: There has been some focus on patients with fulminant hepatitis and fatal, who have non-A-to-E. Were any of the cases that they looked at and found SENV, were these fulminant cases?

DR. TABOR: I am not aware that the data that are resulting from ongoing studies of fulminant cases have been presented publicly, and some of the investigators that are involved in these studies have been very concerned about the preliminary release of information without the data being provided, so I am not at liberty to discuss any other data I may have heard about.

DR. HOLLINGER: Thank you, Ed.

Dr. Stroncek.

DR. STRONCEK: My understanding is that this information was available some by the company through the newspapers, and it is really disconcerting, it is troubling to me that companies will provide information in a limited fashion probably for their own benefit, yet, not provide full scientific information.

DR. HOLLINGER: Thank you.

Thanks very much, Dr. Tabor.

The next update is on the Status of Blood Regulations. Dr. Martin Ruta.

Status of Blood Regulations

Martin Ruta, J.D., Ph.D.

DR. RUTA: Good morning, everyone. Thank you, Dr. Hollinger.

For several years now the FDA has been working to update and revise blood regulations, and I wanted to draw everyone's attention to the fact that FDA has published two Proposed Rules, an Advanced Notice of Proposed Rulemaking, and a direct Final Rule in the August 19th Federal Register, and that comments can be provided to these rules in written form.

I also want to let you know that we are planning on having a public meeting on November 22nd at Mazur Auditorium to allow for oral comments, if people want to come in and tell us face to face what their thoughts are on the Proposed Rules or the Advanced Notice of Proposed Rulemaking, they may do so.

[Slide.]

The first Proposed Rule I want to bring your attention to is entitled, "Requirements for Testing Human Blood Donors for Evidence of Infection due to Communicable Disease Agents." This revises and extends requirements for testing to include not just HIV and hepatitis B, but also to include hepatitis C and HLV-1 and 2.

There is also a requirement that individuals who

test repeatedly reactive by these tests would then be deferred.

[Slide.]

There is a companion proposed rule entitled, "General Requirements for Blood Components and Blood Derivatives, Notification of Deferred Donors," and this ties into the testing rule in that individuals who are deferred under the testing reg would be notified that they were deferred and notified of the reason of the deferral including their test results.

[Slide.]

If you want to submit comments--and all this information is in the Federal Register--we are asking that you submit written comments to the Docket Management Branch at 5630 Fishers Lane, and in addition, OMB is asking for these two proposed rules if you have comments on the information collection provisions, to submit comments to them, and the information is contained in the Federal Register as to where to submit the comments to.

[Slide.]

Also, I want to draw your attention to the fact that in the same edition of the Federal Register, the FDA has published an Advanced Notice of Proposed Rulemaking. This is a mechanism that we use when we are not quite ready for the proposed rule, but want to solicit comments on what

we are thinking about putting into the proposed rule.

It is entitled, "Plasma Derivatives and other Blood-Derived Products, Requirements for Tracking and Notification." What we are thinking about including in the proposed rule, I think the committee heard about from Steve Falter last December, but we are thinking about proposing that there be requirements that for certain blood-derived products, such as Factor VIII, that there be tracking down to the end user and notification in the case of certain withdrawals and recalls.

[Slide.]

Finally, I want to draw your attention to the fact that we have also published a direct final rule. This is a mechanism that we use when we think that the changes we are suggesting are going to be noncontroversial, and so if there are no significant comments, this will go into effect at the end of the comment period, which I think is about the middle of November. If there are significant comments, in addition to the direct final rule, the companion proposed rule goes along with it, and we will take a look at the comments if there are any significant ones there.

[Slide.]

For the last two, for the Advanced Notice of Proposed Rulemaking and for the direct final rule, again, we are asking that you please send written comments to the

Docket Management Branch of the FDA at 5630 Fishers Lane. For any of these rules, if you have questions, you can contact Steve Falter, who is in charge of the reg writing at the Center for Biologics, and his phone number is also in the Federal Register, as well as his address.

So, I would just remind you that again the comment period for these rules is open. We would ask that you please provide comments in writing. We also want to remind you that we are intend to have a public meeting on November 22nd at Mazur Auditorium to allow anyone who wants to give verbal comments to come and do so, and we will extend the comment period for the two proposed rules and for the Advanced Notice of Proposed Rulemaking to allow for comments during that open comment period.

I am done.

DR. HOLLINGER: Any questions of Dr. Ruta?

Dr. Ruta, I didn't read through all of these comments that were here, but the question is sometimes it doesn't say about whether blood can be used. It says it often seems that it will restrict the use of blood for only certain things.

Will there be something there that will also say, though, that blood could be used for research purposes? Sometimes they forget that word, and although it is often used in those purposes, it sort of goes against the

regulations. I think that it should specifically state that somewhere, I think, if there is no problems with that.

DR. RUTA: There is exceptions in the current regulations, as well as in the proposed regulation, for a certain type of research. Of course, that depends on whether you are testing humans and if it is linked, et cetera, but for a general type of research, there are exceptions currently in the regs, as well as within the proposed regs.

DR. HOLLINGER: Thank you very much.

The next update is HVC Lookback. Dr. Paul Mied is going to tell us about that program.

HVC Lookback

Paul Mied, Ph.D.

DR. MIED: Thank you, Dr. Hollinger.

This morning I will provide the committee with an update on HCV lookback. Specifically, I will discuss the June 1999 FDA Draft Revised Guidance for Industry document focusing on how it differs from the guidance issued on September 23rd, 1998.

I will cover some of the comments we have received and some of the revisions to the guidance that we are considering, and I will provide a review of the recommended time frames for implementation of HCV lookback by the industry.

[Slide.]

Now, the current status of the implementation of HCV lookback may be summarized as follows. The blood organizations report that blood establishments have implemented HCV lookback programs prospectively or based on current donor testing and retrospectively or based on review of records of historical donations tested using EIA 2.0 or EIA 3.0.

They have established written SOPs for lookback based on current and historical donations. They have conducted record searches to identify prior collections from donors who were reactive on multi-antigen screening and supplemental tests, and have been performing additional tests on stored samples or in some cases on fresh donor samples.

Now, some blood establishments have already begun doing lookback based on EIA 1.0. The Chiron RIBA 3 supplemental test was licensed in February and it is useful for resolution of the donors' infectivity status to minimize false notifications of recipients.

Blood establishments have begun to notify consignees and the deadline for this consigning notification to begin was specified as March 23, 1999, in the FDA guidance document issued last September 23rd.

In coordination with the public education and

physician education efforts of the CDC, transfusion services have begun to notify recipients.

The Advisory Committee on Blood Safety and Availability met on January 28, 1999, to consider options for implementing the November 24, 1998 recommendation of the Advisory Committee to expand the targeted HCV lookback program to include recipients of blood from donors subsequently identified as repeatedly reactive by the single antigen or EIA 1.0 screening test that was licensed in 1990.

[Slide.]

The committee considered that in cases where no supplemental test result is available, it was reasonable to limit the lookback for EIA 1.0 based on the signal-to-cutoff ratio of the screening test, in other words, that it was optimal to perform lookback on a subset of the EIA 1.0 repeat reactives to capture the vast majority of the true positives and minimize the unnecessary false recipient notifications.

[Slide.]

At the committee meeting in January, Dr. Michael Busch estimated that if direct notification was to be based on an EIA 1.0 signal-to-cutoff ratio of 2.5 or above, about 100,000 notifications based on EIA 1.0 would be triggered, about 10,000 of these individuals would be alive and be traced by the notification effort, and about half of these,

or 5,000 individuals, would have been previously unaware of their potential HCV infection.

Dr. Busch estimated that using a signal-to-cutoff ratio of 2.5 as opposed to using simply a repeatedly reactive EIA 1.0 test to trigger direct notification would prevent about 452 false positive notifications for every true positive notification that would not occur.

[Slide.]

So, having considered a signal-to-cutoff value of 2.5 as being the optimal ratio for triggering lookback based on EIA 1.0, the Advisory Committee on Blood Safety and Availability unanimously recommended that targeted lookback should be initiated based on a repeatedly reactive EIA one test result on a repeat donor unless (a) a supplemental test result was performed and did not indicate significant risk of HCV infection; (b) no supplemental test result is available, but the signal-to-cutoff ration of the repeatedly reactive EIA 1.0 test was less than 2.5; or (c) followup testing on the same blood donor is negative, and that follow-up testing could include a negative EIA 2.0 or 3.0 or any supplemental test result not indicative of infection.

[Slide.]

In accordance with this recommendation, FDA issued a revised guidance of industry document that replaced the guidance issued on September 23rd, 1998. This draft revised

guidance was posted on the World Wide Web on June 17th, 1999, and the Notice of Availability was published in the Federal Register on June 22nd.

This draft guidance was distributed for comment only, however, FDA is aware that many blood establishments began to implement this recommendations immediately upon the issuance of the guidance.

The recommended period of 60 days for submission of comments ended on August 23rd, however, written comments and suggestions regarding this document may be submitted to FDA at any time.

[Slide.]

The revised guidance differs from the September 23rd, 1998 guidance in the following significant ways: Lookback has been expanded to include EIA 1.0. In addition to the previous sections on prospective lookback based on EIA 3.0, and retrospective lookback based on EIA 2.0 or 3.0, a new Section 3 in the guidance contains recommendations for dealing with lookback based on EIA 1.0 test results.

For an EIA 1.0 repeat reactive, if additional testing using EIA 2.0, EIA 3.0, RIBA 2.0 or RIBA 3.0 was or is performed on the original sample or on a later sample from the donor, the guidance addresses whether recipients should be notified and whether product should be destroyed or re-labeled or released depending on the outcome of that

additional testing.

If no additional testing was or is performed following the historical EIA 1.0 repeatedly reactive result, then in accordance with the recommendation of the Advisory Committee on Blood Safety and Availability in January 1999, the blood establishment should base it lookback actions on the signal-to-cutoff value for the original donor sample.

A signal-to-cutoff value of greater than or equal to 2.5 indicates that the transfusion recipient should be notified unless a RIBA 3.0 is done and is negative or indeterminate.

For EIA 1.0 lookback, it is recommended that the record search for prior collections extend back indefinitely, not just to January 1st, 1988, to the extent that electronic or other readily retrievable records exists.

The recommendation that the record search extend back indefinitely was made because a record search extending back to January 1st, 1988, based on EIA 1.0 screening that started in 1990, would only give you a little more than two years of retrospective record search and wouldn't be a meaningful lookback.

The only remedy for this was to call for an indefinite retrograde search provided that the records can be found.

In the September guidance, the record search for

prior collections from a donor with a current repeatedly reactive EIA 3.0 or a historical repeatedly reactive EIA 2.0 or 3.0 was to extend back 10 years or to January 1st, 1988, but this June version of the guidance extends that record search back in definitely also to the extent that electronic or other readily retrievable records exist.

This recommendation was made to be consistent with the record search for EIA 1.0 to avoid the situation of having the record search extend back different lengths of time depending upon the screening test that was used and to avoid the situation of neglecting to notify certain at-risk recipients simply on the basis of the screening test that was used for a later donation from that donor.

Now, several of the comments submitted to the docket have focused on the increased inefficiency of the lookback effort if the record search is extended back indefinitely, that is, prior to January 1st, 1988.

At a meeting of Advisory Committee on Blood Safety and Availability, on August 27th, 1999, the committee recommended that the lookback continue to be constructed in accordance with the prior recommendations of the committee, that is, that the record search extend back only to January 1st, 1988.

This recommendation of the Advisory Committee is being reviewed within the Department of Health and Human

Services. Extending the lookback period back indefinitely did have extensive prior discussion within the Department, and although it is now being rediscussed, we have no expectation of a change in the policy at this time.

For supplemental testing of EIA 1.0 repeatedly reactive samples, the guidance states, "If a RIBA 2 or a RIBA 3 was used previously under an IND exemption, or was provided as an in-house service by the test kit manufacturer, the results of such testing may be used to determine the need for further action."

So, here, FDA is saying that the result of any RIBA 2 or RIBA 3 is acceptable whenever it was performed whether or not the test was licensed at the time.

Some other changes include more detailed information regarding how the recommendations apply to lookback for repeatedly reactive plasma donations and specific recommendations on dealing with prior collections from a repeatedly reactive autologous donor.

Now, FDA has been reviewing the comments submitted to the docket and will be making revisions when the guidance is reissued for implementation. One of the clarifications FDA will be providing is to define "readily retrievable records," so that blood establishments will have clear recommendations to follow with regard to the scope and intensity of their record search.

In the guidance issued in June, FDA recommended that blood establishments maintain records in a manner which permits their rapid retrieval, for example, within five working days. Our current thinking is that readily retrievable records are those that are available within five working days by a routine procedure, however, we would welcome comment from the industry regarding how readily retrievable records should be defined.

[Slide.]

Now, in response to comments received, here are some of the changes that FDA is considering making when the guidance is reissued.

If the blood establishment has information to assure that there are no in date prior collections, there is no need to trace those products. We have a number of comments requesting that nucleic acid testing be permitted to serve as a supplemental test. We are considering the use of NAT prior to licensure to indicate appropriate actions to be taken in retrospective lookback subject to certain limitations. Use of NAT in lookback prospectively may depend upon the licensure of the NAT assay.

In the June guidance, it was recommended that blood establishments identify and quarantine prior collections and notify consignees to do the same within three calendar days of the date of identification of a

repeatedly reactive donation.

Requests have been received to extend this time period, however, our current thinking is to continue to recommend that these actions be taken within three calendar days because of the public health benefit that lies in quickly removing potentially contaminated products from the shelf.

For EIA 1.0 repeat reactives, when the signal-to-cutoff value is greater than or equal to 2.5, as an alternative to running a RIBA 3, we intend to recommend that an EIA 3.0 may be performed followed by a RIBA 3 if the EIA is repeatedly reactive and that lookback be waived if the EIA 3.0 is negative.

For notification of transfusion recipients, the hospital or transfusion service need only identify the patient's physician of record or the physician responsible for the patient's transfusion order, not both.

With respect to the last one, extending the time frames for implementation of the retrospective HCV lookback by industry, let's first look at what was recommended in the June 17th guidance.

[Slide.]

These dates are for notification of consignees in the June 17th guidance. For the record search extending back to January 1st, 1988 pertaining to EIA 2.0 and EIA 3.0

repeatedly reactive donations, as recommended in the September guidance and which the industry has been doing, blood establishments should complete notification of consignees by March 23rd, 2000, which is unchanged from the September guidance.

That still represents one year from the date March 23rd, 1999, by which blood establishments were to begin consigning notification for EIA 2.0 and 3.0, but now we have given blood establishments more time to extend the record search for EIA 2.0 and 3.0 back indefinitely, that is, prior to January 1st, 1988.

Blood establishments should begin notification of consignees as soon as feasible and should complete all consignee notifications based on EIA 2.0 and 3.0 by September 30th, 2000, which is six months later than the completion date for consignee notification for the record search going back to January 1st, 1988.

For implementation of retrospective HCV lookback pertaining to EIA 1.0, repeatedly reactive donations, FDA recommended that blood establishments begin notification of consignees by December 31st, 1999, and complete all consignee notifications for EIA 1.0 by September 30th, 2000.

Due to concerns raised by the blood organizations with respect to having adequate time to perform the record searches for EIA 1.0, and to lessen the impact on EIA 2.0

and 3.0 lookback efforts already underway, FDA is considering extending the date for beginning notification of consignees by six months to July 1, 2000 and for completing all notifications pertaining to EIA 1.0 by six months also to April 1st, 2001.

[Slide.]

FDA recommended that transfusion services begin notification of the recipient when notified by the blood establishment and complete all notifications of transfusion recipients identified in the retrospective record searches by September 30th, 2001, that is, within one year of the last of the notifications that they receive from blood establishments. However, if the dates for blood establishments to begin and complete consigned notification for EIA 1.0 lookback are each extended by six months, this date of September 30th, 2001, would also be extended by six months to April 1st, 2002.

Thank you.

DR. HOLLINGER: Any questions of Dr. Mied? Yes, Dr. Linden.

DR. LINDEN: If you are going to be recommending indefinite lookback, is there going to be at least an implicit recommendation for hospitals to keep records, disposition records indefinitely, then, to facilitate such an indefinite lookback?

DR. MIED: Yes. We say in the guidance that records should henceforth be kept for a minimum of 10 years, and that is the current recommendation. That will remain unchanged. So, the implication there is that records should continue to be held for as long as possible.

DR. HOLLINGER: Mr. Dubin.

MR. DUBIN: This one has raised a lot of questions for us. The first thing, we are very pleased to see the discussion and recommendation of extension back to the EIA 1.0, the 1988 period. We also think it is a very good idea that FDA define retrievable records and set some deadlines on (a) how long they have to be kept and reporting standards. We agree with all that and are very pleased to see that happen.

A couple of comments that need to be said from a consumer perspective on this issue in 1999. We have always felt that if it is dangerous enough to screen for, then, it is dangerous enough to look back. We are 10 years after the adoption of the EIA 1.0 test, 10 years after understanding that we had a dangerous pathogen on our hands.

Much of the reason we have heard why people chose not to look back was there is no treatment. I was reminded recently by a former blood banker from Dallas that--and I went back and checked it--alpha interferon was licensed as a treatment in the early 1990s, I believe February of 1992

that licensure occurred, and there was a treatment, but we don't even have to get to questions of treatment to get to questions of right to know and questions of a lifestyle-affected illness if someone is coming home and pouring back three martinis and they find out.

Our biggest concern on lookback is while we support the targeted lookback 100 percent, you are still talking about missing two-thirds of those identified by the Congressional Oversight Committee that may have been exposed in the 1980s, and we were very pleased to see the work done by Miriam Alter and Harold Margolis at CDC, the public media campaign developed. We thought it looked quite good.

We were very troubled to find that there was only money to fund the pilot part of that for D.C. and Chicago, and that HHS had neglected to ask Congress for the rest of the money - not that Congress neglected to give it, but that HHS didn't ask.

The other question I have is how many of the blood banks have a line item in their budget entitled Lookback, and I don't want to suggest for a minute that the blood banks should be dealing with this in a vacuum. This is a societal question. This one of the things we have been trying to say in terms of connecting these issues, but we remain--it's hard to find a word other than "appalled" that 10 years later we are still promulgating guidelines.

We are happy to see movement, but I think hepatitis C lookback represents a litmus test for what have we learned and how far have we come. I think over the last three months, we have learned that there is quite a bit more distance to go and want to see the equation move there, and want to see this addressed together because obviously, there are questions of expenditure for blood banking institutions and survivability, but those are also societal issues.

These things need to be taken in a larger context, so we can ensure that when a pathogen is discovered to be dangerous enough to screen for, that we look back.

Now, I think in part FDA is laying the groundwork for that with setting up record retrieval, defining that. I think that is very good, but I think we have to reflect very strongly that 10 years later we will haven't notified a lot of these people, and we don't seem to ever hear the question right to know in this debate, and from a consumer perspective, we think that has got to be part of the debate.

Since this is my last meeting, I just can't behave.

[Laughter.]

DR. HOLLINGER: Dr. Chamberland.

DR. CHAMBERLAND: Just a couple follow-up comments to Corey Dubin regarding the general effect that he referred to, I will just amplify a little bit on that.

He referred to a transit ad campaign that those of you that live in the D.C. area hopefully have seen evidence of. Thank you, and I will convey your comments back to Miriam and Hal Margolis.

Beginning September 1st, and for a period of two months ending October 31st, based on some focus group research, it was decided that an effective way to try and reach people via the general education campaign would be transit ads placed in bus stations and commuter trains, et cetera, and these have been launched in Washington, D.C. and the Chicago area for a two-month period of time.

It is a pilot and the expectation in talking with Hal Margolis is that we will see how it goes, kind of get the feedback in it and assess the results of that, and Hal tells me that we do have every hope and expectation to try and expand that two additional cities beyond these two after we have evaluated the pilot phase.

Importantly, in addition to these very visible ads in the two cities, there has been a lot of print and media PSAs both in English and Spanish advising persons who have received transfusions prior to July 1992 to go back to their doctor and discuss the need to be tested.

These have been distributed to media markets throughout the country. Obviously, though, we don't have a lot of control whether these markets, whether it be print or

radio stations, et cetera, will choose to run them.

We are pursuing approaches to funding the transit type ad in additional cities through a mechanism that CDC has with a foundation that allows us to work with partners, such as industry and the like, to try and get additional money to do things like this.

As far as the other thing I wanted to follow up on is your comments about funding in general. CDC has--meaning Hal Margolis and others from our Hepatitis Branch--have in recent weeks, months, been meeting with a number of congressional staffers from Appropriations Committee--Corey knows all this, but perhaps not all of you do--meeting with congressional staffers to try and really, at that request, which is my understanding how this has to work, but at their request, we have been meeting with them to discuss what we feel needs to be done vis-a-vis hepatitis C, education for both the public and providers.

My understanding is that, at least when I last checked on this, the President's budget did contain for the new fiscal year an appropriation for this, but my understanding--and perhaps can update me--is that that budget has not yet been finalized.

CDC has received monies through its emerging Infectious Disease Program that now a subset of those monies are going to be permanently redirected to fund hepatitis C

lookback-related activities, general education, et cetera. So, hopefully, that is a little bit more information to follow up on Corey's comment.

DR. HOLLINGER: Mary, how are they going to determine success of this ad campaign in Washington, D.C. and Chicago, what preceded it, and then how are they going to determine if it has been successful compared to none at all?

DR. CHAMBERLAND: It's a tough question to assess. One marker that we have is that tied in with this transit ad campaign is that there has always been, if you will, people can access information through CDC's general 1-800 number, et cetera, but we felt it was important with the transit ad campaign to have available live operators standing by, so that people can actually call in and speak to a person to answer questions, get referrals, get additional information, et cetera.

So, one of the rough gauges that I know they plan to use is assessing number of calls to the hot line, hits to the web site, et cetera, and that at least is going to be a beginning, a way to try and assess this.

Already the hepatitis web site is probably one of the most frequently hit web sites that we have, and there will be other mechanisms that they will be using to try and assess this.

DR. HOLLINGER: Corey.

MR. DUBIN: I want to again underline I think the Hepatitis Branch has taken a serious chomp on this and really tried to do a good job, and we see that. I think our concerns are above the branch, because once you develop the program, it is out of your hands.

I think outcome measurements are extremely important and I think we have got to look at that. We had proposed and continue to propose as an alternative a Dear Resident letter ala what C. Everett Koop did in the 1980s over HIV. I think that that could be an issue.

There is another issue that doesn't seem to get to the table, but what is interesting is we hear it in Congress all the time. In many offices in Congress, we are asked about hepatitis C culpability, the government, and do we have any idea when the massive lawsuits are going to come at the United States Government.

We don't put that out there because it is not something we are usually up there talking about, but invariably, we get asked. I think liability is an issue for everybody, and yet as part of this discussion, we don't really talk about it, it's a subplot, and I think rather than, you know, individual blood banks and their attorneys thinking, well, what is going to happen, again, this should be a big issue that we should talk about as a society.

Liability is a big driver in this issue, and we hear that in Congress all the time, and we know it.

But rather than kind of have it as a subplot, why don't we get it out in the open, have some honest working groups on it, and look at ways to address it, because it is clearly a subplot to this.

I still want to throw the Dear Resident letter on the table as an alternative even though we very much like the program from what we have seen, and I do think outcome measurements are critical. I think you are clearly thinking about that, and I think that is important.

Again, I think the Hepatitis Branch has done a great job. I think above that, we have some real concerns about what is happening.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: I would like to agree with what Corey said earlier and most specifically, that this information is absolutely critical to the affected patients, but I would like to take it a step further in terms of looking forward rather than looking back.

What we hear here and in other areas is something can't be done or something can't be done quickly because the information is not collected, maintained in such a fashion that it can be obtained readily, and so we can't do certain things.

So, one of the things that I am astonished by when I see the nonstandardization of questionnaires, the nonstandardization of the types of information that is viewed as critical, the fact that information that is required for ready review is not automated, so people can't get at it easily, is I would certainly like the FDA and the rest of us to think in terms of the standardization of the information being collected and the ways in which it is being collected and can be retrieved, so the types of issues we are talking about here and in the future can be resolved more readily.

DR. HOLLINGER: It is interesting, isn't it, that we are always sort of going backwards with these whole things. We are now starting to talk about things that perhaps ought to have been talked about 10 years ago and set up initially, and thought about, like retrievable records and everything like this.

Now we are talking about when perhaps the risks are much less, so you have a lot of regulation and perhaps much less of an issue at the present time.

Colonel Fitzpatrick.

DR. FITZPATRICK: I just wanted to follow up on Dr. Linden to clarify what I thought I heard Dr. Mied say. She asked if you were going to ask for indefinite record storage, and I heard you refer to a regulation that said you

are asking institutions to keep them for 10 years, so the follow up to that would be are you going to change that 10 years to indefinite.

DR. MIED: No, not in terms of a recommendation for now. The recommendation is to maintain records for 10 years.

DR. HOLLINGER: Dr. Epstein.

DR. EPSTEIN: We have in the proposed rules a proposed requirement for 10-year recordkeeping. There is a distinction in that we can't create records that don't already exist in terms of existing lookback.

So, the idea of the indefinite lookback is not to ignore records that do exist and may be retrievable, but prospectively, our concept is 10 years as a reasonable place to draw the line.

I just wanted to respond to some of the thoughts that Mr. Dubin expressed and to follow up on the notion of sort of the perils of looking back in order to look forward, and the main thing that I want to say is you have to be beware of a telescoping effect of history.

I think we all ought to recognize the debt that we, as a society, owe to the very positive contribution that has been made by consumer organizations of bringing a perspective to the table on how we should weigh the societal risks and benefits of lookback and many other issues, that

it has been very constructive having that voice heard more loudly on our committee, and I think it is important to acknowledge that.

Having said that, though, I think that it's a bit of a simplification to look at the 10-year debate over lookback and say that the answer was obvious on the face of it, because the problem is that our understandings of the issues evolved over the course of the 10 years as did the underlying science, and the issues, as you know, were debated in many fora, many advisory committees, that the spectrum of concerns was very, very broad including assessment of the potential public health benefits, as well as the risks and the costs.

There were many concerns including the issue of false notifications, the limitations to test accuracy, the availability of follow-up testing, the cost and mechanisms of funding of a lookback effort, debates over the relative benefit because of the limited effectiveness of the record search, the fact that transfusion recipients represented only 7 percent of those with the chronic infections, and then the whole issue of to what extent we knew that tracing would be beneficial, for example, the issue of lifestyle change and avoiding alcohol.

Well, you know, the data on the impact of alcohol consumption on the course of chronic hepatitis C are, in

fact, very recent data. Even just the data establishing to scientific consensus the life-long risk of chronic hepatitis C emerged much later than the lookback debate started.

So, I just think that whereas I concur with your underlying point, which is not to ignore safety risks and to be willing to look back, the problem that we face is that every particular condition has its framework both from public health and science, and the danger that we face looking forward is to have telescoped the debate and to assume that everything we know or knew in March 1998 was something we knew in October 1999, and unfortunately, it's not true.

MR. DUBIN: Jay, I have got to admit I am really going to miss these debates between us because they are really important. I don't want to oversimplify you or FDA, and I don't want to be oversimplified. That is not my point, to break it down to a basic, boiled-down simplification.

It is an evolutionary process, but we are late, way late on the evolutionary process, and certain pieces of data were later in coming. I don't disagree that the conclusions of alcohol and a direct relationship were not present in 1992 and 1993, that data was not there, but again, there was treatment on the table, and we have consistently heard that that was a major reason we heard

from the Stanford blood bank and others, and my point being I don't want to telescope it at all.

I have said that we are pleased to see FDA setting up recordkeeping because I think what FDA is doing is establishing the groundwork that this won't happen again, and we want to ensure that, because beyond all of this debate, we believe there is a right to know issue.

That has not been debated very well, and that right to know existed in 1988 or 1990 or 1995, and this is part of the debate that we don't believe as consumers does get to the table very often in these discussions.

When you are talking about a pathogen that has serious morbidity, potential mortality, chronicity, huge impact on one's life, human beings have a right to know, and we believe that stands above the rest of the debate.

That said, absolutely, it's an evolutionary process, but we are evolutionary about six years late in finally doing it. Now, that said, as I have said, we are pleased at certain parts of this, and there is effort, serious effort on the table, but let's make sure we get going and we notify, not only those in the targeted program, but let's make sure the money gets put on the table, the outcome results are done, and we ensure that the two-thirds of the puzzle that don't fit the targeted lookback do, in fact, get looked back.

But I am going to miss it, Jay.

DR. HOLLINGER: Go ahead, Dr. Nightingale.

DR. NIGHTINGALE: I want to, on behalf of Health and Human Service, make three brief comments in response to Mr. Dubin's comments.

As Corey knows, Larry Allen, a member of our Advisory Committee, asked Dr. Satcher these same questions in slightly different words, and Dr. Satcher's response at the Advisory Committee to the question about funding for the hepatitis C lookback was that funds were limited for all purposes, but the Department feels it will have the resources to carry out the programs it has proposed.

The second comment I would make is something that not only Corey, but I think that everyone in the room knows, that requests for special appropriations can be a two-edged sword in the midst of a budget negotiation process, and both Mr. Dubin and the Department have prior experience with that double-edged sword.

I would finish then by saying that the Department policy of record is the Secretary's letter to Dr. Kaplan of January 28th, 1998, that is available on the World Wide Web at our web site, and the policy, which I would summarize by the quote that I believe is verbatim, is that the intent of the Department is to reach as many people as possible. That policy stands.

DR. HOLLINGER: John, do you have a question?

DR. BOYLE: I would just like to echo the last line that Corey gave, and that is I want to make sure people do understand this, that there is a lot of medical ethical debate about whether or not you inform somebody with a fatal untreatable illness, and so on, but survey after survey after survey of the public and patients say that if I have a fatal, a serious, whatever illness, I want to be informed, and I want to be informed for two reasons.

One reason is that treatment may become available at some future time, and secondly, for lifestyle reasons in terms of planning, and so on.

So the only thing that I would say here--and I don't want to get into the past history--is that in terms of if we are going to measure viruses, if we are going to identify these things, the patients who are affected do want to be informed, and we should think through policies that would make that possible.

DR. HOLLINGER: Paul, I have just one question on something you presented, and I just want to clarify it.

You said that there is an option to run the 3.0 when the EIA 1.0 was over a certain level. You are talking about on a stored sample, not on a new sample, is that correct?

DR. MIED: Yes, that's correct. That would be

current testing of an EIA 1.0 repeatedly reactive where the signal-to-cutoff value is greater than or equal to 2.5. We said in the guidance run a RIBA 3. What we are saying now is that you have the option of running an EIA 3.0 or a RIBA 3.

If you run an EIA 3.0, and it's negative, then, lookback is waived. If it's repeatedly reactive, then, run your RIBA 3.

DR. HOLLINGER: I just want it clarified that they are not going to be called back in and then a test be done on the new blood.

DR. MIED: The follow-up testing of that sort, additional testing, could be done on an original donor sample where no additional testing was done originally or it could be done on a follow-up sample freshly obtained from the donor.

DR. HOLLINGER: But that's my point, I said, I mean because they may have been positive back then truly infected and negative now, and we know that. We have seen that in patients who have acquired hepatitis C and have been followed for a period of time. About 10 percent of them have actually no markers, and so I think it has to be done. If you are going to put that rule in there, it has to be done on the initial, original sample, not on any sample.

DR. MIED: We say in the guidance that if a frozen

sample from the original donation is available, test that. If it is not, then, try to obtain a fresh sample from the donor, but I understand what you are saying about the limitations of that.

DR. HOLLINGER: One more question and then we need to move on. Yes, Dr. Macik.

DR. MACIK: I just wanted to add a little bit to the education aspect of this. This came up before I was a member of BPAC and not very much informed about various things that were happening, where a patient calls in and says, "I heard that if you got a transfusion before 1992, you probably have hepatitis C and you have to get tested. My child was transfused and what do I do?"

I was like I really don't know what you are talking about. I think the education also, because the implied--and this comes up more than just hepatitis C--the implied implication, if you have a medical question, ask your doctor.

It is in all the advertisements for these new drugs that are allowed to come out, ask your doctor as if your doctor knows it. The problem is we have to make it equally, because there is two problems here. One, of course, you put the doctor in a bad spot, but you also limit the credibility of how serious this is. If a patient has their family doctor they have been going to for 20 years,

they hear this information, they call their family doctor, and family doctor acts like he doesn't know what is going on, then, how important could it be? That's just another big government thing going on, it must not be very important.

So, we really also need to make sure that physicians, whose patients already are being referred to go and ask, know what is going on, and that's outside of the blood bankers. We talk about general practitioners and the people who are going to get the first-round questions, and that is really missing big time.

By the same token, there is also a problem with--I think one of the big things to come out of the AIDS epidemic was the idea that there is informed consent and that it should be put forward that blood is a dangerous product, and every time we give blood, we are giving you something that may eventually be found to have something that will impact on your health.

We have tried to do that. By the same token, we find ourselves getting in the dilemma of someone refusing a product that will save their life now because we overemphasize how bad the product might be, and where do we put all of this information in?

The patient's right to know is there. They know for the last 10 years that blood is not safe. Now, we have

to go back and say, okay, we have now found that there is a virus that we could find, and now we are going to let you know you have that virus, and how far back do we need to go?

I am a little concerned with this indefinite lookback idea, how far can we go, what information do we have, what are patients--should we just say every patient who has ever had a transfusion, go and get a hepatitis C screen? That is another question that comes up.

DR. HOLLINGER: Thank you, Dr. Macik.

We are going to go ahead and move to the last topic for Committee Updates. This one probably has generated as much letters as I have seen for a while. I think most of the committee has gotten several, and I think they have been good letters, I think they have been important and brought up some issues that I think were not quite appreciated perhaps by the committee, and I think some of these perhaps need to be resolved.

This is on Post-Donation Information Affecting the Safety of Plasma Derivatives: Revised Algorithm. Dr. Tabor is going to talk about this.

Post-Donation Information Affecting the Safety of Plasma Derivatives: Revised Algorithm

Edward Tabor, M.D.

DR. TABOR: As you know, we have been discussing at BPAC since 1997, the topic of what we previously called

"Inadvertent Contamination," but is now called "Post-Donation Information," I might add after a very long search for a new and better name.

Let me remind you that so far, these discussions have involved only those viruses for which serologic tests exist and which can be inactivated or removed by procedures applied during the manufacturing process for plasma derivatives, namely, the hepatitis B virus, the hepatitis C virus, and human immunodeficiency virus.

In summary, BPAC voted in March 1999 in favor of what we refer to as the "Test Positive" algorithm; in May 1999, BPAC voted in favor of the "Risk Factor" algorithm, with the proviso that Footnote "i" be shortened. A copy of the "Risk Factor" algorithm has been given to you today for reference. It's Document A in your handout.

Shortening of Footnote "i" was requested by BPAC because the number of risk factors in Footnote "i" that could activate the algorithm was so large that post-donation information would affect every lot of every plasma derivative.

A major effort was made by FDA to shorten Footnote "i". Document B is a copy of the original Footnote "i," annotated with a list of the number of post-donation information reports for each risk factor received by FDA during FY 1998.

I will not take time now to go through this list with you, although you are welcome to ask questions at the conclusion of this update. The main purpose in showing this to you is to remind you of the extent of the problem of post-donation information.

We then tried to reduce the number of listed risk factors based on several approaches. Some of the risk factors were eliminated based on lack of evidence of a significant risk of transmitting hepatitis B, hepatitis C, or HIV.

Some were eliminated because they were "secondary risk factors," whose risk only reflected the risk associated with other high risk activities. In these cases, it seemed more reasonable to limit the algorithm to the "primary risk factor," since potential donors with the "primary risk factors" should include all donors with the "secondary risk factor" who were truly at risk.

Document C lists the risk factors that we removed from Footnote "i" and the reasons they were removed. I will now go through these with you briefly.

The risk from a needlestick or transfusion within 12 months were removed because we were aware that these rarely transmit HBV, HCV, or HIV.

Tattoos within 12 months were removed because we were informed by scientists at the CDC that there is really

no data to support transmission risk by tattoo except for one or two reports of hepatitis B transmission.

Body piercing was removed because we were informed by the CDC that there was no data to support transmission risk unless there was also drug use involved.

Sex with an intravenous drug user was removed as a secondary risk.

History of incarceration greater than 72 hours was removed because it is really just a surrogate for intravenous drug use or males having sex with males.

AIDS related signs and symptoms were removed because these are not markers of acute infection. There actually were very few reports during FY 1998, only 27 reports to FDA of AIDS related signs and symptoms as post-donation information, but what we are really trying to do with these risk factors is pick up window period cases, those individuals who are not yet detectable by the licensed tests.

A female who has had sex with a male who has had sex with a male was removed as a secondary risk.

Sexually transmitted diseases, other sexually transmitted diseases were removed because it is really just a surrogate marker.

Travel to or immigration from a Group O endemic area was removed because it's really a very remote risk for

the U.S. blood supply at present.

There remained thereafter four risk factors in Footnote "i," as shown in Document D. Although we do not yet know the precise number of reported events associated with the first two of the remaining four risk factors, because in our list on Footnote "i" we limited them to occurrences within 12 months, and our currently available data is for ever having had the risk factor specifically, we were listing needlestick or transfusion, for instance, if they had occurred within 12 months, and we have data only for someone who has ever had a transfusion or ever had a needlestick event.

Although we do not yet have the number of events for hepatitis B virus alone in the third remaining risk factor, these numbers are currently being obtained from the original reports and will be available at a later date.

Nevertheless, Document D clearly shows that even when Footnote "i" is reduced to these four risk factors, the number of events shown on the righthand column of Document D is almost certainly so large that nearly every lot of every product would have to be quarantined, and life-threatening shortages would occur.

It seems as if the algorithm just could not be made usable by reducing the number of risk factors that would activate it. We therefore decided to reconsider the

algorithm in view of this and in view of two other developments. Those two other developments were the following:

1. Nucleic acid amplification tests on minipools for detecting hepatitis C virus RNA have been applied under IND to almost all units of plasma collected in the United States since sometime in 1998, and NATs on minipools for HIV will be similarly applied to all units of plasma by the end of 1999.

The second development is that an industry association, the IPPIA, has developed a set of GMP enhancements that they say will do the GMP evaluation in the algorithm before the products are released. They will be presenting a summary of these enhancements in the open session today. It should be noted, however, that their plan has not yet been submitted to FDA, and it has not been, of course, reviewed by FDA.

Based on these considerations, FDA plans to modify this algorithm. This session today is an update session, and our intent in this presentation is to inform BPAC of what we are doing with an issue that has been actively discussed at numerous prior meetings.

We will bring a further revised algorithm to you for discussion and, most likely, for a vote, at a subsequent BPAC meeting. One concept under consideration would be to

make the following change in the algorithm:

All units entering plasma pools will have been found to be negative for hepatitis C virus and HIV in minipool testing using NAT prior to pooling. If post-donation information is received that a donor is in a listed risk group, we could suggest that the pool itself be tested as a precaution for HCV and HIV by NAT under an IND, and for HBV DNA by a NAT test that had been validated by the manufacturer under an IND.

If all of these tests are negative, and, of course, the testing done by NAT prior to pooling was negative, then, the pool or products would be releasable without the need for quarantine and without the need for further GMP review. A positive test would trigger quarantine and mostly like further GMP assessment, especially, I think, if the testing done prior to pooling were found to have been positive.

We welcome your comments now. However, I want to emphasize that a formal modification of the algorithm will be developed and brought to a future BPAC meeting.

Thank you.

DR. HOLLINGER: Thank you, Ed. I think what we will, right following after this is a couple of other issues and then we can bring it up for the committee to discuss.

Mr. Bablak, for the IPPIA, is going to present

some of their updates. After that, we will have one other speaker, and then we will open this up.

IPPIA Presentation

Jason Bablak

MR. BABLAK: I thank the committee chair and the committee for allowing us this time to address you on this important issue. Hopefully, you realize from the letters that we have sent and all the effort we put in, that the industry takes this very seriously.

[Slide.]

My name is Jason Bablak and I am with IPPIA. I want to briefly go over with you the alternative strategy that we have developed regarding post-donation information. Hopefully, you all received the letter we sent with our white paper addressing the subject, so I am just going to really briefly go through some of this, and at the end, if there are any questions, I would be happy to answer them.

[Slide.]

Basically, we have come up with an alternative strategy. I think we presented part of it at the last BPAC and we have added to it a little bit. Basically, we have a strategy to provide a prospective enhanced GMP review of the viral reduction procedures and records for all new production lots and a retrospective review for all released lots, and this is regardless of post-donation information.

The participating companies, it is our four members plus the American Red Cross and the ZLB, so we have Alpha Therapeutics, the American Red Cross, Baxter Hyland-Immuno, Bayer Corporation, Centeon, and ZLB.

[Slide.]

Briefly, just to put this all in perspective, I think there are some goals that the FDA had--and certainly this is our words, not the FDA words--but when we looked at what they are trying to do, this is what we thought, first, further increase the margin of safety in plasma derivatives. I think that is a laudable goal, and we all agree that that is something that should and could be done.

Secondly, specifically, address the potential safety issues associated with window period units.

The rationale for that, it makes some sense. Donors are deferred through questioning related to specific risk activity in order to reduce the risk of including newly acquired but undetectable infectious units, which we all know are called window period units.

If additional information regarding a donor becomes available after a donation, post-donation information, that would have excluded the donor, there is a theoretical risk that the donor is in the window period, and that donations from this donor may present a potential risk to the product.

[Slide.]

In response to that, the FDA developed some algorithms, and we have viewed these as potential draft guidances. They actually haven't been released under a formal process, but if they were to be released, we assume that they would be done through a guidance process, and that allows us some other procedures to address this issue, and that is the alternative procedure which basically, if the industry can up with an alternative procedure that meets the goals of the implementing regulations and laws, then, the FDA can accept that as an alternative procedure.

[Slide.]

There are some obstacles to implementation of the FDA algorithms. Hopefully, that has been pointed out in detail in other BPAC meetings and also in the paper that we put together, but basically, there were aspects of the NAT option that were not feasible, and I think Dr. Tabor recognized that, and they have changed their thinking on that.

With the GMP review, there were a couple of obstacles. One, numerous reviews are necessary, and I think it basically comes out that all product lots would eventually be required to be reviewed, and the 72-hour time frame was also a very difficult implementation timeline for that.

[Slide.]

This is just a slide to kind of put it all into perspective. It is one of the instances that we took out of the white paper that was passed out to everybody, but basically, there is one report of a PDIR.

There were seven units taken from that donor. Six of them were removed from inventory from the voluntary 60-day hold that the industry has on source plasma, so that leaves one unit that was actually pooled.

From that one unit, there were four, Factor VIII lots, one Factor IX, eight albumin lots, one IVIG lot, plus eight more intermediates that had not been further processed into final products. Under the current algorithm, basically, this would require reviews for all of these lots within 72 hours or else they would have to be put on quarantine.

What I want to stress here is this was only one unit that got through. There were many other examples that we provided that showed many more units getting through, which multiplies this number here that has to be done, and the problem you have here is this all has to be done within 72 hours of then put on quarantine. So, obviously, the creates some problems.

[Slide.]

I want to go over just very briefly some data that

was not included in the white paper that was presented to you. This is from the ZLB, and they were kind enough to present their information as an additional source of information.

I think this is important because, first of all, this is all plasma that is sourced from the U.S., fractionated by the Swiss Red Cross, and then sent back as final product to the U.S. So, this is not including everything that the Swiss Red Cross, just the material that comes back to the U.S.

Basically, the total number of PDIs that they had were 12,000 in 1998, and for the first half of 1999, a little over 5,000, and then if you had the original Footnote "i" that was presented in June, these are the numbers that went along with that, so significant numbers, but I think the next picture is more telling of what this would do for them.

[Slide.]

I will just let the numbers speak for themselves, but down at the very bottom, the average number of PDIRs, according to Footnote "i" per lot of IVIG that is manufactured by them is, in 1998, 7.7. So, not only do they have each lot is associated with a PDIR, but there are many per lot because of the way they bring their fractions together and they use recovered plasma, which has a smaller

volume, and therefore required more units. So, this is just some additional information to show you the difficulty of complying with that particular algorithm.

[Slide.]

So, basically, we developed an alternative procedure which we think will hopefully meet the requirements of what the FDA was trying to accomplish from the earlier slide, but do it in a way that we can continue to release products and make these available for patients to use.

First, we have an up-front "enhanced" GMP review of viral reduction records for new production. This is the really important part here. There will be an enhanced review, and that will be performed by staff who are specially trained, and I think what is really important in this is the training of the staff, there will be additional, and they will understand principles in virology, the product-specific processes for viral inactivation and reduction steps at that particular manufacturer, and then the critical operating parameters for each step.

So, this is additional information that these reviewers will be trained to, so that they have a better understanding when they are reviewing the release records for these products and understand what the importance of those numbers are.

This also will include new documentation which then will provide a certification of review, and in the package that we provided you, there was an example of one for an albumin, that there was some additional documentation that would be included with each product lot.

Then, obviously, implementation of NAT testing. We have talked about that many times, and that is an ongoing thing that the industry has committed to do.

[Slide.]

A new part that we didn't talk about at the last meeting was a retrospective review, similar to what we are doing for ongoing lots. We would take this up for lots that have already been released, and that was really to address what I think the committee and the committee and the FDA was concerned with, was the interim period, what do you do for the product that has already been released, that doesn't get this review going forward.

What we decided is we would review at least three months previous inventory, and this was basically decided upon because the inventory is not available in any quantities, and we thought a three-month time period would be a good indication of what was actually out in the field, so this would basically include all product that has not been used. So, therefore, everything that is out in the field would be receiving this new GMP review, as well as

ongoing review for all newly released product lots.

What we said we would do is we would do it in order based on any potential risk that would be associated with the products, and we would start this with the coagulation products and the go to the IVIG products, and then based on the safety history of albumin, we felt there was really no need to go and do a retrospective review, but going forward, all products including albumin would receive the enhanced GMP review.

[Slide.]

The implementation timeline that we have developed for the enhanced GMP review for new production, as of yesterday, we have prepared check-lists for these enhanced reviews, and these have been done for each product lot by each manufacturer.

Then, based on those, each company will develop SOPs for implementation of the enhanced GMP review including reference documents and the training materials that will be used, and they by December 15th, all the training to those SOPs will be completed and it will be implemented for all lots released after that date.

[Slide.]

Going to the retrospective review, beginning January 1st of 2000, we will go back for at least three months and do the review for products that have been

released, and that will hopefully take care of the interim period for all products that are available to be used that are on the market, and implementation of NAT testing by the end of 2000 for the three viruses listed.

[Slide.]

Path forward. Basically, we have the timeline. We are implementing this. We have had a meeting with the FDA to advise them on our plan, to get input and comments from them, and we are going forward with this.

We are today updating BPAC as we had promised we would in our letter, and we hope to receive FDA concurrence sometime in the near future that our alternative meets the intent of their algorithm.

Hopefully, that wasn't too fast for everybody, but I was only given about 10 minutes. I wanted to make sure I got it all in. I would be happy to answer any questions or go into further details if there are questions.

DR. HOLLINGER: Yes.

DR. BOYLE: Jason, let me compliment you on coming up with some improvements, but let me ask you two questions about the improvements.

One of the issues is in going forward, the type of documentation of the certification that you are talking about. Will this be done in some type of electronic format, so that the FDA could see, you know, check the thing within

24 hours rather than being told that it can't be done within 72 hours?

MR. BABLAK: All of these reviews will be done and accompany each product lot. Whether or not it will be done electronically will be left up to the manufacturer as they determine is the best way for them. But what is important is because the review has already been done, all the documentation is included with that particular batch record for that particular product, so documentation of the review is included with each product lot that has been released.

DR. BOYLE: Let me phrase it slightly differently. I have two reasons for talking about electronics other than it is a nice word. Number one is obviously information retrieval in a very quick fashion.

The second issue is that we have been told that a lot of the GMP failures have been as a result of lack of information, that critical information just simply isn't there, you don't know whether something is done or not.

When we used to do surveys on paper and pencil, if the interviewer failed to note something, the interviewer failed to note it, and you found out about it afterwards.

When you do it electronically, the program doesn't let you move forward if you don't enter the information, and that is one of the reasons why I am asking, when you are thinking through this process, to not only enhance GMPs, but

in cases where the GMPs need to be reviewed, that the information is there and accessible in a reasonable time frame. I would certainly urge you to think about it in that way.

MR. BABLAK: Okay. Certainly the companies will take that under consideration, and I can't speak--because each company is developing their own SOPs and their own programs, and they have their ways of operating--but I think that is a very relevant comment, so thank you.

DR. HOLLINGER: Dr. Stroncek.

DR. STRONCEK: On page 90 for handouts, you indicate that the NAT testing will be implemented for HIV, HCV, and HBV by the end of 2000. Will those be using licensed tests, because according to the way things operate, if a test is not licensed, it is not really proved, it has not been documented to prove it to be efficacious, so I really think you need to make sure these tests are licensed.

The second issue is on page 6. I understand that one plasma product can go into a number of different types of derivatives, for example, albumin and intravenous immunoglobulin, but why is one plasma product going into eight different lots of albumin? Aren't you trying to minimize the number of products that are in each lot?

MR. BABLAK: Let me respond to your first question. I think under the NAT testing, each company is

doing this through the IND process, so our commitment is to have basically developed an IND and submit it to the FDA by this date. The license will come after that.

DR. STRONCEK: I think that people in the industry have to push these manufacturers to license the tests. Licensure is the way this society documents efficacy, and if it is not licensed, it is not effective, and you need to get with the program.

MR. BABLAK: I understand there is a process to license that, and the IND is the process is to get the license. It takes time in order to prove that, so I guess what I am saying is our intention is to get licenses. You just have to do it through the process that the FDA has outlined.

DR. STRONCEK: Centeon has an overhead later on that 3.6 million donations have been screened by PCR. How many donations do you need to get licensed? Isn't that enough?

DR. HOLLINGER: Just going back to what Dr. Boyle has said, you presented something from the IPPIA, but then you come back and say now the companies are going to be able to make their own SOPs and so on. There seems to be some difficulties here, at least for me.

In the first place, you are saying here is an alternative strategy and this is what we are going to do

industrywide or through the plasma fractionation industry, and so on, and the second time you are saying that the companies are going to be able to do sort of what they want to do.

MR. BABLAK: No. Let me rephrase that. This is the general strategy that all the companies have agreed to comply with. Each company has to develop their own particular SOPs and their own particular check sheets because each process that is run for each product is different, and so the companies have to develop those based on their own processes, their own parameters, their own licensing, and their own validation material that they have.

So, what will be specific to the companies is the specific check sheets, the specific SOPs, and obviously, the FDA will be able to inspect those and look at them when they come in for inspections to make sure that that has happened.

DR. HOLLINGER: Thank you.

DR. BOYLE: I think we all understand that the manufacturing processes vary by line and vary by company, but we thought what you were proposing was that the industrywide group was going to set minimum standards within which the individual companies could customize those depending upon their own manufacturing processes, but that minimum standards or what is being done, what is being documented, you know, rates of retrieval, et cetera, is