TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

OPEN

BLOOD PRODUCTS ADVISORY COMMITTEE

SIXTY-FIFTH MEETING

OPEN SESSION

VOLUME II

Pages 1 thru 212

Silver Spring, Maryland
March 17, 2000

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

SIXTY-FIFTH MEETING

OPEN SESSION - VOLUME II

Friday, March 17, 2000

8:00 a.m.

Kennedy Ballroom
Holiday Inn Silver Spring
8777 Georgia Avenue
Silver Spring, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

Voting Members

F. Blaine Hollinger, M.D., Chairman

Mary E. Chamberland, M.D.

G. Michael Fitzpatrick, Ph.D.

Marion A. Koerper, M.D.

Jeanne V. Linden, M.D.

B. Gail Macik, M.D.

Mark A. Mitchell, M.D.

Terry V. Rice

Paul J. Schmidt, M.D.

David F. Stroncek, M.D.

Temporary Voting Members

Paul R. McCurdy, M.D.

Carmelita U. Tuazon, M.D.

Jonathan S. Allan, D.V.M.

Non-Voting Consumer Representative

Katherine E. Knowles

Non-Voting Industry Representative

Toby L. Simon, M.D.

Guest of the Committee

Louisa E. Chapman, M.D.

Executive Secretary

Linda A. Smallwood, Ph.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

DR. SMALLWOOD: Good morning, and welcome to the second day's deliberations of the 65th Meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary.

On yesterday I read the meeting statement that pertains to both days' deliberations. If there is anyone that needs to make any declarations regarding any discussion of the topics for today, please do so at this time. This would also include any of the committee members. We would ask that anyone speaking before the committee, if they would please identify themselves by giving their name and their affiliation, and please speak into the mike.

If there are no declarations at this time, then I will turn over the meeting proceedings to the chairperson, Dr. Blaine Hollinger. Dr. Hollinger?

DR. HOLLINGER: Yes, thank you, Dr. Smallwood.

We are going to start the session this morning on the committee updates, and the first one will be given by Dr. Stephen Nightingale on the summary of the January 2000 PHS Advisory Committee Meeting on Blood Safety and Availability.

DR. NIGHTINGALE: Good morning. I am Steve Nightingale, and the meeting that I wish to review was held on January 26th and 27th, and the subject of that meeting

was Errors and Accidents in Blood Administration: What Can Be Done to Reduce Their Occurrence? The meeting was scheduled to begin at 8:00 o'clock on January 26th, but unfortunately there was a snowstorm. This is Connecticut Avenue, looking south, about 10:00 a.m.

And we were faced with actually something that I think was of relevance to the committee, which is, what do you do if you are the executive secretary of a committee and the government is closed officially? This is not in fact a trivial question. There was a meeting of the Committee on Alternative Medicine at NIH that was actually held a couple of hours earlier, and there were congressional inquiries that resulted from the decision to continue to have the meeting.

We did persevere. When we sought advice of counsel, this was all that we found, was "Each advisory committee meeting is to be held at a reasonable time and in a place reasonably accessible to the public." Federal law is actually very explicit about when a meeting can be closed, but it is silent on when a meeting should be open.

So we made the decision to open, and I'm pleased to say that this was the attendance score: 17 out of 18 public members, whereas 4 out of 6 ex-officio members. By Fisher's exact test the P is .14, which is not significant. However, if only one of the members had not been there and

it had been three and three, the P would have been .03 and highly significant. So I thank my ex-officio members.

The quote of the day was by the Surgeon General, who said "It's amazing how much is getting done while the government is officially closed." This was one of the things.

There is actually a substantive point, believe it or not, that I'm going to be making about these slides in a minute, but at the moment let me get to the meat of the meeting, to bring up what we did.

The first speaker was Dr. Kevin Shine, the president of the Institute of Medicine, who presented their report on errors and accidents in medicine. It is in fact not the only initiative. Ours and several others were developed in parallel, but his is certainly the one that has gotten the greatest amount of ink, and I guess electrons as well.

We did have a presentation by Bob Francis, who is the immediate past Vice Chairman of the National Transportation Safety Board. We opened our discussion of the issue with Mr. Francis because there have been substantial advances in aviation safety in the last decade. He provided a perspective on it.

Dr. Bosk, who has written the classic text called "Forgive and Remember: Managing Medical Failure" gave a

historical perspective on this. And I am reviewing these quickly because the interested parties can find them at our web site, which is www.dhhs.gov\partner\bloodsafety. I am hopeful that by close of business today our web site will have been substantially upgraded, and if it is not, I apologize for the delay.

Dr. Westrum provided a sociologic perspective, and Dr. Linden of the Blood Products Advisory Committee to my right here, very generously agreed to come and describe the experience of New York State's medical error reporting system.

We had the perspective of a clinic manager, of a transfusion service manager, Ms. Reardon, who is the director of the Carle Clinic in Urbana. Sharon, Ms. O'Callaghan, of Food and Drug, who is also in the room here, described FDA's current procedures and the regulations on which they are based.

And we concluded with a discussion by Dr. Battles and Dr. Kaplan of the Medical Event Reporting System for Transfusion Medicine that they have developed with the support of the National Heart, Lung and Blood Institute. We also did just very briefly have presentations on the hep C update from Dr. Alter and the Blood Action Plan from Captain Gustafson, who will be presenting I believe shortly after I am. And we had representatives of Hema-Quebec, Canadian

Blood Services, and Dr. Gerry Sandler at Georgetown spoke about patient identification services.

So I think the focus of what I wanted to present to you in the 15 minutes that I have was on where we are as an advisory committee with the issues of errors in management, and this is simply to note that we had relatively broad and generally, I think overall highly supportive comment from the public interest groups and from individuals of the public. What I wanted to get to, then, was this, in this context.

I have summarized the recommendations. They are, again, posted on the web. In a nutshell, what we said, first of all, was "all"--and the italics were the key words--"all" blood establishments should have a quality assurance program that includes an effective, confidential, non-punitive system for the management of errors and accidents not subject to regulatory review.

The substantive issues were, first, I have italicized "all" because, as you know, the Food and Drug Administration plans to issue a final rule that would require this. The question was raised at the meeting, since it has been announced that this is coming, was this superfluous. And the answer was, well, it probably was, but given the delays that can happen to a final rule on its final passage to the Federal Register, the committee

supported the FDA in this.

Probably the most difficult word for the committee to come up with was "effective." "Effective" was perhaps not a compromise, but the word that was chosen in lieu of "mandatory," and I have italicized it here because the committee really did not achieve final consensus on what should be mandatory.

Although "confidential" was not something that we spent a lot of time debating in the system, there were definitely concerns raised within the committee, particularly by the patients, those who have ties to the patient community, about protection of potentially discoverable facts. And that is an unresolved issue, at least at the committee level, and I think well beyond the level of our committee.

And, finally, the language "not subject to regulatory review" was the language that was chosen after substantial discussion. I think the issue here is, for those of us who are in the blood business, in the case of blood those actions that are not subject to regulatory review are, I don't want to say few and far between, but blood is I think a bellwether for some parts of the industry because the regulatory review is--perhaps because of the subject and its history--is quite broad.

These, then, are the issues that remained at the

conclusion of the meeting, and that is--I have rephrased them. In the document that is being prepared for the Secretary's signature, the language will look something like this. We have, I think, three very legitimate interests here, which is the right to be informed, and I have put the duty to inform.

I think both this committee and our own have heard from our British colleagues about the duty to inform in the British common law and jurisprudence. The status of that duty to inform is less clear in American jurisprudence, and I hope to have some discussion of that at our next meeting.

Very clearly, the middle is the baseline, which is the need of the regulator for information necessary to perform its statutory responsibilities. This is something that will not go away. What we are hoping is that the aviation industry, where the FAA has a similar need for information, will be perhaps able to, if not give us guidance, give us a historical perspective. And that is going to happen in the next meeting.

And, finally, the issue which I think is not quite yet well developed in the public mind outside of the aviation community is just exactly what are the benefits to society of protecting information so that it can be analyzed and the conclusions of that analysis acted on. These are the three things that I think need further work.

One possible direction of the advisory committee's deliberation might take this particular form, although this is by no means settled. I am not a lawyer but have been talking to them recently, which is where I picked up the word "hypotheticalS". And things to consider:

An A positive patient receives an O positive unit of blood and nothing else happens. Is this reportable? Many people would say yes. Many people would say it should be. There are two sides to this question, and I hope the advisory committee will explore this.

The other, the contrary hypothetical, an A positive patient almost receives a unit of O positive blood. Again, I think you can look at this from the perspective of the patient, you can look at from the perspective of the regulator, and you need to look at it from the perspective of society, and in fact one also needs to look at from the perspective of the provider because they are also stakeholders.

So the folks that we have lined up for the meeting on the 25th, Dr. Westrum, who spoke at the last meeting on his own research, will discuss in a little bit more detail the scientific basis of current error management strategies. He will talk about the work of Dr. James Reason, "Managing Errors of Organizations," a 1997 book. He will also give his own spin on it.

I am delighted that Ms. Linda Connell, who is the Executive Director of the NASA/Ames, the Aviation Safety Reporting System, and Captain Scott Griffith, who is the chief pilot of American Airlines, have agreed to be present at the meeting. I have asked both of them to discuss, to answer the following questions: Could you describe the development of your system? Could you describe its accomplishments to date? Could you describe the problems that still remain to be overcome? And, finally, what advice would you give us, based on your experience. And this would be the perspective, first of the regulator, which would be Ms. Connell, and the regulated, which would be Captain Griffith.

After the 10 o'clock break that all committees have, Dr. Helmreich, who really was the pioneer of adapting the ideas of aviation safety--not only the psychology to aviation safety, but adapting them to the operating room. Dr. Helmreich was on the far end of the mountain that I showed earlier and did not make it to the previous meeting.

Dr. Small is a mid-career investigator at Harvard University, is moving to the University of Chicago, and I used "mid-career" because he I hope will represent the second generation of error management investigators in clinical medicine. And what I am hoping from him is to get his perspective on what do you do after the pioneers have

hung up their parachute, I guess.

I do have a legal scholar in mind. I do not have the commitment from that scholar at this point in time. I have asked Dr. Linden and Dr. Kaplan to conclude the morning and lead the afternoon discussion by summarizing their views on where they feel the committee's guidance has come and where they feel the committee could provide further guidance. One of those areas where I am sure there will be further guidance is in the source of the funding that will be necessary to implement any effective error management system.

And in the afternoon--I'm sorry--on the following day, the 26th, we will discuss the issue of how advances in blood safety should be reimbursed. This will be a follow-up of our August 26th and 27th advisory committee meeting, mating numbers, suggestions. There was a letter from the President on October 19th, I believe, to Senator Roth, that discussed some changes that the Health Care Financing Administration would be making in the outpatient prospective payment system.

This slide is a little thin here, obviously, because the Health Care Financing Administration's final rule has not yet been published. The deadline that I believe will obtain is April the 10th. There is a legal issue with which I am not familiar, but again, as I said, I

have been talking to lawyers a lot recently, and I have reason to believe that the final rule will be published in the Federal Register on or before April 9th. It is in the final stages of clearance right now.

And I believe that that final rule will quite certainly not be the last word on this issue which has come before your committee, of course, yesterday and before. I do believe, however, that it will provide a constructive foundation for future discussion of this issue.

And with that, again, obviously this will be a short time line for people, and I have taken the last of my 15 minutes here to try and explain why it will be a short time line. I really don't think that discussion would be really productive until the HCFA final rule is out, and from the 10th to the 26th is enough time for those who have had it.

This, finally--I'm sorry, I got my son to scan this in for me--but if you didn't see last week's New Yorker, there is a doctor there and he is saying--I will use my pointer here--on my way out the door, here, medical school equivalency diploma, "To err is human. That's why they put erasers on pencils. Mistakes happen." And the nurse is saying to the doctor, "Some guys from the State Board of Medicine are here to see you."

And that's the context in which we are operating

today. Thank you.

DR. HOLLINGER: Thank you, Steve.

Any questions of Dr. Nightingale?

[No response.]

DR. HOLLINGER: Okay. Thanks, Steve.

The second presenter today is Dorothy Scott, and she will talk to us about the CJD policy.

DR. SCOTT: Good morning. I'm just going to summarize for you what's new in CJD since this committee last met, but I'm going to start off with what's now old.

As you recall, FDA published a revised guidance on November 23, 1999, entitled "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of CJD and New Variant CJD by Blood and Blood Products." Implementation was recommended by April 17, 2000, if not before. And just to remind you, this guidance formalized the recommendation that plasma derivative containing material from donors with CJD or CJD risk not be withdrawn, and it summarizes the scientific rationale supporting this decision.

Linked to this was a recommendation that all blood products have labeling which mentions the theoretical risk of CJD transmission. So we are in the process of receiving those labeling supplements for plasma derivatives.

In addition, this guidance contained a new donor deferral for people who have traveled to the United Kingdom

or resided there for six months or more between 1980 and 1996, which were the peak years of the BSE epidemic.

Since release of this guidance, we have had a lot of questions about implementation. In fact, they are coming faster now as April 17th arrives, and we have done our best to provide clarifications.

Other events in CJD: We have formed a PHS interagency ad hoc working group on new variant CJD in blood. This is in response to requests by the Surgeon General, David Satcher, that we set up a mechanism to regularly review the scientific basis of the United Kingdom donor deferral.

And the first meeting of this committee was on November 17, 1999. It reviewed the current new variant CJD epidemiology, and it was also apprised of current lab experiments going on in new variant CJD which are concerned with the possibility of transmission by blood or blood products. And the next meeting is scheduled for May of 2000.

Other current concerns that the FDA has are the cases of new variant CJD which have occurred in France--there are now three such cases--and also the extent of European surveillance for bovine spongiform encephalopathy. And we expect that some of these issues are likely to be addressed at the next meeting of the TSE Advisory Committee,

but the agenda is only tentatively planned at this point. There should be a Federal Register notice coming out soon.

So that's all I have to say about CJD issues for now. I will take any questions about the guidance or other events.

DR. HOLLINGER: Any questions from the committee about CJD, nvCJD or otherwise? Yes, Dr. Stroncek?

DR. STRONCEK: Has anyone implemented this, and have they given us any information on how much, how many donors they have had to turn away or lost?

DR. SCOTT: To my knowledge, this has not been implemented, but we have received a lot of questions in the past month about donors. For example, there is one fairly large blood bank which has 300 donors that they are turning away, and they are concerned about this issue very much.

And we have been told, when this guidance came out and when the earlier guidance came out in August, that this could be a big problem. But I think that it really hasn't generally been implemented yet, because of the questions we are receiving now about donor deferral.

DR. HOLLINGER: Marion? Dr. Koerper?

DR. KOERPER: Could you elaborate a little bit about the three cases of new variant in France?

DR. SCOTT: These are three cases that have been documented by brain biopsy or autopsy, and in terms of the

amount of time that they resided in the United Kingdom, I don't have all of that information, but it's my understanding that there's also a French BSE problem and that France has received a lot of beef from the United Kingdom in the past, during their BSE epidemic. We don't have the exact numbers on the time, if any, that they spent in the United Kingdom. Jay might have some

DR. EPSTEIN: What's important about the cases is that the individuals had not been to the United Kingdom, so that they were indigenous to France, suggesting that it was either due to imported beef from the U.K. or due to the BSE epidemic in France, and that's why there is additional concern.

DR. HOLLINGER: Any cases of transfusion-associated in the CJD?

DR. SCOTT: No, none known.

DR. HOLLINGER: Dr. Simon?

DR. SIMON: One answer to Dr. Stroncek's question. We implemented the first of the year and have been a little bit surprised by the numbers. And it's larger than we anticipated and, as you might expect, particularly in centers located near Air Force bases. So the warnings from our Air Force friends were appropriate. They have a lot of people that have been there, to the U.K.

The other thing, for those who have not

implemented it, as often occurs, the law of unintended consequences, besides the donor losses, the lookbacks have been a pretty significant issue and problem, and I think people who are yet to implement will be unpleasantly surprised by some of the situations with the lookbacks and how extensive they are, and the issues and questions of how far back you need to go with particular plasma products, and the variance among the manufacturers in terms of the amount of unpooled material they had.

The one question I was going to ask is, can you give us an update on the number of cases of new variant? Is this beginning to show epidemic type proportions, or is it still running at a low level?

DR. SCOTT: It's still running at a low level but, as you probably know, it's estimated that we won't have a good idea of whether this is going to rise for another three to five years. But there is no startling increase in cases, number of cases, as of this point.

DR. HOLLINGER: Thank you very much.

The next topic is on HCV lookback guidance, and Dr. Paul Mied will present this information.

DR. MIED: Thank you, Dr. Hollinger.

Before I discuss the revised FDA guidance on HCV lookback, I have been asked to review for the committee exactly what is meant by HCV lookback and what FDA guidance

on lookback is meant to accomplish.

Multiple layers of safety, as you know, including donor screening and testing, are used to reduce the risk of transmitting infection through blood transfusion. However, a person may donate blood early in infection, during the period when a testable marker is not detectable by a screening test but the infectious agent is present in the donor's blood. And that's what we have been referring to as the infectious window period.

Now, if a donor donates blood on a number of occasions and each donation tests negative for antibody to HCV, but the donor subsequently returns and tests repeatedly reactive for antibody to HCV at a later date, prior collections from such a donor would be at increased risk for transmitting HCV. In addition, a recipient of a transfusion of blood or blood components collected from such a donor during the window period would not know that he or she may have become infected with HCV through the transfusion unless they were notified. Furthermore, prior unscreened collections from donors who later were found to be repeatedly reactive when screened for antibodies to HCV since 1990, when screening began, may have been at increased risk for transmitting HCV due to a prevalent chronic infection in the donor.

Chronic hepatitis due to HCV is a major health

problem in the U.S. The infection is usually clinically silent until serious damage has been caused to the liver, and as a result, infected people are unaware of their disease until such damage has already occurred. Advances in medical diagnosis and therapy have created opportunities for disease prevention or treatment many years after recipient exposure to a donor later determined to be at increased risk of HCV infection.

Now, although transfusion transmitted infections account for only a very small proportion of HCV infections, it is possible to identify and look back at prior donations that might have been collected during the window period. FDA is recommending that blood establishments perform such lookback activity, and that this activity include, first of all, quarantine of any affected prior collections that remain in inventory; further testing of the repeatedly reactive donor; thirdly, notification of consignees that have received shipments of such blood or blood components; and notification of transfusion recipients who have received blood from a donor later determined to be infected with HCV.

FDA is recommending that blood establishments perform a retrospective review of testing records when a current donor tests repeatedly reactive for HCV. Now, this records search is intended to identify prior to collections dating back to January 1, 1988, or back indefinitely for

computerized electronic records. In addition, FDA is recommending a historical record search to identify prior collections from donors who had tested repeatedly reactive for HCV in the past and were deferred from further donation, and the retrospective records search in this case should be of historical records, historical testing records extending back to January 1, 1988, or back indefinitely for computerized electronic records.

Now, FDA published this most recent guidance on HCV lookback, and the title of it is here, as a draft document for comment only on June 17, 1999. This document contained proposed recommendations for extension of HCV lookback to address donor testing back to May 1990, using EIA 1.0, as recommended by the PHS Advisory Committee on Blood Safety and Availability at its January 1999 meeting.

The comment period for this guidance closed on August 23, 1999, although we are still receiving comments and are discussing them, considering them and incorporating them. And these comments have been summarized and discussed in several public meetings: First of all, the August 1999 meeting of the PHS Advisory Committee; the September 1999 meeting of the Blood Products Advisory Committee; and the November 1999 Annual Meeting of the American Association of Blood Banks.

This morning what I am going to do is provide a

summary of the status of industry implementation of HCV lookback, including voluntary compliance with the June 1999 FDA guidance, and I'll also summarize the agency's current thinking regarding revisions to the June 1999 guidance that may be made when that revised guidance is issued in the near future for implementation.

The next couple of slides I will be showing you were prepared by Miriam Alter at CDC. According to CDC's nationwide evaluation of the effectiveness of targeted notification for HCV infection, as of December 1999 nearly 80 percent, 59 plus 18, nearly 80 percent of blood collection establishments have completed at least 90 percent of their consignee notifications based on EIA 2.0 and EIA 3.0 multi-antigen testing. And American's Blood Centers or ABC has reported this week that all of their member blood centers who responded to their recent survey indicated that they had completed 100 percent of their consignee notifications for prior collections dating back to January 1, 1988.

Now, as stated in the June 1999 FDA guidance document, the deadline for completion of this notification of consignees for prior collections dating back to January 1, 1988 is March 23, 2000, so they are well on their way. Approximately 20 percent of blood establishments, most of the smaller ones, have begun, 80 percent have not begun, and

15 percent have completed notification of consignees based on EIA 1.0 single antigen screening.

In addition, transfusion services have completed the notification process for 80 percent of recipients of components from EIA 2.0 and EIA 3.0 multi-antigen tested donors. According to the CDC survey respondents, the recipient notification process had been completed for 33,098 recipients, of whom 70 percent are deceased, 23 percent were actually notified, 12 percent were tested for HCV antibody, 2 percent were positive, and half of those recipients learned for the first time that they were positive. Thus, the effectiveness of the targeted lookback for identifying HCV positive recipients is approximately 1 percent.

But what is the bottom line of this massive lookback effort? If we were to project this yield from the respondents of this CDC survey to a nationwide level, it is estimated that as of December 1999, approximately 900 recipients have learned for the first time that they are HCV positive, as a result of the targeted HCV lookback effort.

Now, FDA's current thinking regarding revisions to the June 1999 guidance is that, first, the scope of the indefinite search of records prior to January 1, 1988, should be limited to computerized electronic records. This would make the pre-1900 lookback based on readily retrievable records, as FDA stated in the June 1999

guidance, meaningful, but it would limit it in a practical way. All other records searches, such as microfiche and paper records, would extend back to January 1, 1988 for a current repeatedly reactive donation or for a repeatedly reactive donation found in the retrospective review of records.

Secondly, Nucleic Acid Testing or NAT as a trigger for lookback, both prospectively and retrospectively, should be included. Use of NAT as an additional test to clarify other screening test results would be permitted, subject to certain limitations. For example, a positive NAT can confirm a repeatedly reactive result and trigger lookback. But considering that in many cases HCV viremia is intermittent or is resolved, a negative NAT cannot obviate lookback for a repeatedly reactive donation, and a supplemental test for antibody would still need to be performed as a basis for determining the actions to be taken with regard to lookback.

Also, as part of lookback based on EIA 1.0, consideration of supplemental test results of record for the RIBA 1.0 performed under IND or as an in-house testing service by Chiron, and the Abbott neutralization peptide assay performed in-house by Abbott, as possible indicators for recipient notification, should be added.

As I said, FDA plans to issue a draft revised

guidance for industry on HCV lookback for implementation in the near future.

This table summarizes the time frames for beginning and completing consignee notification that would be included in the revised FDA guidance for industry document. These dates are for notification of consignees by blood establishments.

In the June guidance it was recommended that for the records search extending back to January 1, 1988, pertaining to EIA 2.0 and EIA 3.0 repeatedly reactive donations, blood establishments should complete notification of consignees by March 23, 2000, which was actually unchanged from the September 1998 guidance. That still represents one year from the date, March 23, 1999, by which blood establishments were to have begun consignee notification for EIA 2.0 and 3.0.

In the June guidance it was recommended that for the records search for EIA 2.0 and 3.0 extending back indefinitely, that is, prior to January 1, 1988, and this would now be for computerized electronic records only, 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 30, 2000.

Now, that was in the June 1999 guidance, and that

was to be six months later than the completion date for consignee notification for the search of manual records going back to January 1, 1988. However, since the revised FDA guidance has not yet issued, our current thinking is to recommend that consignee notification based on the search of computerized records for EIA 2.0 and 3.0 be completed within 12 months following the upcoming date of publication of the revised guidance for implementation.

In the June guidance, it was recommended that for implementation of retrospective HCV lookback pertaining to EIA 1.0 repeatedly reactive donations, blood establishments should begin notification of consignees by December 31, 1999 and complete all consignee notifications for EIA 1.0 by September 30, 2000. However, due to concerns raised by the blood organizations about having adequate time to perform the record searches for EIA 1.0 and about needing to lessen the impact on EIA 2.0 and 3.0 lookback efforts that were already underway, as well as the fact that the revised guidance is not yet issued, FDA is considering extending the date for beginning notification of consignees for EIA 1.0 and the date for completing all notifications pertaining to EIA 1.0 to 6 months and 15 months, respectively, following the upcoming date of publication of the revised guidance for implementation.

Lastly, this table summarizes the time frames for

transfusion services to begin and complete recipient notification that would be included in the revised FDA guidance for industry document. In the June guidance, it was recommended that transfusion services begin notification of consignees--I'm sorry--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 30, 2001; that is, within one year of the last of the notifications that they receive from blood establishments.

However, if the dates that I just mentioned for blood establishments to begin and complete consignee notification for EIA 1.0 lookback are extended to 6 months and 15 months, respectively, following the upcoming date of publication of the revised guidance for implementation, this date to complete all notifications of transfusion recipients would be extended to one year beyond the date for completion of consignee notifications, or 27 months following the upcoming date of publication of the revised guidance for implementation.

Thank you.

DR. HOLLINGER: Thank you, Dr. Mied.

Questions? Yes, Dr. Boyle?

DR. BOYLE: Points of clarification: Since half of those who were notified were not tested, what constitutes

notification? And, secondly, is there any plan to sample that group that has not been tested to see if they are different or why they are not being tested?

DR. MIED: The first part of your question is?

DR. BOYLE: What constitutes notification?

DR. MIED: We recommend that three attempts be made to notify a recipient. If the recipient is deceased, then the notification process does not extend to their family members. So that, if three attempts have been made to accomplish the notification, that ends the process as far as the transfusion service is concerned.

Now, the second part of your question?

DR. BOYLE: The second part was, since 50 percent of those who are notified are never tested, is there any plan to look at a sample of those people to see whether or not in fact they never received notification, or they know that they are positive so they don't feel they need a test, or exactly what's going on with that group? Because if they have the same characteristics as the other group, you've got 900 more cases in that group.

DR. MIED: That's an excellent question. I'd like to address that to Miriam Alter if she were here today. But Mary?

DR. CHAMBERLAND: Obviously Miriam would be the ultimate source on this, but just a little bit more

supplemental information. Miriam presented a slightly updated version of the data at a recent meeting that was held here in Washington, I believe it was a couple of weeks ago, as part of the general notification effort. There was a meeting with various groups who--health care providers and patient groups--who likely would fit in the category of having been transfused, and she presented some updated numbers at that meeting.

My understanding that of those individuals that were notified, it was found that about 25 percent of them were dead, so obviously it was next-of-kin that ended up being notified. So some of those notifications were to people that were already deceased, and 50 of the--as Paul said, 50 percent of those notified were tested for HCV, and according to the survey to date, 50 percent of those already knew they were positive, so I think that explains some reason why people may not have sought testing.

As part of the evaluation that CDC, in collaboration with ACPER and FDA, is doing on the lookback effort, besides these surveys of blood collection and transfusion centers, there is going to be an attempt to try and evaluate the effectiveness of the lookback from the perspective of individual persons. And that, the methodology, as I understand it, as to how to go about doing that and sampling and all of that hasn't been--is still in

the process of being developed because it's going to be challenging, but I would like to think that there would be some information that we can try and glean from that kind of a further evaluation.

DR. HOLLINGER: Yes, Dr. Koerper?

DR. KOERPER: I am speaking from my own experience in dealing with our blood bank, our local blood bank, but the way the notification is happening is that our blood transfusion service is identifying the physician who was responsible for the transfusion, notifying the physician, and then leaving it up to the physician's discretion whether the individual is actually notified or not.

So, I mean, we have an elaborate form we have to fill out saying whether we notified them or not and whether we recommended testing or did the testing, what the result was, but there are certain physicians who feel that because it's an elderly person or someone who is dealing with a terminal illness, that it may not be in the best interest of the individual to physically get this notice that, "By the way, you've got one more thing to worry about."

So sometimes the physician is notified but the actual recipient is not notified. And what I don't know from these statistics that both of you have mentioned is whether that, you know, the person being notified includes these situations where the physician was notified and made a

decision not to actually inform the recipient.

DR. CHAMBERLAND: Regarding this initial survey that CDC did, it was a very preliminary--it was viewed as an interim preliminary survey to kind of get a quick snapshot of what was going on, and I don't believe that level of detailed information was being collected. And there is, right now there is discussion as to whether this should be followed up with another interim survey at a later date.

I mean, I am delighted to hear that ABC did their own survey and found obviously a 100 percent completion rate for the lookback dating back to 1988. But trying to balance the need to get some information on an interim basis without wanting to sort of try the patience of individuals that have to fill out these forms--because ultimately, at the completion of this lookback, is when the very detailed series of evaluations will be planned, so I don't think we have that kind of information, but that's useful to know.

DR. HOLLINGER: Yes, Dr. Katz?

DR. KATZ: Louis Katz, Mississippi Valley Regional Blood Center.

I don't want--the approaches to lookback vary in varying systems. And, for example, my system, in cooperation with our hospital transfusion services, took a substantially more aggressive approach than it sounds like you've got. So that's all over the board, I believe, and I

don't know if there's anybody from the Red Cross that can address what they did.

But in my system, where we have completed that lookback, we find numbers essentially identical to what Miriam has presented from her national survey in terms of yield, just under 2 percent in our system that were newly discovered HCV infection. So it is really quite variable, and some places have been very aggressive.

DR. HOLLINGER: Yes. I'm not sure one should always be a little pessimistic that you only got a 2 percent yield. I mean, the fact is that there is a lot of education going on, a lot of information in the newspapers, and I will tell you from my standpoint that some patients that come to see me have been tested because of all the things in the news about lookback so they went and got tested. So the fact that they were notified but then found to have already been tested I think is a good thing.

DR. KATZ: And one other thing I just wanted to say is that sometimes the relationship of industry and FDA is contentious, and with regards to lookback, I think everybody in the industry or most people in the industry appreciate the approach that Paul and the agency have taken here, that this is doable and has not consumed the resources it might have under other circumstances.

DR. HOLLINGER: Have you found it has been quite

expensive to do? And where have the resources come from to do this? Who is footing the bill for this, Louis?

DR. KATZ: Oh, we just put another $2 on a unit of red cells; it was easy.

A lot of person hours, enormous labor costs, and some of us are trying to figure out how many. And within our system, we're guessing that for each individual that we in fact got to, notified and got tested, it was somewhere in the range of $700 or $800, but those numbers are not reliable yet. Yes, it's pretty expensive.

DR. HOLLINGER: Yes, Dr. Simon?

DR. SIMON: Well, I was going to ask, and I know this is preliminary, I mean I was going to ask about the view from Mary and your point of view on the yield, which to someone like myself seems very low for all of the effort. And I think you commented about all the publicity, but that could have all come from the non-targeted lookback, which I think is another whole area, and one didn't necessarily need the targeted lookback to get the publicity and the public awareness.

Even though it's preliminary, is this considered a good yield for a public health effort of this dimension, in terms of what can be gained?

DR. CHAMBERLAND: This is basically, the yield to date from this interim analysis is not unexpected. I mean,

based on previous experiences of doing lookback and whatever, this is--I think there have been some surprises in terms of notifications being over or under estimated numbers of components that were involved, etcetera. But in terms of the bottom line, in terms of the actual proportion of people that you reach who get tested, who otherwise wouldn't have, it really hasn't been too surprising.

Part of the final, if you will, or comprehensive evaluation of the lookback is going to include a cost-benefit analysis, and so the final series of questionnaires that will go out to blood collection and transfusion services is actually going to attempt to collect information about costs, resources that were used, so that we can actually quantitate this better. Which I think everybody thinks is a good thing to do, because I don't think any of us would be surprised if we would be on the cusp of facing a similar question with a new agent or a different agent down the road. So I think people feel this is a very good opportunity to really try and quantitate this as best we can, and provide that information back.

DR. HOLLINGER: Yes, Mr. Rice?

MR. RICE: Well, I think that the yield--about the yield, it would seem that we would probably try to find more people than 900 out of an effort of this magnitude, but I think if we had actually started to look back at an earlier

point in time, the yield would have been much greater. I think that this particular lookback demonstrates that the regulation which was in place in June of 1977, and I think my comments would be consistent with Mary Pendergast's comments a few years back, that there has been a requirement that we have some sort of process in place to do just this for 20 years.

And I wonder sometimes whether, because blood has traditionally been safe prior to that date, and unfortunately through HIV we learned some hard lessons, but have there ever really been resources set aside, just like if I had to plan, my heating system is going to go, I am planning for resources to replace that? Was this really a budget item for 20 years, to basically say, you know, some day we're going to get something that we're going to have to actually perform a lookback and notify all consignees? Which, if you look at the '77 regs, includes the individual.

So there has always been that problem of how we're going to do it, and with the record-keeping now being electronic, it's much easier. I think that it's been a great effort to basically identify the problems, even though the yield wasn't quite as great as perhaps the resources spent to find these people. But I think that it may identify the problems that will definitely allow us to at least be in compliance, as I read the 1977 regs, on the next

challenge.

DR. HOLLINGER: Thank you. If there are no further questions, thank you very much, Paul.

Oh, yes, Dr. Schmidt?

DR. SCHMIDT: I think the expenditure Dr. Katz has given us is the blood center expenditure, and my recollection is, the American Hospital Association backed off the old HIV concept or looking at everybody who was ever transfused, when it was pointed out to them that the hospitals in the country would have to spend millions and millions that they didn't budget. So when you're talking about costs, it's not at the blood center level. That's a small part of the cost of getting to the patient.

MR. RICE: Well, I think that now that we know this happens, we have to perform it, whatever the chain in that is actually involved in getting these notifications, that perhaps some planning for the future to have resources available, to make this not quite as difficult a task financially than it obviously has been for HCV.

DR. HOLLINGER: Thank you.

The next update is on post-donation information algorithm, and Dr. Tabor is going to give us that update.

DR. TABOR: On previous occasions at BPAC when I have discussed post-donation information algorithms, I used slides, and I was told afterwards that the slides were too

detailed to be useful. So this time we arranged to have the copies of the algorithms submitted to the committee ahead of time in your mailer, so you may want to pull those out and follow them.

We also had planned to have them at the front desk for the audience to pick up, but unfortunately they were not there the first thing this morning, but they will be there, I am told, at the break for you to obtain. And the algorithm is also available on the web, that is, the draft algorithm.

Well, as you know, we have been discussing these algorithms at BPAC almost every meeting since 1997. The topic was previously called "inadvertent contamination," and we searched far and wide for a replacement name for it, and it's not called "post-donation information." Let me remind you that so far these discussions have involved only those viruses for which serologic tests exist, and which can be inactivated and removed by procedures applied during the manufacturing process for plasma derivatives, namely hepatitis B virus, hepatitis C virus, and human immunodeficiency virus.

To summarize what BPAC has recommended, BPAC voted in March 1999 in support of the "test positive" algorithm; and in May of 1999 BPAC voted in support of the "risk factor" algorithm, with a proviso that footnote "i" be

shortened because the number of risk factors that were listed there and that could activate the algorithm was so large that post-donation information would affect every lot of every plasma derivative.

At the September 1999 BPAC, a revised algorithm was presented, along with additional suggestions for changes, based on the fact that by 1999 all units entering plasma pools would have been found to be negative for HCV and HIV by NAT testing of minipools. The revised algorithm presented at September BPAC included the suggestion that if post-donation information were received that a donor was in fact in a listed risk group, the pool itself would be tested, that is, the manufacturing pool would be tested, as an additional precaution, for HCV and HIV by a NAT test under an IND, and for HBV DNA by a NAT method validated under an IND. If all of these tests were negative, the pool or products would be releasable. And of course a positive test in one of these NAT tests would trigger a further GMP assessment.

We have made further modifications to the draft algorithm to reflect the BPAC discussion at the September meeting and to address issues related to prior donations by a donor with post-donation information, so you might want to take a look at the draft algorithm. Aside from several minor corrections to the algorithm, you will find that the

main changes are located on the second page, which is titled "Risk Factor: Plasma," as well as in some of the footnotes.

If post-donation information is discovered prior to the pooling of a donation, the unit from that donor would be destroyed. However, if the unit has already been pooled, NAT would be done on the manufacturing pool, and if NAT for HCV and HIV were negative on the manufacturing pool, as well of course as prior NAT on the minipool, and if a validated NAT were negative for HBV on the manufacturing pool, then the pool and/or the product could be released.

All pools or products containing prior donations by the same donor could be released, as well, provided that a recent donor sample were negative for all recommended serologic screening tests by NAT for HBV, HCV, and HIV, and serologic tests for anti-HBc and anti-HBs.

If any NAT on the manufacturing pool done after the receipt of post-donation information were positive, or if a paper audit by the fractionator revealed that the minipool NAT done prior to pooling had in fact been positive and had incorrectly been reported as negative, or if NAT had for some reason not even been done on the minipool, then the pool and product would be quarantined and a GMP evaluation would be done. The GMP evaluation would be the same type of evaluation that was endorsed by BPAC at a prior meeting, as described in footnote "d".

At a prior BPAC meeting, we had indicated that these algorithms, the "test positive" algorithm and the "risk factor" algorithm for post-donation information, would not be developed into guidance documents until the approval of NAT tests under PLAs. We are now near to the time when one or more PLAs will be submitted to FDA for NAT testing. Therefore, it's safe to assume that the Office of Blood Research and Review will be working on a guidance document for these algorithms during the coming year in anticipation of the submission and approval of NAT tests for blood and plasma.

And I can take any questions that you have about the algorithm.

DR. HOLLINGER: Any questions? Yes, Dr. Chamberland?

DR. CHAMBERLAND: Ed, thanks. A couple questions. In terms of the pieces, the parts of the algorithm that require NAT testing, I think they--I was trying to reconcile the HBV NAT requirement with what we heard yesterday, because obviously it seems that certainly for minipool testing, HIV and hepatitis C NAT testing is much further along. So I wondered if you could elaborate a little bit more about how this algorithm plays out with respect to NAT testing for hepatitis B?

DR. TABOR: Okay, let me try.

DR. CHAMBERLAND: And I was also curious about the data that Sue Stramer presented from the Red Cross yesterday, that seemed to indicate that performance of a hepatitis B surface antigen test with increased sensitivity might even be a better way to go. So I was wondering if you could just sort of help elaborate a little bit on that.

DR. TABOR: Okay. Well, let me first say that the algorithm we're talking about is an algorithm for plasma, and at least some of our discussion yesterday was about testing of whole blood. In the case of plasma, we feel very confident, based on data presented to BPAC over the past two years, and that I subsequently published in a review in Transfusion that was also submitted with your packet, we feel confident, based on the accumulated data, that if all of the GMP requirements are met and appropriate inactivation or removal procedures are followed in the manufacturing of pooled plasma derivatives, that any residual HBV would be non-infectious for the recipient of these products. And we also feel that the HBsAg testing removes the vast majority of HBV-infected units that could enter a pool.

Well, let me drop back to talk about HCV and HIV for just one minute. Those are already being tested in minipools for plasma entering the manufacturing pools, and the addition to the algorithm of NAT testing for HCV and HIV on the manufacturing pool was essentially a back-up method

to allow the manufacturers not to have to do a GMP evaluation on every single lot of every single product based on information that a donor was in a high-risk population.

You must remember that these are all donors, even if they are in high-risk populations, they are all donors who tested negative on all the serologic tests as well as in the minipool testing for HCV and HIV. So in this case the subsequent testing by NAT on the manufacturing pool was basically a sort of fail-safe addition to the algorithm.

In the case of HBV, we don't have minipool testing at present, and as we heard yesterday, it's unclear whether we will have minipool testing or whether, when the technology is available, perhaps we'll go straight to single donor testing. But at present there is no minipool testing on most of the plasma entering products manufactured in the United States.

Nevertheless, based on the serologic tests available, we do feel that there is very little HBV that would enter the pool, based on the testing that's available, and we feel that the evidence is that any HBV that entered the pool would be inactivated by the manufacturing procedures. But it was felt also that adding NAT testing of the manufacturing pool would at least ensure that there was no detectable HBV DNA at a certain level, and that this too provided some measure of additional safety in a situation

where we really don't feel there is any risk at all.

DR. HOLLINGER: And I guess also, Ed, if I am not mistaken, with the plasma these are still anti-core positive, probably anti-HBs positive units also dumped into the pool, which should add an additional safety factor for the HBV. That's correct, is it not?

DR. TABOR: Right, that's correct, because--

DR. HOLLINGER: So there should be some neutralization going on potentially anyway in those pools.

DR. TABOR: That's correct.

DR. HOLLINGER: Yes, John?

DR. BOYLE: I would just like to clarify this, because there are two options. One is the audit trail of the GMPs and the other is the NAT testing. The industry in the past seems to have said that they can't do the audit trail in 36 hours, so the only way to avoid that is to have universal NAT testing. Is that not correct?

DR. TABOR: Well, 36 hours wasn't the actual figure that we had somewhat arbitrarily selected. It was, I think, 72 hours, but it was equally arbitrary, and what you're saying is correct. I don't really buy the inability to do it in that amount of time if resources were focused on it, but it would be a great burden to have to do it on every lot of every product, and it would cause a bottleneck in the supply of these products.

You will be hearing later, probably in the open public session, from the Plasma Protein Therapeutics Association, previously IPPIA, about some further modifications of a plan they are proposing to precertify GMP measures, and we can discuss that when they talk about it. But basically what you said is correct, that this type of NAT testing would be to bypass a reevaluation of GMPs.

But, you know, what it really boils down to is, the only situation in which a manufacturer would end up doing this type of GMP evaluation would be when they failed the testing or when minipool testing had not been properly done. I think that's what it would boil down to.

DR. HOLLINGER: One other question. On page 2 of the things that you sent us, Ed, it says that "all pools or products containing prior donations could be released, provided that a recent donor sample were negative for," and it says "all recommended serologic screening tests, NAT for HBV, HCV, HIV, and serologic tests for anti-HBc and anti-HBs." I guess I would come back again and say, but these are being released into the pool of plasma products anyway.

DR. TABOR: Well, yes. Yes, let me explain that. That was added because of an actual situation that arose since the last time we discussed this with BPAC, and we realized we had to address the issue of prior donations by the donor that might not have been--that might still be in

stock or in the manufacturing line. And what we want to do is make sure that the present donation is not infectious and that the prior donations are not infectious, if they are still in the process of manufacturing.

And let's just say you have a donor who said they were not in any of the risk groups, answered negatively to all the questions in the questionnaire, and then on a subsequent donation or after they went home realized they were, they had had a tattoo or something. They called up and said that they really were in a risk group and had forgotten to tell you.

Well, you want to make sure they were not infectious at the time of the present donation, so you have got the minipool NAT and you have got NAT testing on the manufacturing pool as well as serologic testing on the donor sample. You want to make sure, also, that any prior donations are not infectious.

Well, if you have all of these tests available on the donor, you know that--if you have the tests available, you have serologic tests on the earlier samples, you have NAT testing on the current sample, you might not have NAT testing on the earlier samples, depending on when it was collected, but it is possible that they could have had, say, hepatitis B when they donated six months ago and now be anti-HBc or anti-HBs positive. And that was why that was

added.

But in general anti-HBc and anti-HBs positive units are entering the pool, but in this case you want to make sure they don't have any evidence of prior HBV infection. Now, the one exception, if you noticed in the footnotes, was for plasma that's going into immune globulins, and it was felt necessary to make an exception for plasma that's going only into immune globulins.

DR. HOLLINGER: Yes, Dr. Koerper?

DR. KOERPER: I'm curious why you're testing for anti-HBs, because this means that somebody who has been immunized for hepatitis B would turn up positive for that test only.

DR. TABOR: That was brought up in our internal discussions. What you're dealing with is a situation where a manufacturer wants to use material that they would not have been able to use if the donor questionnaire had been answered honestly and appropriately, and so the manufacturer has the option of evaluating their GMPs for that lot or any affected lots, and if they want to bypass that, they can do this testing. And if the individual in that risk group happened to have been vaccinated, they still have the option of evaluating the GMPs for those lots.

But you're not going to be able to necessarily--I mean, I guess it's something that we can address in the

footnotes to the algorithm, but it seems to me that this pathway of additional testing is to enable the manufacturer not to have to do a GMP evaluation on those lots.

DR. KOERPER: Right, but maybe Blaine can answer this. How often does somebody have an infection with HBV and only be left with an anti-HBs?

DR. HOLLINGER: I have never seen that.

DR. KOERPER: I have never seen that, either. If you take all of our hemophilia patients that we have tested over 20 years, all the ones who were infected have anti-HBc. And the only ones who only have the anti-HBs are the ones that we immunized, so that's why I'm questioning the need to do the anti-HBs.

DR. TABOR: What you're saying is that anti-HBc would be enough.

DR. HOLLINGER: Any other comments to Dr. Tabor? You're very silent over there, Toby.

DR. SIMON: I believe industry is making a presentation, and at the time--is that correct? Okay.

DR. TABOR: Let me just emphasize that this is not final, that the guidance document will be prepared and made available for public comment, and we welcome suggestions, including the ones such as you made about anti-HBc and anti-HBs.

DR. HOLLINGER: Will you still be in the FDA, Ed,

by the time this is all completed?

DR. TABOR: Well, if HCV lookback is any model, I'll probably be walking with a cane.

DR. HOLLINGER: Okay. Thanks, Ed. Yes? Oh, I'm sorry.

DR. MITCHELL: I just wanted to comment that you had mentioned about tattoos, and I wanted to make it clear that that's not in--

DR. TABOR: I'm sorry. Yes, I gave a bad example. Thank you.

DR. HOLLINGER: Okay. The next update is on IGIV clinical endpoints, and Dr. Golding is going to give us an update on that.

DR. GOLDING: Good morning. Before we start with the slides, just a small comment. Dr. Albert Ferrugia is here visiting from Australia. He is the director of the equivalent Office of Blood in Australia, and when he came to our group he asked me how was my labyrinthitis.

I asked him, "How do you know that I had labyrinthitis?" He said, "At the last BPAC, when you went up, you said you had a viral labyrinthitis and if you were disoriented, it was because the viral labyrinthitis." "And how did you find that out?" "It's on the transcript and that's on the web."

So I need to update my medical record that's on

the web. The diagnosis of viral labyrinthitis was incorrect. I was taking non-steroidal anti-inflammatory drugs at the time, and that caused the dizziness. When I stopped the drugs, the dizziness went away. And I just wanted to be sure that that was clear and on the internet.

As for the IGIV update, could I have the first slide? So what I'm going to be talking about is the Immune Globulin Intravenous (Human), a clinical trial proposal for primary immune deficiency, and what I'm going to tell you, this proposal is based on a consensus that was arrived at from discussions with the Clinical Review Branch at the Office of Blood, the senior management at the Office of Blood and CBER, and much help from Peter Lachenbruch and his group at CBER.

At the BPAC in March '99 I emphasized that the plasma fractionation process was complicated. It's a multi-step process. Variations in the manufacture can have far-reaching effects on safety and efficacy, and we regard each product as being unique, and that immune globulin should not be treated as a single generic biologic.

I also stated at that BPAC that we had come up with a proposal, and the proposal for study, for clinical study, was a prospective, double-blinded, randomized Phase III study, in other words, a two-arm study to evaluate the efficacy and safety of new IGIV products by comparing them

to licensed IGIV products, and the sample size that was calculated at that time was approximately 80 patients, which was much less than most of the trials that were being proposed at the time.

So the problems with this trial design that we discovered were that there still were limited numbers of patients with the diagnosis of primary immune deficiency that could be recruited for these trials, and that multiple new IGIV products were in line to be tested, and that the critical shortage of IGIV persisted, which drives the need to seek other means to come to a proposal that would allow foster approval of these products in a safe and effective manner.

So the new proposal that we're proposing now--and I would like to emphasize that this is only a proposal, it does not exclude other proposals that could be made by manufacturers--so according to this proposal, discussion of possible trials that would reduce the sample size were arrived at from internal debate at the FDA, and formal and informal discussions with the Immune Deficiency Foundation, and the discussions centered around many different issues. One was the possibility of using pharmacokinetic data as a basis for approval. Another suggestion was the suggestion that we could use surrogate endpoints such as fever as the primary endpoint.

What we think we have come up with as being preferable to this is using historical controls to justify a single-arm study, and this is based on the fact that IGIV products have been very successful in limiting infections in PID patients, and that acute bacterial infections per patient per year are as many as four or greater than four without treatment, and are in the region of .5 or fewer than .5 on treatment. So this is at least an eight-fold difference between patients receiving IGIV and patients not receiving IGIV.

So the study design that we came up with is a single-arm study. It would be a 12-month open study, and we would be comparing the new product to historical controls for safety, PK data, and efficacy, using 80 percent power and 99 percent confidence level, in other words, an alpha of .01, and the increased rigor is partly to account for the single-arm nature of the study and to do one-sided testing of the data.

In terms of safety, the safety targets are again based on previous trials and historical data. The historical control estimate is that 20 percent of adverse events occur per infusion of IGIV, and the trial target would be to exclude 40 percent or greater adverse events per infusion. And the approximate sample size for this would be about 40 to 50 patients receiving 12 infusions sequentially,

in other words, about a year of follow-up for each patient because they receive these infusions every three to four weeks.

The clinical trial design would include PK studies, so there would be first a washout period. The patients would still be receiving IGIV but after two or three months the data would be collected for the Cmax, the Tmax, the area under the curve clearance, and the half-lives, and importantly also the trough levels, which are used almost universally by physicians to decide on dosage. And the observed values should not be inferior to those concurrently or previously determined for approved products.

In terms of efficacy, the efficacy would be established using an objective, clinically meaningful endpoint. The primary endpoint would be acute serious bacterial infections which would be predefined, and what we're talking about here are infections such as pneumonia, bacterial pneumonia, bacterial meningitis, bacteremia and septicemia, osteomyelitis. Most of the acute serious bacterial infections are in fact pneumonias. By the overwhelming majority are pneumonia, which can be diagnosed by x-ray and which are responsive to antibiotics.

The secondary endpoints could include or should include serum immune globulin levels, other endpoints such as antibiotic treatment, numbers of hospitalizations, fever,

and others. The sample size should be sufficient to determine whether the infection rate for the new IGIV is at or below the "beltline", and the numbers that we came up with were approximately in the range of 40 to 50 patients.

The primary endpoint, as I said, would be acute serious bacterial infections, and this is based on historical controls that the infections per patient per year are less or equal to .5 using approved IGIV products, and the data with the new product must exclude an infection rate of 1 or greater than 1 per patient per year.

The trial would be considered a Phase III pivotal trial sufficient for licensure. Submissions with six-month interim data could be submitted six months after the trial onset to initiate review of the manufacturing, the PK data, and the initial safety data. The efficacy and complete safety data would be submitted after termination of the trial, that is, each patient would be treated for a minimum of 12 months. Initial FDA action is expected within six months of receipt of the completed data.

In conclusion, the number of patients per trial will be reduced, permitting concurrent trials of new products. For approval, the new products will need to have acceptable safety, PK, and efficacy profiles when compared to historical controls.

And the data will be collected during the trials

to validate additional surrogate markers, e.g., for example, antibodies against specific pathogens. For example, we know that Haemophilus influenza and streptococcus pneumonia are the primary causes of pneumonia in these patients, and it seems reasonable to start collecting data to make sure that--to determine whether we could use these as surrogate markers for subsequent trials.

Thank you.

DR. HOLLINGER: Thank you, Dr. Golding.

Any questions for Dr. Golding? Yes, Dr. Boyle?

DR. BOYLE: It's not a question, it's just a congratulations to the FDA on a job well done.

DR. HOLLINGER: Thank you. If there are no further questions, then--oh, yes. Dr. Epstein

DR. EPSTEIN: Yes, I just wanted to add a comment. Well, first of all, thank you for your remark. The central change here is shifting from the notion that we can't approve a new product without comparing it in a two-arm trial to a previously approved product. Instead, what we have done is, we have examined the historic data and established a standard for approval of any new product. That's the central insight here. The fact that we have also added a rolling type review is to expedite the process, but that's really the key point.

DR. HOLLINGER: Thank you.

This completes the committee's updates this morning. We're going to open this up now to the public hearing. There are several people who have asked to speak to some of these issues. So the first will be Jason Bablack from the PPTA. Tell us about the new name, too, Jason.

MR. BABLACK: Thank you. With regards to the new name, it's the Plasma Protein Therapeutics Association, and it reflects a merger, if you will, with our European counterparts, which was the European Association of the Plasma Products Industry, and it is really focusing now of global issues, with a North American component, a European component, and we are expanding also to look at issues in Japan, as well.

With regards to the post-donation information algorithm, I would like to make a few comments. I have about 10 or 11 slides here, and then we would be happy to answer any questions that you have.

First of all, I would like to change the focus of this ever so slightly because we have been talking about post-donation information reports, but I really want to get to what those stand for. And what they stand for are undetectable window period units or the potential of an undetectable window period unit. So we are going to just change the focus of the discussion ever so slightly to address that potential risk, and talk about a proposal that

we have come up with that we hope will address that at least as good as what the FDA proposes, and hopefully a little better.

This is just an introduction slide, and in the past there has been a little confusion about what is currently done, what the FDA has suggested and what we want to do, so I just want to kind of summarize it, start off from that base and then go forward. So currently, when we get information, post-donation information for risk factors, for hepatitis B, C, or HIV risk factors, the units in inventory, and because we have a 60-day inventory hold, all of those units are removed from further manufacture. Non-reactive units, and all of those that actually are in inventory are non-reactive, that have been pooled, continue through normal processing.

So this is currently what is done. It's in the company SOPs. They have all been inspected and agreed to by the FDA. That is what is currently done, and the rationale behind that is, basically there are very robust inactivation procedures, that if there is a potential window period that is below the level of detection, that would definitely be taken care of through viral inactivation methods.

FDA has developed an algorithm to address PDIRs, and it includes NAT testing options that Dr. Tabor discussed just a minute ago. It also involves a potential of tracing

and a retrospective review of viral inactivation data for those impacted lots. And the industry alternative is a prospective supplemental review focused on viral reduction records for all lots, and it also includes NAT testing of minipools and/or manufacturing pools.

So just from the start, I think we are very close, and it's really a matter of do we want to go backwards and look at ones that are identified through PDIRs, or do we want to go forward and say for every lot? Because there's a chance that any unit could actually at some point have a PDIR associated with it, do we want to have assurance for any unit going forward?

With the history of the issue, I think everyone agrees we have an excellent viral safety record profile for these products. Dr. Tabor just recently published an article in Transfusion speaking to that, and I don't think there is any disagreement with that. Nonetheless, there was a recommendation that we can and should continue to look at ways to further improve the margin of safety, and one way is to address any potential risks that would be associated with PDIRs. And here again I want to take a step back from the actual post-donation information report and say it's really the window period or potential that a unit is in the window period that we want to address the risk for.

I won't go through this in too much detail. The

FDA has developed an algorithm that we've gone through many times in recent BPAC meetings, and it's focused on post-donation information reports. That's the trigger to initiate some sort of review. Either it's looking at the unit or the pool, or going back and looking at the actual products made from that pool.

The NAT testing was originally focused on the donor unit, with discussions today which sounded very promising to us. It looked like NAT testing on the manufacturing pool might be sufficient, and one question we have for the FDA is, would a NAT test done prior to finding of the PDIR suffice, or would you have to go back and test retrospectively?

Currently, though, not all the manufacturers are testing for hepatitis B, so right now that is not an option that would exclude the GMP review. So for the FDA algorithm, it would involve a retrospective tracing of each unit to identify all the impacted lots, and then going the comprehensive GMP evaluation. And in the original algorithm, and I think it's still there, is the 72-hour time frame for doing all of these.

Now, this is a slide I think I showed you last September, but I think it's important to kind of understand. This is an example of a PDIR, and this was the example--we collected many examples--this was the one that had the least

amount of impact. There was one PDIR. Of that, there were seven units collected from that individual prior to getting that information. Six of those were removed from inventory, from the 60-day hold.

One of them had been manufactured. And you can see what happened to that one unit. There were four Factor VIII lots; one Factor IX; eight albumin; and one IGIV lot; plus eight intermediates. So there were intermediates that had not been manufactured to final products yet, and it's still unclear what would happen with those under the FDA algorithm. But that's just to show you that one unit from one donor can have that effect on the number of final products, so this is a significant amount of reviews if you're doing it retrospectively.

We also have some additional concerns with the algorithm. We believe it's inefficient in addressing what we're trying to get at, which is the potential risk associated with undetectable window period units. While it can actually address some risk, if you look at the ones that are identified, there are still many that may not be identified, because really what we're talking about is the potential risk is based on the possibility of an undetectable window period unit entering the pool.

Now, these are random events that we believe are not accurate predictors of actual risk through a particular

unit, and in the next slide I'll explain that a little bit further. Also, we have the 60-day inventory hold that reduces the risk already of pooling window period units, because as we get additional sampling from these donors, if one would happen to seroconvert, we can go back and pull out what would be window period units. And then there is also the problem of most if not, many if not most lots are already released, and this requires a quarantine while we do these investigations, and obviously that causes some supply implications.

Now, this is, it doesn't look like it but it's actually a busy slide and I'm going to take a couple of minutes to go through it. Assume that this is your typical plasma donor who would donate once a week, so he donated four times in January, four times in February, four times in March, three times in April, and he comes back in April and gives us some information. Now, it's important to understand that all of these units are negative for all the serological tests and all NAT tests that are currently done by the manufacturer.

Now, if you go back to the first day in January, and I had a little mark on there but it looks like it came off, assuming that first unit in January is actually when the risk activity took place, what this does is, all of those units have an additional level of risk associated with

them, that they could be potentially in the window period unit. We don't know about that until you get down to April, and if you look at what happens then, we get that piece of information, we go back and take out all the units in inventory, so that takes out all of April and all of March, but there are still several units from February and from January that have been pooled and may have actually been manufactured.

Now, if you look at the FDA algorithm, what it does is, it waits until you get that PDIR and then you're going to go back and do some kind of retrospective review. Even if you're just looking at the NAT tests on the manufacturing pool, even if you're going back and looking at all of these reviews, it's still retrospective, without addressing the risk that each of those units has going forward.

What we want to do is, for each of those units as they go through manufacturing, assume the worst, if you will, in that we are going to assume that each of these could potentially be in the window period. And what we're going to do is, we're going to add not only the NAT testing, because we're doing that, but we're going to add the enhanced GMP review for viral inactivation records for every single one, because any of these could at any time have a PDIR associated with it. And rather than wait to get that

PDIR, we're going to go forward saying that any one could have it, and so therefore they should all be treated the same.

So, just quickly going through our proposal, it's a prospective supplemental review focused on the viral reduction records for all lots, and this is performed by staff who are specially trained in virological principles, product-specific processes for viral inactivation and reduction steps, and critical operating parameters for each step.

Now, this is important because we have had some discussion about this, as well. This is conducted as an additional review, so the normal manufacturing review is done, the normal QA review is done, and then this is an additional review by an additional set of eyes, if you will, to look one more time at what we think are very critical parts of the manufacturing process. And the certification of this review is required for lot release, so in order to get the lot out the door, you have to have this additional review done.

In addition to that, we are currently NAT testing for hepatitis C and HIV at the minipool and/or the manufacturing pool, and the manufacturers have submitted INDs for hepatitis B NAT testing. So in essence we're doing both; we're just going to do them up front.

Now, what are the benefits of this? We believe this is an effective alternative to address potential viral risk associated with undetectable window period units, and it doesn't impact supply because we do it up front, we do it on a routine, regular basis that does not require us to quarantine products. It applies to all lots of plasma derivatives, so it does not rely in a random event to trigger this review.

It's something that we do all the time. It's prospective, so, if you will, it's preventative versus reactive. It provides an additional assurance of viral reduction procedures. Any potential safety issue related to PDIR or anything else, because you're not solely looking at PDIR's, are addressed before a lot goes out the door. And, once again, it minimizes the impact of product supply. And with the NAT testing, I think everyone agrees that this is state-of-the-art, and it further reduces the window period, which basically makes this more effective.

Where are we? This is the implementation phase. The companies have all done the preparation of their viral record review documentation, so all the check sheets are made. Revision of corporate SOPs for product release, so in order to get product out the door, this is part of that SOP now. Employees have been trained on virology, the viral reduction processes for their particular steps, and the

program SOPs, so that they understand that this review is required and how to perform the review. And it is implemented for all currently manufactured products, so it is actually in place.

And after some discussions, both with consumer groups and the FDA, we felt that it was important to add this final piece to it. And really what this is, we're going to have an independent third party audit the company's implementation of this program, and we will make those audits available to the FDA so they can say whether or not it's actually being done.

And I would be happy to answer any questions you have.

DR. HOLLINGER: Any questions for Mr. Bablack? Yes, Dr. Boyle?

DR. BOYLE: Just a question on these PDIRs. Are most of them coming from first-time donors, as opposed to continuing donors?

MR. BABLACK: No. PDIRs, by their very nature, come from repeat donors, because if they were coming from a first-time donor, they wouldn't have donated in the first place. So they come back at some point in the future, and you can see from the example I gave that it was, for this first example where there were seven units drawn, it was done very early. It is not always that way, and a lot of

the examples we collected showed 20 or 30 units in manufacturing, not just the ones in inventory hold but in manufacturing, before we got that piece of information.

DR. BOYLE: But looking at the five elements that are in the algorithm, and I'm thinking of your chart up there that shows the donations from January to April, and so at the end of April somebody says, "Oh, by the way, I was an IV drug user," or "Oh, by the way, I've been having sex with other men"?

MR. BABLACK: Right.

DR. BOYLE: That actually does happen?

MR. BABLACK: That actually does happen. Unfortunately, but it does.

DR. SIMON: Well, it's usually a little bit more, you know, a little bit more below the surface, like, "You know, I had something in 1978 or '83." So it's not usually the more overt sort of thing. Or "I forgot that I lived as a child as a missionary in Nigeria." That's the sort of thing we see.

DR. HOLLINGER: Yes?

DR. FITZPATRICK: So, to boil this down, what you're proposing is that if this program is successful, then if you get a PDIR, you would just ignore it essentially?

MR. BABLACK: What you would do, to put it in a more positive spin, you would have already done what the FDA

would like you to do, you would have done up front, and so it would obviate the need to do anything from that particular piece of information. And don't forget, it's also important to understand that the collection center already sends an accident and error report to the FDA regarding that, so this is obviously done in addition to the FDA, understanding that that already happened.

DR. FITZPATRICK: And this is currently being put in place by industry?

MR. BABLACK: It is in place for all currently manufactured products.

DR. FITZPATRICK: So I think we had this discussion a while back, so that I think the committee said that we endorsed what you were doing. We wanted to see a track record before anyone made a recommendation to the FDA that they change their algorithm process, that your program was successful.

MR. BABLACK: Right. So where we are right now is, the program has been implemented and we are in the process of developing this third party audit that we can then share with the FDA and--

DR. FITZPATRICK: Yes. It looks like a great program. We just need to see that it works.

MR. BABLACK: Thank you.

DR. HOLLINGER: Thank you. Yes, Mark? Dr.

Mitchell?

DR. MITCHELL: I would expect, then, when a PDIR comes across, that there would be some kind of documentation of what has already been done. Is that what you're proposing?

MR. BABLACK: Actually we're not, and let me explain why. Doing, basing it on the PDIR, one, it doesn't actually accomplish anything because the risk is either there or it's not. So looking at that as a trigger, if that were a test, it would be very non-sensitive and non-specific.

So it doesn't really tell us anything that we don't already know about that unit, if we already assume that that unit could be in the window period. So, therefore, basing any additional investigations on that particular piece of information I don't think provides us any additional assurance that anything has been done or needs to be done, as along as something has already been done for everything.

That's the way we are viewing this. If we didn't have something in place, then there might be some suggestion that, yes, we should do something with that piece of information. I think that's where the discussion has been in the past, is if you have an additional piece of information, do you need to do something additional? What

we are saying is, if we assume this for every single unit, then getting that piece of information is just--it doesn't tell us anything else because we've already assumed it into the process.

I don't think that answered your question very well.

DR. HOLLINGER: Dr. Macik?

DR. MACIK: In looking at what you're doing, you could in essence call this kind of a universal precaution. You assume every donation is a window unit donation, and you are working it up maximally. And so you accept the risk that with the best possible tests that we have today, there are still going to be a few units in there that you can't find, that are before NAT testing.

In the plasma industry, for most of the processes, then you have the further fail-safe of you're doing an inactivation process which should catch those rare window units that go through. And so it would seem to me, acknowledging that we would like to see that it actually is in place and working as proposed, that this is probably a much safer way and a better way and a prospective way to look at this information, without spending manpower and dollars doing retrospective reviews that we have tended to get into, that really just look back and identify our errors, and not really making efforts to prospectively

prevent errors.

So I would like to commend the industry on pulling this together. It seems to me a good approach. Hopefully some day we'll have a test that can give 100 percent window unit identification, but until that time I think, you know, this is probably about the best we can do.

DR. HOLLINGER: I'm going to take one more question because we're getting a little bit behind. Dr. Schmidt?

DR. SCHMIDT: Well, I'm strongly opposed to the one question issue. I've been on this committee for several times, and we've heard this before and we're hearing this in piecemeal. I've said before that I'm strongly opposed to this, and I want to emphasize that to the FDA. If they're looking for guidance, this is a lousy--this proposal is okay for operations, but in place of the FDA proposal it's lousy. If the FDA wants to take this under advisement, then we need to devote some time to it so we can hear the full story.

The implications of this is that we're negating all our health history questions. You know, someone can say, "Well, what difference does it make to ask for HIV or HCV? Because it doesn't make any difference, we're going to use that lot anyway." So, you know, that has fundamental implications, and that merits a long discussion, not these piecemeal presentations every 15 minutes with little

discussion. I'm appalled at this.

DR. HOLLINGER: Thank you, David. We'll take one more question, then. We'll take other questions, then. That's all right. Paul?

DR. McCURDY: Well, I think that universal precautions example is not a bad one. I don't know how it is now, but early on universal precautions were better when you knew the patient was infected than when you didn't know the patient was infected.

And I think a triggered lookback or a triggered review is going to be more thorough, almost certainly, than a routine review. It is, again, axiomatic that if you have one person doing something and another person checking it, the first person better do it right because the second person will assume that he did, and will likely miss problems of one sort or another.

I think there also needs to be some thought given as to how the auditor is selected. Again, if the auditor is not selected pretty independently, then again they may not pick up all of the potential problems. I think it's a potentially reasonable approach, but I think there are some flaws.

I have one other question: What proportion of the donors in the plasma industry donate once a week or twice week, and for how long? Is this something that happens over

a year or two?

MR. BABLACK: I am not an expert on the donor issues, but I can tell you that typically donors come in and donate once or twice a week for a period of time and then usually drop out. So there is an extended period of time that they donate on a very regular basis.

DR. McCURDY: What's that period of time? Do you have any idea?

MR. BABLACK: I can't answer that question. I'm sorry

DR. HOLLINGER: Yes? Toby Simon.

DR. SIMON: I think one of the things that's been lost sight of during the discussion, and I want to make sure we don't, as I understand it, the PDIR is not being ignored. When the report is received, all units that have not been pooled are removed and destroyed. The issue is the units that have been pooled, and what kind of system can we have in place to protect the patient and at the same time not disrupt supply?

And I think one of the issues that industry--that also may have been lost sight of has been a lot of discussion about whether the GMP review can be done in 72 hours. I think what I got out of the presentation is, it's not so much that that's the time-consuming problem, it's that each time that report is received, there has to be a

tracing of every unit that was received.

So that obviously you'll get a list of units and a list of dates, and you start pulling the units in inventory and then you come to those unit that have been pooled, and you have to identify every pool of every product, multiple products made, and then you have to identify every pool from the intermediates that are made, and then go back and test this all. And I think what industry is saying is that is logistically very difficult and problematic, and can we take the universal precautions approach and, given that, assume that each pool will have a PDI in it at this point, and do this prospectively?

So I think, in answer to Dr. McCurdy's question, there is a little bit of division between specialty and non-specialty. For example, in the ladies with anti-D donating FRH immune globulin, it's not uncommon for them to donate 100 units a year, year after year after year. We have donors that go back 20 and 30 years. Thirty years may be too much. Yes, almost 30 now, getting close to that.

In the non-specialty, I think what Jason described is the most common, but there are donors who stick in there once or twice a week, year after year. Most donors come for a period of time and then either move or for some other reason, become too busy or whatever. So it's a highly variable situation.

I think 10 or 20 units in a PDIR would be common. Of course, the donors who give you a PDIR tend to be somewhat less reliable donors compared to those who donate a long period of time, but still there will be cases in which a post-donation information report will come in with 50, 60, 100 units, and so forth.

DR. HOLLINGER: Mr. Rice?

MR. RICE: Yes, I just had a couple of questions. The PDIR I would hope would pick up due to some of the questions, the behavioral characteristics of the individual, perhaps. I am more concerned about emerging threats than the ones we know about.

Frankly, there are certain behaviors that the questionnaires tries to elicit, which are the types of things that are what I believe the real threat to the blood supply, in that I believe testing and our review procedures, the GMPs are so tight that I think pretty much that the risk of what we know about is dealt with fairly aggressively and completely. I'm more concerned about the things that we don't know about, where that questionnaire trigger may elicit, as we're developing and moving and finding new bugs and new types of threats to the blood supply.

Now, you could say that we can't be concerned about everything all the time, and you have to deal with what you've got. But ultimately the mention there was, the

risk of this proposal is not borne by the industry; ultimately the risk is borne by the recipient of these products.

DR. HOLLINGER: Thank you.

Yes, Dr. Finlayson?

DR. FINLAYSON: I think apropos of Dr. Macik's comments, it's very important to clarify something. And unlike Dr. Golding, I can't take refuge in saying that I'm taking steroids, so I have just plain forgotten which of your four and five letter codes you are under. But I seem to remember that your entire membership would be doing minipool testing for HIV and HCV NAT by now, and on your slide you said minipool or the manufacturing pool. Could you clarify that, please?

MR. BABLACK: That was basically an and/or. I think some--they are all doing minipool testing.

DR. FINLAYSON: Well, do you propose they take this giant leap backwards in dilution and do just the manufacturing pool?

MR. BABLACK: No, I don't think anyone is.

DR. FINLAYSON: So, in other words, you would be willing to strike the "or"?

MR. BABLACK: I don't see any problem with that.

DR. FINLAYSON: Thank you.

MR. BABLACK: Now, the reason we said and/or is

because not everyone was doing the manufacturing pool. There had been some discussions whether someone could do the manufacturing pool under the particular IND that they had submitted, and so we had and/or because everyone was doing at least the minipool; some were doing the minipool and the manufacturing pool.

DR. FINLAYSON: So you would be willing to do a little rewording there?

MR. BABLACK: If you can come up with a better way to say that, I'd be happy to take it.

DR. FINLAYSON: I'm sure I can. All right. Point two: I also seem to remember at one of these gatherings that you said that your membership would, by the end of calendar 2000, be doing minipool testing on HBV.

MR. BABLACK: Correct.

DR. FINLAYSON: Is that also correct?

MR. BABLACK: That is correct, and it is still true. It is my understanding that all the INDs have been filed and are in the process of beginning implementing that at the sites.

DR. FINLAYSON: Thank you.

DR. HOLLINGER: Yes, Dr. Fitzpatrick?

DR. FITZPATRICK: Well, with what Mr. Rice has said and the universal precautions, I think I'm distressed by what Dr. Simon said, because we've talked a number of

times to the industry about they need to be able to quickly identify where the blood products from these donors go, and it should be automated and readily available and easy to do. And there still is that need for these emerging agents. Something's going to happen, that you're going to have to do a lookback. It's unavoidable. And so to say that that's an undue stress upon the industry to have to do that is, I don't think, acceptable.

MR. BABLACK: If I could address that, I don't think that's what we're saying. In fact, that's currently done for many types of failure investigations. For example, if you have inadvertently put in a positive unit, that actually would be done, where you would trace that unit through the manufacturing process, find out all the intermediates, all the final product lots that went to, and do an investigation on those, as well as the typical failure investigation as to how this happened in the first place.

What we're saying, on an ongoing basis, because of the sheer number of final product lots that will be implicated by the number of PDIRs, doing that on a routine basis is not the most efficient way of manufacturing product and getting it out the door. What we're trying to do is develop a system that allows us to have the same or greater levels of safety to what the FDA has required, but doing it in a systematic approach that prevents the types of errors

that you get from ad hoc types of investigations that you're trying to do in a finite period of time so that you don't have to quarantine product that's already been released in the field.

DR. HOLLINGER: Yes? Oh, yes, Kathy Knowles?

MS. KNOWLES: I think there have been several times at this committee meeting where also we have discussed the problems with the donor history questionnaire, and at some point in time I think it's really important to get an update, because I know there have been workshops on that issue. I'd like to see what has happened and what kind of progress is being made to streamline that, to help people give the most honest answers possible.

DR. HOLLINGER: Thank you, Kathy.

Yes, Dr. Boyle?

DR. BOYLE: Jason, if you could just clarify, at some level it seems like we're reasonably close, because your industry is going to do universal NAT testing. Universal NAT testing would allow us to deal with the issue of errors and omissions or the PDIRs, but the problem is, is the linkage in terms of being able to document a specific case has gone through a specific process. And I guess the question that I'm raising, I've raised before, others have raised is why, going forward prospectively, can't you set up the system so that you can identify automatically the

numbers of the lots and how they get--where they go to, so that all you have to do is pull it up on a computer and be able to demonstrate that that in fact has gone through the proper gate?

MR. BABLACK: I don't think that is unrealistic. The problem we have with that is, having done it for every lot, having assumed that every unit was in the window period, I don't think it actually gets you any additional pieces of information that you don't have without that. And, two, what do you do with that information once you find it? I mean, if all you're going to do is take that and hold it somewhere, I don't think it accomplishes anything.

There has been some talk in the past that the FDA might want some of these reported to them, and that would be one way to accomplish that. But the question is, does the FDA have the staff and the time to review all of these, because there will be a significant number of reviews that are done. Even, as you see, from one unit you had almost 20 final product lots that would have these reviews, and therefore that would be documentation then sent to the FDA, requiring them to review it.

If you're just going to sit on it, isn't it better to just assume that every lot was in the window period and have that associated with every final product lot, that you have done this review? Which is what is incorporated in our

program. So as part of the batch record review and the documentation for a particular lot, you have this enhanced second review accompanying that, so it's attached to every single lot going forward.

DR. HOLLINGER: Dr. Stroncek?

DR. STRONCEK: I'd like to follow up on Mr. Rice's point. These questions are very important. They not only screen for HCV, HIV and hepatitis B virus, but they probably screen for other agents we can't test for, and they will likely screen out people at high risk for new problems coming along that may or may not be inactivated. So these post-donation inquiries I still consider a serious matter, even with all the testing we have and with all the inactivation.

I think the FDA proposal provides more oversight, and I'm in favor of that. Quite honestly, you know, I don't trust any industry as a whole to just say that they're going to handle this all on their own. I think that's the FDA's role. I want to point out that you represent an association of a number of companies. Some of these may deserve trust and may be able to make this work, but I don't think all of them will. I know that companies come and go. I know many companies are for profit and they're going to cut corners. And I just think this is too important, and the safety of our recipients is too great to put this much trust in these

organizations.

DR. HOLLINGER: Dr. Macik?

DR. MACIK: Just to readdress a couple of issues, one, what Mr. Rice has brought out is that ultimately it is the receivers who bear the ultimate burden. It is also the receivers who bear the burden of not having a product available, if you're busy quarantining every unit that goes through and they can't get product.

So what we're really looking at is ways to balance this in the safest possible way, so if you use universal, you accept everything is at risk, one. And I'm not a statistician, and so please don't jump on me too hard, but in some ways screening for and ruling out the hepatitis C, because those units are all going to be thrown out, in some ways those are linked also to those individuals who have the at-risk behaviors. It's not 100 percent, I realize, but you are in some ways impacting those who may have the at-risk behaviors and throwing those bloods out up front.

And so you've done now, you've looked--and what I would agree with is, you need a way that you know where every single unit went at any given time, so when we find that we now have a "mad rabbit" disease and people were exposed to it, and we have to pull that unit, then you go in and you grab it. You know where everything went and you know who got every unit. But not to put the restrictive--if

we've done everything we possibly can up front, that we don't restrict the flow of supply as much as possible.

And again, I totally agree also that this isn't an issue that--maybe this requires an entire discussion a little bit more on where we're going, instead of just as part of the industry hour. Thanks.

DR. HOLLINGER: Yes, Mr. Rice?

MR. RICE: Just a quick point, is that that was my point, is that the PDIRs would--I'm looking for the fact that we're going to do the same checks that they're going to do, prospectively, and ultimately the lots would be released anyway. But if a new virus comes down the pike, we have some sort of record-keeping that says we've identified this behavior, and if we hadn't had this particular pathogen associated with this behavior, we now know that it is.

And do we keep a track? And we still need that trigger mechanism to be able to go back and find everyone, so when the PDIR comes in, not only do we just check to see if this prospective mechanism suffices or is equal to the current standard the FDA has, but also that we need to keep the information or some sort of tagging so we can respond through a lookback type provision more quickly than we currently do. It took us 10 years to do HCV. That's too long.

DR. HOLLINGER: Yes, Dr. Simon?

DR. SIMON: Just quickly in response to that, I think my earlier remarks were somewhat misunderstood about the industry needing to track this and the amount of time it would take. I think we all agree, and the industry would also, I assume, that they need to know and be able to quickly determine where every unit went, and every lot.

So that could be quickly determined, but as part of the algorithm they would then have to go and verify all your pool and minipool testing, create a record, and this would take a certain amount of time to complete. So that was the point I was trying to make there, though perhaps not that well.

But in response to Dr. Stroncek's comment about trust, I think in either plan, industry would carry it out. I mean, industry would carry out the algorithm or industry would carry out the prospective review, and in either case it's subject to review by FDA, either inspection or otherwise on submitted. So I don't see that as a difference between the two, in terms of that situation.

MR. JACKMAN: May I make a comment, please? Dennis Jackman with PPTA. On the question of trust, there was a comment made by Dr. Stroncek about not wanting to trust any industry. And setting that aside, I just want to point out that we're not counting just on trust here. We have third party review and certification of adherence to

the prospective review, and we would make those audit results available to the agency as well, and those would be attached to the lot.

So it's not just a matter of trust, but even saying that, I just want to make it clear that this industry is very committed to producing safe and quality products. It's in our direct interest to do so, for patients and for the viability of the industry, as well.

DR. HOLLINGER: Dr. Schmidt?

DR. SCHMIDT: Supporting Mr. Rice's worry about who is holding the mortgage at the end, the situation in the hospitals, what happens to these products and who gets them, is absolutely chaotic compared to blood. You have no way of finding out, when this is bought by a hospital, who got it.

DR. HOLLINGER: David, my apologies for starting to cut down on the questions. I think it was important, and I think the issues that have been raised here are critical. Perhaps it needs some further elaboration, further discussion outside the update session here. So, with that in mind, perhaps that's something we can perhaps put on the agenda in the future if it seems to be necessary.

We're going to go on with the other public hearings. The next person that asked to speak was Miriam O'Day from the Immune Deficiency Foundation.

MS. O'DAY: Thank you. Good morning. I'm Miriam

O'Day and I'm Vice President of the Immune Deficiency Foundation, and we're making a comment on the IGIV clinical endpoints.

The Immune Deficiency Foundation is a patient advocacy group dedicated to improving the lives of individuals affected with primary immunodeficiency disease. IDF has presented testimony and data documenting the depth of the IGIV shortage and its human consequences before BPAC on numerous occasions.

In addressing the ongoing shortage, IDF has recommended various strategies, a number of which are aimed at rationing the available supply of IGIV based on medical necessity. In cooperation with IDF, the agency has supported and endorsed prioritization protocols and emergency supply programs such as the IDF Safety Net Program.

Since the fall of 1997, industry estimates have consistently projected that demand will continue to outstrip supply well into the foreseeable future. It is estimated that the current annual supply gap for IGIV is approximately 5 million grams. For this reason, the Foundation has encouraged additional strategies, such as expediting licensure of new IGIV products and processes to alleviate the shortage.

IDF and its medical advisors support the FDA's

revised guidance on IGIV clinical trials. The immunology community and immune deficient patients believe that the recommended revisions for IGIV licensure are a significant step towards improving the supply of this lifesaving therapeutic. The IDF commends the agency for adapting endpoints which are measured using the standard of care in the practice of immunology, therefore avoiding undue diagnostic burdens on patients participating in clinical trials.

FDA policy revisions in IGIV licensure are an excellent representation of public and private collaboration, allowing physicians who treat immune deficient patients on a daily basis the opportunity to consult on an appropriate clinical trial design, while ensuring that patient safety has not been compromised.

In cooperation with FDA, IDF is conducting a retrospective data collection project to determine the incidence of serious infection for patients with common variable immunodeficiencies. The data obtained in this study, in conjunction with the published literature, will further assist in substantiating a historical control group of untreated patients.

And, in conclusion, I would just like to say thank you for your ongoing efforts, thank you to the agency, in efforts to help resolve this crisis in health care for

immune deficient patients.

DR. HOLLINGER: Thank you.

The next person who asked to speak was Robert Sandhaus from Alpha One Foundation.

DR. SANDHAUS: Thank you very much for letting me take a few minutes to make a few brief comments. Since this is the first time I have addressed this body, I would like to introduce myself. I am Dr. Sandy Sandhaus, Executive Vice President and Medical Director of the Alpha One Foundation, which is a not-for-profit foundation supporting research in and detection of alpha one antitrypsin deficiency, one of the most common life-threatening genetic disorders in the U.S. I have worked as a researcher and clinician in this area for the past 30 years, and in addition to my new position at the Alpha One Foundation, I currently direct the alpha one antitrypsin deficiency program at the National Jewish Medical and Research Center in Denver, and I co-direct the University of Colorado's new Genetic Lung Disease Center.

I have three related points I would briefly like to cover. First, I would like to thank the members of the Blood Products Advisory Committee and the Food and Drug Administration for the attention and support they have provided during the critical shortage of plasma-derived augmentation therapy for alpha one antitrypsin deficient

patients. Unfortunately, the shortage still exists, and as detection efforts move forward, the shortage can be expected to intensify, since it is estimated that currently only about 5 percent of the alpha one antitrypsin deficient patients in the United States have been identified.

My second point relates to the IGIV clinical endpoints just discussed. The Foundation applauds the work that has been accomplished in this area, and asks only that a similar effort be started in alpha one antitrypsin deficiency.

A major impediment to new drug development in alpha one antitrypsin deficiency is the requirement to demonstrate improvement in the rate of decline of pulmonary function and/or mortality, a clinical challenge and development program that can take many years to complete. If more rapid but relevant clinical and surrogate endpoints, such as reduction in the number or duration of pulmonary exacerbations, could be identified and accepted, additional therapies could be developed for this condition.

Finally, and based on review of the previous iteration of the proposals, the Alpha One Foundation would like to express its support for the alternative post-donation information algorithm proposed by the Plasma Protein Therapeutics Association. While we note the high ideals of patient safety preservation that are the basis of

all the proposed algorithms, we also see problems inherent in each.

The alpha one antitrypsin deficient patient population is most concerned at this time about access to safe augmentation therapy. We see both the agency's proposal and that of the PPTA as leading to a safer product, but we see an advantage in the PPTA's proposal in preventing major product quarantines and providing for proactive rather than retroactive safety enhancements. We see both proposals as being interim solutions while awaiting additional technological advances in unit and pool screening procedures.

And I suppose I should add that while we gratefully accept donations from any source, currently the Alpha One Foundation's budget is supported in less than 5 percent by industry donations.

I want to thank you for keeping patient safety and product availability as your guiding principles. The Alpha One Foundation looks forward to working with you on these same goals into the future.

DR. HOLLINGER: Thank you, Dr. Sandhaus?

Any questions?

[No response.]

DR. HOLLINGER: The next person who asked to speak was Dr. Al Smith, Calicivirus studies.

DR. SMITH: Well, first of all I would like to thank you for giving me just a couple of moments, and I think the things that I might be able to address here are relevant to some of the conversations I have heard just now and some that took place yesterday. It seems that there is a 3 percent hepatitis rate out there that just seems to hang there and doesn't go away, and we have seen that alluded to yesterday by Ian Williams out of CDC.

And then there are a series of viruses that have chased that--G, GB, C, G, and TT, and yesterday we heard about the SEN virus. And all of these, although they may be very important agents, don't seem to dip into this 3 percent. Then, just now, on four occasions, and I had not heard it at all in the last two days, we hear about concern for emerging diseases, which brings me to this particular agent, that is, Calicivirus.

Now, Calicivirus is, the family is divided into four genera, and one of them, vesivirus, is a peculiar virus in that its origins are in the ocean. Primary reservoirs are in the ocean. This virus amplifies in the ocean. And it has been of considerable importance to our livestock regulatory people for nearly 70 years because it causes a foreign animal disease, but only recently has been found to be zoonotic.

So once we establish this concern for a zoonotic

agent, then what do we do about it? Well, we have some data here which, if you can see that, and we have a table to follow on behind, across the bottom, the first blood group we looked at were normal. These were samples from a Red Cross testing lab. There's about 400 sera in that sample, and the percentage of positives within that sample is 5 percent. So we would say that a normal population might have 5 percent positives in it, and that, like we say, is a good large sample. This is an ELISA test.

Now, let me stop here and tell you, we have these viruses in isolation. We have cDNA primers or probes. We have monoclonal antibodies. We can replicate them in vitro. They are plaque purified, plaque passaged. I mean, we know what we're working with. So we have good serologic tests.

The next thing we looked at was a group of donors who had elevated ALTs--and a shopping trip, grant you, because these agents can cause an array of diseases, including encephalitis, myocarditis, abortion and so forth, and hepatitis--but we had the opportunity to look at elevated ALTs. We did that. The percentage positives out of 200 samples bumps to about 8 percent.

Okay, so we went on a further patient shopping trip and we looked at whether these could be blood-borne or a needle transmitted kind of thing. The next thing we looked at were only a few people in that group, there were

16, and these were people who had clinical hepatitis, non-A through wherever you want to go, G at the time, they said. Okay, so now these are 12 percent positive.

If you could move that down just a little, the next group we looked at, and not many people in that group, there were 10, but once again high risk for needle or blood transmission. These were people who were either hepatitis B or C positive, and small numbers, but the percent bumps to 20 percent.

The last group we looked at is a fair number now of 32 individuals, and these were post-transfusion or post-dialysis cases that were negative for all the known viral markers. And the percentages there go to 22 percent.

So if we can have the next table, please, the P values on that become fairly important. Let's look at the top one first, yes. You can only arrange these sample sets in a series of progression in terms of increasing risk for hepatitis.

If you do that, you can get 1 degree of freedom for your chi-square test, and you can see then that we end up with P values and chi-square values that are impressive, a P value of less than .001 when compared to the normal population, that is for a progression in blood transmission. And you can lump the various groups of those bottom four together, groups three, four and five, or groups two, three,

four and five, and the numbers still hold for you in terms of the statistical significance.

So we have already said we have tools to work with, and I just heard Terry Rice talk about emerging diseases. We have laid one out for you. The ocean is a spawning ground. These things occur in tremendous antigenic and pathotypic variability. They are an RNA virus. The quantity species concept is alive and well. Genomic scatter is phenomenal. PCR will not get you there at this point in time because of those factors.

And so I think the last point I would want to make is that this concept of emerging problems in industries such as yours is not just an ephemeral concept. There are things out there going on right now that we can talk about.

And now that I have given you just a small piece of the bad news, Dr. Iversen has come with me, and he is from AVI Biopharma, and wants to talk to you about what in my mind is an entire paradigm shift in terms of what you really do in terms of detection and prevention in some of these issues. And I do thank you.

DR. IVERSEN: Well, thank you for the opportunity to address this committee. I guess I drew some things on the top of that that don't show up very well. Is that true? Okay, they don't. Maybe they rubbed off.

Well, let me just point out that we're a company

that makes an antisense strategy towards inhibition of gene expression, and I've been working in this area for about 12 years. Our company has been working on this area for 20 years. The research has led to what we believe is an improved approach to synthetic DNA analogs which are capable of binding to messenger RNA and preventing gene expression. This is a very specific form of therapy.

And we met with Al Smith because we were interested in a virus that would be able to be the same virus in our testing systems, that is, a zoonotic type of infection where you could treat an animal that has the exact same virus as does a human, for the process of development. How little did we know that it would be found so broadly that animals who eat shellfish, for example, can obtain the infection, and people who then subsequently eat those domestic animals can also gain this infection.

And so we have set about trying to find an inhibitor for the expression of the Calicivirus, and what I am showing here is a Western blot. The Calicivirus capsid protein is at about 60 kilodaltons, and when we add our antisense sequence, as you can see, we suppress the expression of that capsid protein. We show a control in there of the 40 kilodalton actin protein as a loading control, to show that we loaded our blots in an equivalent manner.

And at the bottom, in that same set of experiments, we looked at the viral titer, and you can see we can reduce the viral titer at 1 micromolar concentration of viral oligomers, we can reduce viral titer to about between 60 and 80 percent. This is a highly reproducible result, and the reason for reducing only 80 percent is that our ability to deliver the oligomer in cell culture to cells is only about that efficient; it's about 80 percent efficient.

When we look at electron microscopy, we do see that we do not change the infection in cells that we do not deliver the oligomer to, but that when we do successfully deliver the oligomer, we almost entirely eradicate the infection.

What turns out to be very interesting from these observations is, however, that when this chemistry which has a neutral backbone, which we now have in clinical trial for targeting c-myc, and we are developing a drug strategy for the treatment of restenosis following angioplasty, that clinical trial has demonstrated that we can go GLP toxicology, we do have GMP manufacturing of this material, and the interesting observation was that when this unique neutral chemistry binds to the RNA, rather than all of the other approaches that have been tried to date, this does not cut the RNA.

And that is a very important observation, that when the oligomer pairs, the cell will actually degrade the RNA on either side of that duplex that is formed, and that duplex is so stable that the cell will actually export that, and we can detect that in blood and urine. This means that we have a scheme to not only inhibit the virus but also detect our success or detect the presence of virus by detecting the duplex, and we think that this has broad implications in use in improving the quality of the blood supply.

Thank you. I would be glad to answer any questions.

DR. HOLLINGER: Thank you, Dr. Iversen.

Is there anyone else from the public that wants to make a comment?

[No response.]

DR. HOLLINGER: If not, we're going to take a 15-minute break. We'll meet back here in 15 minutes and start the next session, where we will take up on the Blood Action Plan.

[Recess.]

DR. SMALLWOOD: We are ready to reconvene. May I ask all committee members to return to their seats?

I would just like to make an announcement to clear any confusion. Dr. Tabor had stated that a copy of his

algorithm would be available. That will not be available today. However, you may retrieve it from our web site; my understanding, that it has been placed on the web site so that you may look there to get a copy of the algorithm. Unfortunately, I do not have the correct web site address, so I do not want to misdirect you, but I'm sure that you will be able to find it, as I know you can. Thank you.

DR. HOLLINGER: We are going to begin with the Blood Action Plan: Supply Issues. This is informational, and we have asked Dr. Mary Gustafson or Captain Mary Gustafson to tell us about this.

CAPTAIN GUSTAFSON: Thank you. The title of this is "Implementation of the Blood Action Plan: Initiatives to Promote Blood Availability."

The Blood Action Plan has been presented to the BPAC before. However, there are several new members who may not be aware of the Blood Action Plan. It's a plan that was undertaken in 1997, and is a collection of initiatives in the blood area supported by the Department of Health and Human Services. The initiatives, many of which require interagency coordination, include activities related to recommendations from various oversight groups, including congressional committees, the General Accounting Office, the Inspector General, and the Institute of Medicine.

The true beauty of the action plan is that it

publicizes the work being performed and prioritizes the work efforts, which helps to ensure that the work efforts will result in a finished product. The complete action plan is available for viewing on the CBER web page.

Today I'm going to review with you the most recent addition to the Blood Action Plan. This addition includes initiatives to improve blood availability. The Blood Action Plan amendment on monitoring and increasing the blood supply resulted from a report requested by Dr. David Satcher, our Surgeon General and Assistant Secretary for Health, who also serves as the Blood Safety Director.

Dr. Satcher requested that a report addressing strategies to increase the blood supply be developed in light of two major developments. One was our recommendations that donors living in the United Kingdom for a cumulative period of six months from 1980 through 1996 be deferred, with an estimated nationwide decrease in blood collections of 2.2 percent. The second was a report from the National Blood Data Resource Center comparing 1997 blood collection and utilization data to data from 1994, with a projection that if everything remained the same, blood demand would overcome supply sometime in this year 2000.

A report was developed by an ad hoc interagency task group--some of you on the BPAC were members of this group--working under the auspices of the PHS Working Group