TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE

58TH MEETING

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Pages 1 thru 308

Rockville, Maryland
March 19, 1998

MILLER REPORTING COMPANY, INC.
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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE

58TH MEETING

Thursday, March 19, 1998

8:00 a.m.

Doubletree Hotel
Plaza I and II
1750 Rockville Pike
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
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PARTICIPANTS

F. Blaine Hollinger, M.D., Chairperson
Linda A. Smallwood, Ph.D. Executive Secretary

MEMBERS

John M. Boyle, Ph.D.
Peter Callero, M.D.
Corey S. Dubin
Norig Ellison, M.D.
Jerry A. Holmberg, Ph.D.
Rima F. Khabbaz, M.D.
Marion A. Koerper, M.D.
Jeanne V. Linden, M.D.
William J. Martone, M.D.
Mark A. Mitchell, M.D.
David F. Stroncek, M.D.
Joel I. Verter, Ph.D.

TEMPORARY VOTING MEMBERS

Pamela M. Hartigan, Ph.D.
Paul R. McCurdy, M.D.

NON-VOTING CONSUMER REPRESENTATIVE

Katherine E. Knowles

NON-VOTING INDUSTRY REPRESENTATIVE

Donald H. Buchholz, M.D.

C O N T E N T S

P R O C E E D I N G S

Statement of Conflict of Interest

DR. SMALLWOOD: Good morning and welcome to the 58th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary.

At this time, I will read the conflict of interest statement that applies to the proceedings for this meeting that will take place on March 19th and 20th, 1998. This announcement is made a part of the record to preclude even the appearance of a conflict of interest at this meeting of the Blood Products Advisory Committee on March 19th and 20th, 1998.

Pursuant to the authority granted under the Committee Charter, the Director of the FDA's Center for Biologics Evaluation and Research has appointed Pamela M. Hartigan, Ph.D. and Paul McCurdy, M.D., as temporary voting members. Based on the agenda made available and all reported financial interests as of this date, it has been determined that all interests in firms regulated by the Center for Biologics Evaluation and Research, which have been reported by the participating members, present no potential for a conflict of interest at this meeting.

The following disclosures are presented: Dr. John Boyle reported that he and his wife are unpaid trustees on the board of directors for a non-profit organization. This

organization receives unrelated funding from several regulated firms.

Dr. Donald Buchholz, the non-voting industry representative, is not subject to conflict of interest under Section 208. He is expected to have financial ties to industry.

Mr. Corey Dubin has an approved appearance determination regarding his litigation with several regulated firms.

Dr. Jerry Holmberg is a member of several Department of Defense committees involved with blood products, blood banks and computer software as part of his official government duties. In addition, he provides technical expertise for the American Red Cross under an NIH contract.

Dr. Rima Khabbaz' employer, the Centers for Disease Control, has unrelated CRADAs with two firms which could be affected by the general discussions.

Miss Katherine Knowles reported that her employer, a non-profit organization, provides AIDS training to blood bank employees. Miss Knowles participates in the teaching of this course. She receives no personal remuneration.

Dr. Marion Koerper reported that she consulted with a regulated firm on an unrelated topic. She received a fee for her services. In addition, she serves as the

principle investigator on an unrelated grant awarded from a regulated firm. She received financial support to attend a yearly investigators' meeting.

Dr. William Martone is a government employee detailed to the National Foundation for Infectious Diseases. The foundation received an unrelated donation and an unrelated grant from regulated firms. Dr. Martone receives no personal remuneration from the grant or the donation. Also, Dr. Martone's employer, the Centers for Disease Control, has unrelated CRADAs from regulated firms.

Dr. Paul McCurdy serves as a consultant to the National Heart, Blood and Lung Institute on unrelated topics. Also, his wife consults with a small regional blood bank. She receives a fee for her services and serves as a consultant to a blood foundation.

Dr. David Stroncek, a government employee, is the principle investigator on an unrelated grant from a regulated firm. He receives no remuneration from this grant. Also, he served on a past unrelated grant from a regulated firm which was awarded to the University of Minnesota. In addition, Dr. Stroncek was formerly a consultant to and an employee of the American Red Cross.

In the event that the discussions involve any other products or firms, not already on the agenda, for which an FDA participant has a financial interest, the

participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

In regard to FDA's invited guest speakers, the agency has determined that their service is essential. Their reported interests are being made public to allow meeting participants to objectively evaluate any presentation and/or comments by the speakers. The interests are as follows:

Dr. Michael Busch reported that he serves as an adviser the Alpha Therapeutic on an unrelated issue. He also collaborates with the community blood bank of Kansas City. In addition, the blood centers of the Pacific, with which he has an association, does quality assurance for the blood bank of Alaska.

Mr. Glen Satten reported that he is employed by the Centers for Disease Control, and consults with a regulated firm on unrelated issues.

Dr. Ronald Strauss did not have any financial interests to report.

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

Are there any declarations to be made at this time

from anyone?

[No response]

At this time, I would like to take the opportunity to introduce the most recently constituted Blood Products Advisory Committee, principally in its entirety at this time. As I call the name of the member, would you please raise your hand?

The Chairman, Dr. Blaine Hollinger, Dr. John Boyle, Dr. Peter Callero, Mr. Corey Dubin, Dr. Norig Ellison, Dr. Jerry Holmberg. Dr. Richard Kagan is a member but he is absent for this meeting. Dr. Rima Khabbaz, Dr. Marion Koerper, Dr. Jeanne Linden, Mr. William Martone, Dr. Mark Mitchell, Dr. Kenrad Nelson. I believe Dr. Nelson will arrive later, Dr. Ohene-Frempong is a member but he will be absent for this meeting. Dr. David Stroncek, Dr. Joel Verter.

Our temporary voting members -- Dr. Pamela Hartigan has not arrived, and Dr. Paul McCurdy. Our non-voting consumer representative, Miss Katherine Knowles, and our non-voting industry representative, Dr. Donald Buchholz. This is the Blood Products Advisory Committee.

I would also just like to make an administrative announcement, and that is that we appreciate the concern and the willingness for all individuals that would like to participate in the Blood Products Advisory Committee

meetings. However, I would just like to remind everyone that at the time of the meeting it is somewhat difficult to provide the committee members with material at the last minute. They will not have an appropriate opportunity to read all of the material. So, just a reminder, if we could have material a little sooner so that I may make an appropriate distribution, and I thank you.

At this time, I would like to turn the proceedings over to the Chairman, Dr. Hollinger.

Welcome and Opening Remarks

DR. HOLLINGER: Thank you, Linda, and we want to thank you for getting all of the information that we have at the present time. There is a lot of information here.

Today is a good day to have a meeting. It is not very nice outside, so we might as well be inside, doing things. We do have a lot of very important issues raised today, as we do at most of the committee meetings. So, we are going to start out initially, as we always do, with committee updates. These are things which have usually been discussed in the past and have either been acted on are at least discussed at length. So, we will start out the first part of the meeting with Dr. Elliott Cowan, who is going to discuss the HTLV-I and II issue, which have some important ramifications for the blood banking industry.

Committee Updates

HTLV-I/II

DR. COWAN: Thank you, Dr. Hollinger.

[Slide]

My purpose this morning is to provide this committee with an update on issues related to donor screening for antibodies to HTLV-II. At the December, 1996 meeting of the Blood Products Advisory Committee, the committee recommended that donated blood be routinely screened for antibodies to HTLV-II.

On August 15, 1997 FDA issued the guidance for industry on donor screening for antibodies to HTLV-II, which included a recommendation that blood establishments implement screening of whole blood and blood components intended for use in transfusion and source leukocytes intended for manufacturing use. Screening was to be implemented within 6 months of the licensing of the first test kit labeled for this purpose.

[Slide]

The first kit, the Abbott HTLV-I, HTLV-II EIA was licensed on August 15, 1997. Since that time, on January 17, 1998, FDA licensed a second test kit to screen for antibodies to HTLV-II, the Vironostika HTLV-I/II Microelisa System from Organon Teknika. Also, the date for implementation of screening units from donors for antibodies to HTLV-II passed, occurring on February 15, and testing is

now expected to be in place in blood establishments in the U.S.

[Slide]

Two panels have also been developed to support screening for antibodies to HTLV-II. The first is HTLV-II reference panel 1, which has been provided to all manufacturers of HTLV-I or HTLV-II test kits. It is designed to aid in the lot release process by ensuring that each lot of a screening test kit meets consistent levels of sensitivity for antibodies to HTLV viral proteins. This panel is comprised of eight members. Six of the panel members are derived from sera containing antibodies to HTLV-II and are diluted in a nonreactive serum pool. Three of these members must be detected and the other three are borderline reactive and may or may not test positive on a particular master lot of kits. The remaining two panel members are pools of nonreactive sera from uninfected individuals.

[Slide]

The second panel is an HTLV-II qualification panel 1. The purpose of this panel is to aid in determining the sensitivity of test kits for antibodies to HTLV-II, and it is used to assess the validity of labeling claims for the detection of antibodies to HTLV-II by screening tests that lack HTLV-II antigens. It consists of 117 members, and 79

of these members are specimens that the FDA had accumulated over the years but were originally detected by screening with licensed HTLV-I test kits. The remaining 38 panel members are HTLV-II antibody-positive specimens that had not been initially identified by screening using a licensed HTLV-I EIA.

It is anticipated that more panel members will eventually be added to generate an increasingly diverse set of specimens that can be used to determine the efficacy of current screening for antibodies to HTLV-II. These new specimens will form the basis for future qualification panels.

[Slide]

One last item I would like to touch on is the issue of supplemental tests for HTLV-I and HTLV-II, an issue which has caused some concern in the blood banking community in recent months.

First, in the guidance document issued last August, FDA indicated that it viewed supplemental testing as useful in donor and patient testing, notification and counseling by aiding in the interpretation of a repeatedly reactive EIA test result. I should point out though that no supplemental tests are currently licensed for this purpose. Until recently, products labeled for research use only, or RUO, have been used for clinical purposes outside of an IND

exemption. However, RUO tests should not be used routinely for donor or patient testing or counseling, and such use resulted in an importation ban for one such test kit.

Since that time, FDA has been informed by blood establishments that they are no longer able to counsel donors, and are having to defer high volume donors with what they believe are false-positive HTLV-EIA results.

[Slide]

FDA recognizes that additional, more specific testing could be done under an IND. Such an IND could be submitted by a manufacturer or a product user, such as blood organizations, or a group of blood establishments. It is FDA's expectation that such INDs would be supportive of a test kit manufacturer's application for product approval.

The use of a second licensed EIA test, which was discussed in last August's guidance document, as a value in release of units from quarantined donor referral, may also be of value as an additional test for purposes of counseling.

With regard to long-term solutions, FDA is currently exploring options to encourage manufacturers to develop these products and bring them to licensure. I would be happy to discuss this further with any interested parties. I can be reached at the address and phone number which are listed on the cover page of the August, 1997

guidance to industry for screening for antibodies to HTLV-II. Thank you very much.

DR. HOLLINGER: Are there any questions from the committee? I know we can do this at the end but I think we might as well handle any questions here. Yes, Dr. McCurdy?

DR. MCCURDY: I would like to make a brief comment. The National Heart, Lung and Blood Institute, as everybody knows, has a responsibility for safety of the blood supply and developing tests, and so forth, and we have no formal program focused on this type of supplemental test but we would be pleased to have some discussions also if there is anybody that has an interest in developing and licensing such a test.

DR. HOLLINGER: Yes, I don't understand this, the two terms, research use only and investigation. This is government's way of making a change here? I mean, what is required of investigational or an IND instead of a research use only?

DR. COWAN: It is a difficult distinction which has become somewhat blurred over the years. An investigational test would be one which would be used under an IND. In other words, the use of that test would have to be filed with FDA through the submission of an IND. Now, it is certainly possible that a research only test could be used in a clinical setting, but an exemption to filing an

IND would have to be submitted by that particular company, such that FDA could review the use and determine that it would be exempt from filing an IND so it could be used under clinical conditions.

DR. HOLLINGER: But it seems like you place the blood banking community in a really tenuous position. You tell them that you want them to counsel their members with a test that probably has a fairly high false-positive rate but do not provide them any specific outlet of how to do this. There are some manufacturers that have some supplemental tests and maybe, as you mentioned, through research use only or an IND would be the way to go. Even though there may not be a disease associated with HTLV-II, a human disease, one still has a group of patients out there who are going to be positive for one or the other and they are still going to need to be counseled, and certainly a supplemental test of some sort would be useful. As I say, I think there is a real concern for how this is going to be handled without them not being in compliance with what the FDA wants them to do.

DR. COWAN: I understand your concern. It is a difficult situation. I think the tack that we have been taking is that when a test is used for clinical purposes, especially with regard to the screening of blood donors, the FDA needs to have some control over that test, and anyone

developing a test or people using that test should be confident that it will be giving a true result, which to our mind is the purpose of licensure and oversight. Our job now is to determine how we can encourage manufacturers to work within our framework so that we can use these tests in an appropriate way.

DR. KHABBAZ: I am a little puzzled. The use of unlicensed supplementary tests for HTLV-I has been going on for ten years, since licensing of HTLV-I tests. I am puzzled as to why it is coming to a head with the licensure of HTLV-II tests. I view them not as useful but essential. You can't counsel somebody as to HTLV-I/II false positivity without these tests. Can you tell us why it is coming to a head now with the HTLV-II test, the timing of that?

DR. COWAN: That is an excellent question. Again, it has been a very difficult area, and within FDA I think there was an appreciation within other parts of the agency that the use of these tests outside of an IND or IND exemption was considered not appropriate. It was a relatively recent realization, and it was decided to act on it at this time to try to tighten up the controls. I think that is about the best answer that I can give you at this point. It was not intended to occur simultaneously with the HTLV-II licensure. That was purely coincidental.

DR. KHABBAZ: Thanks.

DR. HOLLINGER: Thank you, Dr. Cowan.

DR. COWAN: Thank you very much.

DR. HOLLINGER: The next update is by Robin Biswas, who is going to give us an update on the HCV partner deferral.

HCV Partner Deferral

DR. BISWAS: Good morning. At the December, 1997 Blood Products Advisory Committee meeting the issue of whether or not sexual partners of persons who test positive to antibody to hepatitis C virus should be deferred was addressed. FDA did not request committee recommendations at the December meeting as it was not clear before that meeting whether sufficient scientific data from the studies would be available for presentation. It was also thought desirable that the committee should have sufficient time to consider the scientific information.

At the December meeting, three scientists from the NIH, CDC and Harvard School of Public Health presented data from studies involving anti-HCV negative spouses or sexual partners of individuals with anti-HCV. The data presented indicated that transmission between sexual partners or spouses occurs very rarely, if at all.

Based on the evidence that sexual partners of HCV-positive persons are not at significantly increased risk for HCV, FDA is not developing a donor deferral policy for such

partners at this time. This issue will be brought to a future meeting of BPAC if emerging scientific data suggest that a risk exists which should be addressed.

DR. HOLLINGER: Thank you. Any discussion?

[No response]

The next update is on IGIV shortage. Dr. Golding is going to tell us about the problems that have occurred this past year and what has transpired since that period of time, and what were some of the reasons for it.

IGIV Shortages

[Slide]

DR. GOLDING: First of all, how do we know that there is an IGIV shortage? The reasons are explained on this slide. During November-December of 1997, the FDA received numerous phone calls, about 20 to 30 per day, from physicians, pharmacists and pharmaceutical distributors about difficulties in obtaining sufficient amounts of immune globulin intravenous for their patients.

[Slide]

The causes of the IGIV shortage -- we think these are multifactorial. I mention the ones we think are the most important on this slide. The first one I mention is decreases in production. Then we have product recalls. Some of these are related to CJD; withdrawals, also related to CJD; and progressive increasing usage. I will go into

this in a lot more detail later, and this may be the single most important reason for the IGIV shortage. That is, a proliferation of indications and usage over the last five to ten years of a supply which has not essentially increased and has probably decreased during 1997. This other possible cause here is hoarding or other market phenomena.

[Slide]

Just quickly, I am not going to do this in detail, but there are FDA-approved indications. There is off-label use. Some of the off-label use is believed to be due to well characterized clinical studies that justify that usage. On the other hand, there is off-label use which is based on anecdotal reports.

Now, I don't think it is the job of the FDA to dictate to physicians how to use this product, but we did send out a letter trying to indicate that the use should be prioritized, and it should be prioritized based on the indications. The indications should be prioritized on those that have a clinical trial basis for the use of it. These are the FDA-approved indications: primary immunodeficiency, immune-mediated thrombocytopenia or ITP, Kawasaki disease --

[Slide]

-- bone marrow transplantation, chronic B-cell lymphocytic leukemia and, actually, this is the newest indication, approved in January of 1996, pediatric HIV

infection.

[Slide]

In addition to these indications, there is off-label use, but some of the off-label use is regarded by some of the major clinical centers in this country as the standard of care. Again, I am not going to go through the listing in a lot of detail, but just to mention a few of the conditions, chronic inflammatory demyelating polyneuropathies, or CIDP, Guillain-Barre syndrome, multifocal multineuropathy --

[Slide]

-- and on and on and on. There is a whole list of autoimmune diseases that are commonly treated with IGIV.

[Slide]

Then we have off-label for use which, as far as we can tell, there are no clinical trials which prove efficacy. In any event, many patients out there are receiving IGIV for these conditions: multiple sclerosis, optic neuritis, and many of these other conditions, including common conditions such as rheumatoid arthritis.

[Slide]

There are many hematological disorders that are treated with IGIV.

[Slide]

So, in an analysis of the shortage, or the causes

of the shortage, we think that increased usage for approved and non-approved indications has increased progressively and dramatically during the last five to ten years. Production has remained flat, except for a decrease during 1997 and this was partly due to a voluntary suspension of production by one of the manufacturers responding to a compliance action.

[Slide]

Multiple IGIV lots were withdrawn because donors were later found to be at risk or donors developed CJD. Many of these lots were distributed, and largely consumed before the withdrawal came into effect. However, implicated intermediate products at the firms cannot be processed.

[Slide]

What are the FDA actions? What have we done to try and alleviate this shortage? The lot release process has been shortened from 2-3 weeks to 2-7 days. The FDA has been working with manufacturers to facilitate increased production and distribution without compromising the safety or efficacy of the product.

[Slide]

This involved discussions with industry on plans to comply with current Good Manufacturing Practices without disrupting production, and the FDA has asked manufacturers to establish inventory reserves for emergency use that can

be accessed through 1-800 numbers.

[Slide]

The Immunodeficiency Foundation and FDA have also held discussions to facilitate the availability of IGIV. A "dear doctor" letter has been sent out to physicians to provide guidance for prioritizing the use of IGIV, and this letter lists the 1-800 numbers which are now in operation.

[Slide]

IGIV lots that were placed on hold because the albumin excipient that was produced from a pool containing a unit derived from a donor who was at risk for CJD -- in light of the shortage and based on recommendations of the TSE advisory committee, these lots were released for emergency use, with special labeling regarding the theoretical risk of CJD.

[Slide]

What is the current status? Well, the phone calls regarding the IGIV supply received by the Office of Communications and Training at the FDA have decreased from 20-30 per day to 5-10 per day. Between November of 1997 to February of 1998 there has been approximately a 40% increase in the number of lots released through the FDA. These are lots released per month, compared to the period before 1997.

[Slide]

IGIV is available on an emergency basis using the

1-800 numbers directly to the companies, through the Immunodeficiency Foundation and through a distributor named FFF. However, inventories of major supplies and pharmacies at major medical centers remain low.

[Slide]

So, although we think we have alleviated the shortage, the shortage is still out there and it is going to take months, if not years, to return to the situation where IGIV is in adequate supply. Thank you.

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

DR. BOYLE: Good morning. In asking some of these questions I would like some clarification, in part because I am a trustee of the Immunodeficiency Foundation. My son was one who was turned away because they couldn't get the stuff. So, let me ask you just a couple of questions from your statement.

Number one, you are talking about the indication of the magnitude of the crisis as being calls being between 20-30 a day over the November-December period. If my math is correct, that talks about 500-1000 calls. Is that approximately correct?

DR. GOLDING: That is approximately correct.

DR. BOYLE: Okay. I believe the Immunodeficiency Foundation has received over 2000 calls, but some of those were from patients.

The second issue is that you are talking about the perceived decline in the degree of the shortage based upon the number of calls you are receiving. My assumption is that when people call -- let me not say that. Were you able to provide product or do something else effectively for those people who called, such that if they had another occurrence they would call back at a later point in time? Or, does the decline in calls reflect the inability to do something and, hence, you don't call again?

DR. GOLDING: Well, the calls were made, for example, from pharmacists from major medical centers across the country. Some of them were made to OCTMA and they were referred to us and we, including myself, spoke directly with the pharmacists saying at the time we were aware which company had what, and we could direct them to a particular company. So, as you know, many of these pharmacists are dealing with a particular company and have a contract and are not aware of what other companies have at a particular time.

So, one mechanism was to be aware of what inventories were out there and to direct pharmacists to companies that had material. Another mechanism that developed was developed through the Immunodeficiency Foundation where people would be referred -- physicians and pharmacists would be referred to IDF and they would then

have access to the 1-800 numbers of all the companies and they would divert them in that way.

What also happened, and I think it was a major event because there was a large amount of material that was being held by Alpha Therapeutic because of CJD -- that material became available under emergency use. A large number of the callers were able to access that material. Now, the FFF Company has an agreement with Centeon and with Alpha, and will triage the calls that come in from physicians and pharmacists.

So, you know, it is very hard to be absolutely sure what is going on, and if the number of calls is decreasing because people just throw up their hands and say, "well, we can't get any material." But I know of multiple situations where we were able to direct pharmacists to companies or to organizations that were able to help them and provide them with material.

DR. BOYLE: So, the number of calls could have declined because you were successful in the first call in directing them to the appropriate person to contact, or because people gave up, or because the shortage has declined. It could be any of those three things.

DR. GOLDING: Yes, that is correct, but we are continuing to monitor the situation and I don't think, by any means, that it is solved. I think there is a shortage

out there, and I think we still have to be very vigilant in terms of monitoring what is going on. One of the things we are monitoring, now that we have emergency phone calls in place at the companies and through some distributors, we need to monitor those to see how many calls they are getting, and how many of those calls are leading to the caller being supplied with product. So, that situation needs to be monitored on a continuous basis.

DR. BOYLE: Let me ask for clarification of one other statement that you made, which is that production has remained flat and it is based on lot release data. The question I have is do you have information on the number of units produced or the number of units shipped over this period of time?

DR. GOLDING: Well, no. Because the FDA has a lot release program, some companies have to send in material for lot release, others are on surveillance and they have to send just reports of what they have released. So, we have access to that information but we don't have direct access to information from the companies about how much they are actually shipping out to their various distributors, and how much they are shipping to this country or how much they are shipping overseas. So, there are many unknowns in the distribution that are very hard to get at.

DR. BOYLE: So, just to summarize, in terms of

trying to analyze the nature and the causes of the situation, the FDA does not know the number of units produced. It does not know the number of units shipped. It does not know the number of units shipped outside the United States for export. Certainly, if it doesn't know that, it doesn't know how many units are being used for off-label versus on-label.

DR. GOLDING: That is correct. Just your last point, you know, we are trying to get this information. It is not as if we are just sitting there, not aware that we don't know this, but it is very difficult to get this information in an organized manner.

But regarding the off-label use, it is very clear from talking to physicians at major clinical centers and talking to the advisory committee of the IDF, that it is the impression of all those physicians that off-label use accounts for 50-70% of the use of immunoglobulin, IGIV.

DR. BOYLE: I would just like to make a final statement that in a regulated industry it is amazing that this kind of information is not available to the regulator, much less, say, to any type of scientific advisory board that is supposed to make decisions on these types of things.

MR. DUBIN: John, I just smiled because this is something that we have been saying for the two and a half or three years that I have been sitting here. We continue to

urge the production of this kind of data because the committee is consistently asked to make recommendations regarding what ultimately are important public policy decisions, and we certainly feel somewhat hamstrung regularly, and somewhat frustrated that the regulatory body -- not only are we talking about IGIV, we are talking about this in Factor VIII and IX, that we can't get these kind of numbers. This is a struggle that is ongoing that I think both the Blood Products Advisory Committee and the FDA as a whole is going to have to look at. I think sometimes we hear that this is proprietary information. We understand, I think, the boundary between what is proprietary and what is not, but we are still being asked to reflect on important decisions where this data is a critical component.

DR. HOLLINGER: Thank you. Thank you, Dr. Golding. Dr. Indira Hewlett is here now and she will give us an update on male/male sex deferral.

Male/Male Sex Deferral

DR. HEWLETT: Good morning.

[Slide]

At the December, 1997 meeting of the Blood Products Advisory Committee, we brought the issue of deferral from blood donations of men who had sex with men since 1977. This issue was, in fact, presented to the committee by Andy Dayton. He is not here today so I am

going to be doing the update on where we stand on this issue.

[Slide]

The original policy had been part of FDA strategy of temporary deferral of donors who had experienced high risk exposure, and lifetime deferral of donors from groups identified as high risk based on behavior. Male homosexual activity had been identified as defining a high risk group for HIV, and a deferral criterion was identified based on such behavior. 1977 had been chosen to limit the deferral to the time of the AIDS epidemic in the United States.

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At the December meeting we presented a quantitative analysis which took into account the best available data on homosexuality prevalence rates, test-seeking behavior, donor truthfulness issues, prevalence and incidence of the three major viruses, HIV, HBV and HCV, in the male homosexual population, and error rates in blood screening. The analysis focused on how changes in policy would quantitatively affect the number of infected units that might be introduced into the blood supply.

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The analysis demonstrated that donor truthfulness issues and test-seeking behavior made quantitatively insignificant contributions to possible effects in changes

in policy. Furthermore, for both the 1- and the 5-year deferral periods HIV incidence rates, that is, donors in the window period, would also make quantitatively insignificant contributions to the effects of changing policy.

[Slide]

However, interestingly, it turned out that prevalence issues were, in fact, the key consideration. Switching from a 1- or a 5-year deferral policy for MSM behavior would theoretically result in an additional 2000 to 1000 additional HIV-positive units being donated per year respectively. The number should be inverse from what is shown on the slide.

Given that the screening test sensitivity is close to 100%, this normally should not present any danger. However, it is possible that blood bank errors or the emergence of new undetectable strains of HIV, for instance, could allow some of these units to slip through the screening process. Unfortunately, blood bank error rates are poorly quantified, and it is impossible to predict the frequency of newly emerging undetectable strains.

Currently, about 100-1500 HIV-positive units per year in the U.S. make it past the questionnaire stage and are picked up by blood screening assays. Whatever risk this number poses to the blood supply would, therefore, be at least doubled for either a 1- or a 5-year deferral policy.

[Slide]

The consensus of the committee at the time was that a policy change seemed appropriate but they felt that the issue warranted further study, and the agency was requested to return to the committee with a more exhaustive analysis, including better modeling of the policy options.

So, towards this end, the agency is in the early stages of planning a workshop on the topic of blood donation deferral of men who have had sex with other men. This will be part of a workshop on donor suitability issues planned for the fall of this year. This workshop may also include other issues, such as deferral of IV drug users and deferral of sex workers and their clients.

The MSM portion of this workshop will focus on accurate determinations of the prevalence and incidence in the MSM population of HIV, HBV and HCV; examination of male homosexual activity patterns; errors in blood banking; newly emerging pathogens; truthfulness issues and test-seeking behavior, as well as questionnaire design. The utility of deferring but testing first-time donors with MSM history will also be discussed as an option.

[Slide]

We hope that this workshop will allow more accurate quantitative estimates of the effects of changes in donor deferral policy and that it will indicate what

relevant studies are most urgently needed to refine those estimates appropriately. Thank you.

DR. HOLLINGER: Thank you.

MR. DUBIN: Just quick comments. One, we are pleased to see staff doing this workshop and moving in this area in a fairly in-depth way. We recommended in a memo we sent to the FDA our science and medicine working group, in December, and we certainly continue to urge that we think the policies, rather than focused on individuals should be focused on risk behaviors associated with the transmission of virus rather than individual communities or groups of people. Thank you.

DR. HEWLETT: Thank you.

MR. DUBIN: That report wasn't one of the written reports in the materials we got. Is there a chance we can get copies of the slides?

DR. HEWLETT: Sure, yes.

MR. DUBIN: That would be helpful for us. Thank you.

DR. HEWLETT: Thank you.

DR. HOLMBERG: I would also recommend that when this workshop takes place in the fall maybe the agency can cluster it to the IPAC time so that the out-of-community members can make their presence.

DR. HEWLETT: I think that is what is planned at

the moment, but we are not sure about the dates yet. You know, it will depend on what dates that are available but we hope to have it in the fall, possibly sometime in September.

DR. HOLLINGER: Thank you. The final update is on pool size, and Dr. Lynch is going to provide us that.

Pool Size

DR. LYNCH: Good morning.

[Slide]

This is an issue that has been considered by the committee on three prior occasions, most recently in September of last year, where it was a component of the voluntary safety initiative proposed by the IPPIA. If you recall, the elements of that proposal included a 60,000 donor limit on plasma pools used to manufacture plasma derivatives. This would include all components in the final container, including stabilizer protein, and would apply equally to products made from source and recovered plasma. The products specifically included in this proposal were the albumin products, IGIV, Factor VIII and Factor IX.

In January of this year, IPPIA communicated to CBER that their members intended to implement this plan by starting all new plasma fractionations within the limits set by the end of the first quarter, and by the end of the year all pipeline products, that is, inventory extant at the end of the first quarter of this year would be completed by the

end of the year.

Before turning to the steps that were taken to implement this plan, it might be useful to consider the state of manufacturing prior to the imposition of these limits.

[Slide]

This is a partial summary of some of the results of an audit that FDA requested the manufacturers of plasma derivatives to conduct late last year. Shown on this slide are two products, albumin and IGIV. On each graph the number of lots produced is shown on the Y axis, and the size of those lots is shown on the X axis. The 60,000 donor limit is indicated by the broken lines. The top graph represents product made from source plasma; the bottom graph is recovered plasma.

Several things are evident from this slide. First of all, for the majority of the bulk of product made the 60,000 donor limit is, in fact, observed. In the case of IGIV, however, these numbers do not take into account the albumin excipient. However, for at least source plasma the addition of albumin made at typical scales would not increase most of the lots of IGIV produced above the limit. However, in all cases you can see that some lots are, in fact, produced that exceed the 60,000 donor limit. This will be the first target of any cap on pool size.

[Slide]

This is similar data for Factor VIII, and the situation is very similar. The bulk of material, particularly made from source plasma, is within the 60,000 donor limit. The addition of representative lots of albumin to this would not push the bulk of material above the limit. However, there are outliers here that are made from very much larger pool sizes. For recovered plasma the situation is the same, but when one adds in the contribution of albumin the size of the plasma pools would be increased beyond the limit. So, additional action would have to be taken there. I will return to that in a moment.

[Slide]

Several steps have been taken by the manufacturers. First of all, recording and tracking systems have been put in place that trace the number of donors or donations, as the system allows, through the manufacturing process to the final container product. Where donors can be traced the cap is expressed in terms of the number of donors represented in the final container. However, if discrete numbers of donors cannot be tracked, donations are used as the cap instead. This is a more stringent limit. All downstream pooling of intermediates are captured by the system, and the addition of albumin is added into the final pool size.

As part of the record review on release of final product, quality assurance review of pool size has been included in all cases. This assures that the limitation is adhered to.

[Slide]

Now, having that information in hand, manufacturing decisions can be made based on it, including selecting pools of intermediates, selecting intermediate lots for pooling based on the size on the pools of each intermediate to assure that extraordinarily large intermediates are not combined one way or another.

Selective use of albumin is also an example. Albumin that is derived from smaller pool sizes can be selected to stabilize products such as IGIV and Factor VIII. In one case it has been possible to pair the albumin used as an excipient with the Factor VIII that it is used to stabilize.

Finally, pooling and remanufacturing of small volumes of material, such as inspectional and packaging rejects, laboratory residuals, and so on, has been eliminated in all cases.

Finally, in some cases it has been possible to manage the donation process itself, such that a collection center can accrue donations from individual donors to increase the repeat donation rate.

[Slide]

I want to return to the issue of recovered plasma. The pool sizes for products made with recovered plasma are larger. This is expected because the volume of those donations is smaller and the repeat donation rate is lower for recovered plasma than it is for source plasma.

This is, again, the example from IGIV. You can see that the bulk of the material is very close to the limit as it has been proposed, and the addition of albumin would push much of this over that limit.

Now, CBER has received a rather detailed report from one manufacturer of IGIV that makes this product from recovered plasma. Although considerable progress has been made, the manufacturer's process is constrained by a penultimate pooling step just before the product is lyophilized, freeze-dried. This pooling is done to make optimal use of the capacity of the freeze-drying units. Should this pooling step be eliminated in order to conform production to the 60,000 donor limit, the manufacturer claims that a 30-40% drop in product would result.

We are still studying this report and have no conclusions at this time. But, with that one caveat in mind, the 60,000 donor limit, first of all, appears achievable; secondly, would accomplish significant gains in reducing the production of product made from extremely large

pools; and the third can probably be accomplished without significantly impacting production capacity. Thank you.

DR. HOLLINGER: Yes, Dr. Boyle?

DR. BOYLE: Could we obtain copies of those slides? They don't appear to be part of our materials.

DR. LYNCH: Yes, I can get those to you this afternoon.

DR. BOYLE: Could we also get the methodology upon which the audit was based since that would be extremely interesting from our perspective? In other words, you described an audit but we don't know whether all manufacturers were included in the audit, over what period of time.

DR. LYNCH: In brief, we gleaned the data from the nine largest manufacturers. There are more than that but this captures the vast majority of product that is made, and certainly all of the major products that are manufactured, and we requested data from a representative 6-month period.

DR. BOYLE: So, do we have that in proportion to how much they are manufacturing so that we have a snapshot of what the total product looks like?

DR. LYNCH: Yes, we actually have that data. I presented it in terms of lots, as you suggested in an earlier comment, but in fact we do have total production as well and that can be broken out.

DR. BOYLE: That would be terrific. One last question, that is, you raised the issue of one manufacturer who indicates that they cannot comply with the 60,000 limit without production loss. Can you give us some sense of what the magnitude of that loss is in the total amount produced?

DR. LYNCH: Yes, we tried to address that. Although marketing data should be fairly straightforward, in fact we have conflicting reports on the exact market share that that manufacturer has. Without knowing that, without having a hard number there, it is very difficult to assess what the impact on the overall supply would be. So, we are trying to resolve that discrepancy.

DR. HOLLINGER: Dr. Lynch, you are talking about 60,000 donors, not donations.

DR. LYNCH: Right, 60,000 donors in the case where the individual donors can, in fact, be accounted for. Not everyone has that capacity. If one cannot trace donors, then the cap is expressed in terms of donations. Now, that would produce, on a volume basis, smaller pools than if one were to count donors and allow for a repeated donation.

DR. HOLLINGER: But the limit is basically on donors if you can count them?

DR. LYNCH: That is correct.

DR. STRONCEK: If, for example, you are making a lot of IGIV and you have to add a small amount of albumin,

does a 60,000 donor limit mean the IGIV can be made from 60,000 donors plus the albumin can be made from another 60,000 donors?

DR. LYNCH: No. No, it is the sum of the donors to which both components can be traced. So in a trivial example, if the albumin had 30,000 and the IGIV could be traced to 30,000 that would just meet the limit.

DR. STRONCEK: Thank you.

DR. MITCHELL: I see that you have done some analysis as to whether it is possible to do this. I guess my question is does it provide an additional amount of protection? Do you have some sense as to how much additional protection this would provide if we eliminate the much larger lots?

DR. LYNCH: Yes, we have performed a number of risk analyses. I have to tell you that in my view, for the majority of agents with a reasonable prevalence this will not have much of an impact on risk. This has been considered at length in prior meetings of this committee. So, I won't review that now. However, in the marginal cases where one has an extremely rare agent emerging into the donor population, whose prevalence is extremely low, we think that this limit would impact the rate of the risk of transmitting that agent through manufactured products.

DR. HOLLINGER: Dr. Linden, do you have a final

comment?

DR. LINDEN: Based on your presentation and the information sent to us, it seems that very few of the manufacturers link the lot of the excipient albumin to the other product and, yet, it is done with some and is clearly feasible. Can you explain to me, from a logistics standpoint, why the manufacturers are so reluctant to do that? I mean, isn't it a matter of just holding the one product until the other is ready, or do I not know enough about the process?

DR. LYNCH: That is a reasonable question. I don't think it is a question of reluctance. I think it is a question of what the approved manufacturing process allows. You must recall that the manufacturers have very little leeway in how they can modify their manufacturing practices. Those are constrained by their product licenses. So if, for example, one does not have the ability to store one or the other of the components for a sufficient period of time to allow for full manufacturing of the other to catch up, one couldn't pair those two. In the case that I cited, the pertinent license does allow for that storage period but that is not true in all cases.

The other problem arises where manufacturing is done at more than one location. An intermediate can be shipped to a second site for finishing, whereas the

excipient would remain at the original site of manufacture, and that raises certain problems in coordinating those two activities. Now, it is certainly not impossible to achieve this but it is not a trivial matter to simply match up these two components.

DR. HOLLINGER: Thank you. This concludes the updates. Dr. Epstein, I wonder if perhaps at the next meeting you could just have somebody provide us with a little update on the issues that Mr. Dubin and Dr. Boyle indicated about the difficulties in determining these issues about export of IGIV or numbers of vials available, things like this that you all face, so we can get an appreciation of why this is a problem either legally, proprietorially or otherwise?

DR. EPSTEIN: We would be happy to do that. Let me just remark that the PHS advisory committee, at the January meeting, indicated its desire to look at the supply and other issues. We can certainly come back with a summary more globally about the whole issue as to what extent FDA has authority to look at the supply, and we would be happy to come back and summarize for you.

DR. HOLLINGER: I would appreciate it. That would be helpful to us. We are going to move on to the sessions that need some input from the committee and discussions about recommendations, and so on. First is the summary of

emerging infections plan. The initial presentation will be by Dr. Tabor on this, and then we will move to some of the comments from industry.

Summary of Emerging Infections Plan

DR. TABOR: In recent years, the world supplies of blood for transfusion and plasma for fractionation have been beset by the emergence of new infectious agents that have challenged the scientific community's ability to develop ways to exclude or inactivate them.

Twenty years ago the primary known infectious agents that were threats to blood were the hepatitis B virus, non A-non B hepatitis, which we now know was hepatitis C virus in about 90% of cases, and rare cases of cytomegalovirus. Other threats included syphilis which has been essentially eliminated by screening tests, and other bacterial infections which were felt to be adequately controlled by cold storage.

By the early 1980s it was recognized that new agents could enter the blood supply. Although the first of these to be recognized was human T-lymphotropic virus type I and HTLV-I. In fact, the first to raise intense concern was the human immunodeficiency virus type 1, HIV-1.

At first it was felt that these were viruses that have recently entered the human population and have been transported to many continents by the pace of modern travel.

Later, it was recognized that HIV-1 had probably been infecting humans in isolated areas of the world for several decades or perhaps even longer, and might have entered the human population from non-human primates. In the case of HTLV-I, it is possible that this virus existed as long ago as the 16th century based on a comparison of the geographic distribution of high prevalence countries for the virus and the history of journeys of discovery and trade in the past centuries.

However, infectious diseases can emerge from various sources. New variants can emerge from known agents, having acquired increased pathogenicity. Agents that normally affect animals can acquire the ability to infect humans, and previously unrecognized infectious agents in humans can become recognized due to increased vigilance or due to increased surveillance.

The wide-ranging travel from one continent to another, from rain forests to industrial cities, has made the planet a global village in which an emerging infectious disease anywhere in the world can represent a potential threat to the blood supply in the United States. These facts make worldwide surveillance and constant laboratory readiness essential for a safe blood supply.

Now, the world looks to the United States for leadership in making the blood supply safe from emerging

infectious agents. This is due in part to worldwide recognition that the U.S. Food and Drug Administration is tougher and more vigilant than any similar organization in any other country. The same view makes these other countries look to us for leadership in approving and disapproving pharmaceutical drugs as well. But this is also due to recognition that advanced technology is available through the coordinated resources of the U.S. Public Health Service agencies to identify and study infectious disease agents.

To deal with the problem of emerging disease agents in the blood supply, the Food and Drug Administration has organized a Committee on Emerging Infectious Diseases, consisting of representatives from the Centers for Disease Control and Prevention, the National Institutes of Health and FDA. This committee was asked to develop and maintain a plan for evaluating and managing any emerging infection with potential to threaten the blood supply; to develop a database of known emerging infectious agents with this potential; and to meet at regular intervals to evaluate any new developments. All of these goals were met during 1997.

A written plan has been prepared as an in-house document to guide the PHS agencies in responding to reports of new infectious disease threats to the blood supply. The responses fall into four phases which, in some cases, would

be conducted simultaneously depending on the magnitude of the threat.

In the first phase, the epidemiologic characteristics of the agent will be identified, and its transmissibility by blood ascertained. This process will involve field investigations, seroprevalence studies if the agent is already known using bank and recently acquired specimens, literature reviews and consultations with outside experts.

In the second phase, the agent will undergo extensive laboratory investigations, including attempts to culture it, attempts to infect laboratory animals, and the development of serologic and gene amplification assays. In addition to the laboratories of the three PHS agencies, assistance may be requested from outside laboratories wherever appropriate expertise exists, either through collaboration or by the supplementation of existing grants.

In the third phase of our response, blood and plasma establishments will get sent recommendations for donor screening and deferral, for product retrieval, and for lookback.

In the fourth phase, PHS coordination will be fine-tuned by setting up emergency communications for the current situation, coordinating further epidemiologic investigations in collaboration with state and local health

departments, and by interacting with international health authorities.

A database has been created to tabulate those infectious agents that potentially could be transmitted by blood or plasma. Not all of the agents on the list have been documented to have been transmitted by transfusion. The mere potential for transmission is the sole inclusion criterion. Viruses, bacteria, and parasites are included on the list. The database, which has been given to the committee, is being updated whenever new information becomes known. For instance, a report at a scientific congress of the discovery of a new virus identifiable in human blood would result in its being added to the database.

The emerging Infectious Disease Committee holds both regular quarterly teleconference meetings and ad hoc meetings. The ad hoc meetings will be scheduled whenever news of an emerging infectious disease is too threatening to delay discussion until the next regular meeting. The agendas of these meetings include the discussion of recent reports of new agents or new manifestations of transfusion transmitted disease and the updating of the database and procedures.

I am now going to describe for you two examples of the PHS response to information suggesting that a known infectious agent might be transmissible by blood

transfusion, or that transfusion transmission might be occurring in an unexpected way. In each of these examples, the PHS response has so far focused mainly on the first phase of the plan, that is, seroprevalence surveys, literature reviews, and technical consultations. In the examples that I am going to describe for you response has been limited mainly to the first phase because the threats were not confirmed to be serious and, I might add, we have been very lucky so far.

In the first example, a paper reported transmission of human herpes virus 8, HHV-8, from CD19 cells from one individual to CD19 cells from susceptible individuals, in vitro, which was accompanied in the paper by the suggestion that blood from a donor might similarly transmit HHV-8 to recipients.

A literature search was conducted and the issue was discussed by representatives of FDA, CDC, and NIH. It was concluded that the number of samples reported tested so far was very small, and that further studies were needed. Contact persons in the PHS agencies were identified. Laboratories at CDC and in academia that have expertise in this area were identified for the purpose of sending samples obtained from NIHLBI-sponsored studies for evaluation, and a study of 1000 samples from the REDS study collection has been organized, and should be completed in a few months.

Reassuring evidence that HHV-8 is not transmitted easily by blood transfusion was found in an analysis of banked specimens from the Transfusion Safety Study, in which 14 recipients of cellular components from HHV-8 positive donors did not become infected.

In the second example, FDA received a report from an outside investigator that nucleic acid sequences of the HTLV-I tax could be found in the serum of healthy blood donors who were nonreactive for anti-HTLV-I, and the report we received said that tax sequences were found in 11 of 100 healthy donors. This raised the question of whether tax or HTLV-I itself could be transmitted by transfusion from HTLV-I negative individuals, and whether the presence of tax could be a marker for HTLV-I infectivity that would not otherwise be detected by the currently licensed tests.

The investigator who reported these findings was invited to FDA to describe the data to the PHS agencies. Then a coordinated evaluation by FDA, CDC and NIHLBI was undertaken, in which blood samples from 110 normal donors without detectable HTLV-I were obtained, and have been sent and are in the process of being sent to each of four laboratories for evaluation. This includes the laboratory at FDA, the laboratory at CDC, the laboratory of the investigator who originally reported the findings, and a laboratory under contract to the REDS study, each of which

would test the samples using a protocol supplied by the original investigator. These studies are still in progress, but we expect results within a month or two. If the original findings can be reproduced, further studies will be carried out on donor-recipient pairs to assess the transmissibility and the potential for disease. Simultaneously, laboratory work is ongoing at FDA to develop assays to detect tax nucleic acid and TAX protein in blood donors.

In summary, it was felt that a written outline of procedures such as these for dealing with infectious agents would help ensure that no essential item is overlooked in the pressure that could occur during efforts to prevent a crisis. In combination with the database prepared by this committee, this written plan will provide a starting point for discussions about the level of risk of any infectious agent and about our ability to deal with it. Thank you.

DR. HOLLINGER: Thank you. This was just a presentation I think for information. So, I think we will go on, unless there are any questions. Thank you.

Let me sort of outline a little bit what we are going to do at this point. We are going to start the discussion on the FDA proposal on plasma inventory hold. We will initially start out with an introduction and background and a presentation, following which we will take a short

break, and then we will come back to an open public hearing, for which there are three individuals who have asked to speak, the American Red Cross, the industry and the AABB. With that in mind, Dr. Biswas, would you please provide us with the introduction and background for this issue?

FDA Proposal on Plasma Inventory Hold

[Slide]

DR. BISWAS: The current safety of plasma derivatives from infectious diseases depends on several layers of precautionary measures, including careful selection of donors, laboratory testing of collections for infectious diseases, validated viral removal or inactivation steps, accurate record keeping, and appropriate use of products. The absence of transmission of infectious diseases at the present time attests to the effectiveness of this multi-layered approach.

[Slide]

Another step which we are going to consider today is a plasma quarantine procedure. According to this procedure, a donor is screened and the unit is tested, and if all donor suitability criteria are fulfilled and their unit is collected, that unit is placed in inventory and withheld from pooling. If the criteria are not met, then the unit is discarded, of course.

If the donor again meets all suitability criteria

after a period of time based on the window period, the unit is released for pooling and for manufacture into plasma derivatives. Of course, if the donor is now not suitable, then any previously collected units in quarantine would not be used and, of course, the currently donated unit would also not be used.

[Slide]

As the period of time for quarantine should be based on the window period, what is the definition of window period? Is it the time from exposure to the virus, a needle stick or a transfusion, until detection of the marker? Or, is it the time from the beginning of infectiousness until detection of the marker?

[Slide]

This diagram demonstrates the difference. Is it this time, from exposure to the virus to the positive test? Or, is it beginning of infectiousness to the positive test here?

For the purposes of quarantine, what we are really interested in is the period of time from the beginning of infectiousness replication until a positive test. The problem is it might be difficult to know when infectiousness or viral replication actually begins, and Dr. Mike Busch will be going into this in detail afterwards.

[Slide]

The effectiveness of plasma quarantine increases when the time period of the quarantine approaches the longest reported window period for the infectious disease using a particular test, i.e., a greater number of potentially contaminated units would be intercepted the longer that hold is as it approaches the full window period.

Note that a more sensitive test moves this line, here, over here, to the left, making the window period shorter. The test with a particularly long window period for the infectious markers that they are tested for, HBV, HCV and HIV, is, of course, HCV and, in that case, this positive test line would move over here and the window period is longer.

[Slide]

Plasma quarantine promotes collections from low-risk, reliable donors who return; reduces the risk of collections from test-negative, infectious window period donors; reduces the risk of pooling test-negative infectious window period units and, thus, decreases the viral burden of plasma pools.

[Slide]

At the September, 1997 BPAC meeting, the International Plasma Products Industry Association, IPPIA, described several procedures for increasing the safety of product safety. I need to describe two of these procedures.

One is the applicant qualified donor concept and the other is the inventory hold. Both these procedures have been implemented, I believe, by all or most U.S. fractionators.

I should mention that IPPIA's procedures are for source plasma only. Just to remind you, source plasma is obtained by plasmapheresis from donors who may donate 2 times a week but with at least 48 hours between consecutive donations. So, according to the IPPIA definitions, an applicant donor is a first-time donor or a previously qualified donor, and we will get to that in a moment, who has not donated within the past 6 months. Donations from applicant donors who do not return are not used to make plasma derivatives. Thus, plasma from first-time donors or the occasional donor, ones who come, say, in 7 months, who have higher viral marker rates than repeat donors is not used.

[Slide]

A qualified donor, according to IPPIA, is a donor who must pass 2 history interviews and have 2 negative sets of screening tests within a 60-day period, and must have donated at least 1 time within the prior 6 months, otherwise number 2, the donor, goes back to number 1 and has to go through 2 history interviews and have 2 negative sets of screening test results. Plasma only from these qualified donors is used, but note that the 2 negative donations and

histories could be as close as 48 hours and the donor is then qualified. However, plasma from an individual who is a one-time donor is not used.

[Slide]

The second IPPIA procedure that needs to be mentioned is the inventory hold. Collected source plasma is put into inventory for 60 days. If the donor returns within 60 days and is positive for a test, the donor's positive unit and prior negative units in inventory are not used. If the donor is negative, then the donor's previous units are used to make plasma derivatives. However, if the qualified donor does not return after 60 days the units are used.

So, theoretically, a donor who is within the window period, say, of hepatitis C could return several times after the first donation, go through the testing and screening procedures, and the units collected would be used if the donor just didn't return one day.

Also, it seems that 60 days might be a bit short, especially for HCV. However, using this procedure certainly some window period units would be intercepted as the donor returns.

[Slide]

Here is a comparison of the two schemes. In IPPIA the qualified donor does not return when this occurs. With ahe plasma quarantine we are proposing, release is always

linked to donor return. IPPIA has a 60-day inventory hold. Under plasma quarantine the period of quarantine would be based on the window period, not saying that this isn't based on a window period but this might be sort of more based on data that perhaps Mike Busch will give us.

I also need to mention that the IPPIA proposal only refers to source plasma. I put recovered plasma down there, under the plasma quarantine. There are some problems including recovered plasma but we put it in for the same reasons that we proposed to do this with the source plasma, that it would intercept some window period units. As we know, for recovered plasma those numbers might be quite low. Recovered plasma, as you all know, comes from voluntary whole blood donors, and they donate at most once every 8 weeks. The average, in fact, is about 1-2 times a year. So, the problem is that a lot of the high percent of recovered plasma would not be pooled for many months or well over a year, leading to possible deterioration of the product.

To end up, the positive side of the IPPIA procedure is that the one-time donors or the first-time donors are excluded and they do have higher marker rates than repeat donors. Certainly some, if not many window period units would be excluded, depending on the rate of donor return. In the plasma quarantine proposal a majority,

if not all window period units could be intercepted, depending on the length of the quarantine.

I think I would like to stop there. Mr. Chairman, I don't know if you would like me to go through the questions now, or shall we leave them for later?

DR. HOLLINGER: Let's go through with Mike's and then we will go to the questions. We have a presentation then by Dr. Michael Busch, from the Irwin Memorial Blood Centers, on this issue. I believe there is a handout here, isn't there?

Presentation

DR. BUSCH: I did distribute a couple of manuscripts and a few portions of a handout, but I also have a complete copy of all my slides that Linda is going to have copied for distribution, hopefully by mid-day today.

[Slide]

The first overhead here summarizes what I am going to present. Robin asked me to review what we know about window periods, and it is more complicated than one might think at first blush because, as Robin summarized, we really have to distinguish a variety of types of window periods based on exposure to seroconversion versus detectable viremia to seroconversion, and detectable viremia can be defined in different fashions and, of course, we have lived with the evolution of antibody and development of antigen,

and nucleic acid testing that have reduced the back end of the seroconversion window. So, we will talk about a sort of summary of definitions of window periods and then review several sources of data for each of the viruses that yield estimates for these various window periods.

Relevant to this issue is the relationship between viral load as the virus ramps up through the dissemination phase in the blood to infectivity. To address that, with each virus I go through I will summarize human data. I was going to present data on relationship between viral load and infectivity beyond the issue of transfusion, but I am going to limit it to transfusion-related transmission and what we know about the relationship between viral load in blood and the probability that that blood transfusion will transmit HIV.

At the end I will come back to some animal data that I think is most relevant, and offers the promise to really finally nail down when infectivity occurs as virus becomes detectable through the evolution of viremia.

Finally, just very briefly, to put this into context I will discuss how our understanding of window period plays into our estimate of risk from seroconversion donors, and also how the risk attributable to seroconverting donors, window period-related risk, weighs in to the overall risk because there are other sources of risk with issues

such as reducing incidence rates or reducing window periods effectively through inventory holds or quarantines that will not address risks attributable to either testing error, variant viruses, things of this nature. So, at the very end I will just put that into a broader context so that people realize that the measures discussed today, even if all were implemented, would not totally eradicate risk.

[Slide]

So in terms of window periods, we can talk about a family of window periods for each of the viruses, not only HIV but HCV and HBV, which are the agents I will talk about. There is the period from exposure to when people develop symptomatic disease, be it primary HIV syndrome or hepatitis.

There is exposure to antibody seroconversion. The data on this is relatively limited because there are relatively few situations where discrete exposure has occurred and serial samples are collected to monitor for evolution towards seroconversion. This is really limited to situations like transfusion transmissions and things like healthcare worker accidents where there is discrete exposure and people, in prospective studies, are sampled regularly and then one can estimate the time period from exposure to seroconversion.

We also know, as I will talk about and Robin

summarized, that there is a brief period following exposure during which the virus is probably replicating at very low levels in the tissue in the region of inoculation prior to dissemination into the blood stream and the person becoming infectious. So we have ways to evaluate the period of infectivity to antibody, and there are several,

One is studies that are based on lookback of prior donations from seroconverting donors, and evaluating whether or not those prior donations transmitted viruses. This really gives us our most accurate assessment of what is relevant to us, the period of infectious viremia prior to antibody, and I will briefly summarize data on that.

Then, there is a lot of work going on in terms of trying to estimate how long there is detectable viremia, using nucleic acid amplification assays which have become exceedingly sensitive, and understanding the dynamics of the ramp up of viremia prior to seroconversion and then, through modeling, estimating when people would have theoretically had some minuscule level of potentially infectious viremia. This will be the focus of the discussion.

[Slide]

So, in terms of where we get the information to evaluate these window periods, we have had a lot of data recently, and I will summarize a fair bit of it, from seroconverting plasma donors. These are source plasma

donors giving 2 or so times a week, and when these people seroconvert, fortunately for practical reasons historically and now operationally, these prior donations are not pooled until several months after the donation is given, and when a donor seroconverts we are able to retrieve the prior donations from these seroconverters and then characterize the evolution of viral and serologic markers in these serial donations in what we call plasma seroconversion panels. This is extremely useful data to evaluate the marker window period. Unfortunately, we don't know when these people became exposed or technically infected so this is really data that is relevant to the marker's evolution prior to seroconversion.

Known exposure cases, needle stick, transfusion -- we will talk about that. I won't talk about primary infection syndrome. The problem here is these people, when they present with hepatitis or acute symptomatic HIV infection, are actually well into seroconversion, typically at peak viremia and actually have symptoms associated with the early immune response and organ damage. So, these people are a major focus of research in terms of HIV now but they are not terribly useful for the early infectious window period. We will talk about recipients of seroconverting donors. I will briefly allude to some animal data. But all of these data, in essence, have to be puzzled together to

derive a full picture of the window phase.

[Slide]

This is just a cartoon of studies that have been done in the SIV system, inoculating SIV through mucosal routes and then sacrificing or biopsing these animals over time. It is important to this principle that there is this period of time following exposure before the virus gets into the blood and an individual would become viremic. This is well documented in these animal studies where, immediately in the days following inoculation, you can detect virus in the submucosal lymphoid tissue, and then over a period of days you can actually watch as the virus-infected cells migrate to the regional draining lymph nodes, and these become literally factories of early virus replication but it takes a period of several days for the virus to actively expand in these regional lymph nodes before one detects transmission of virus through lymphatics into the blood stream and then systemic replication, typically in an exponential fashion that triggers seroconversion. So, these animal data are important in principle to tell us that there is this phase of pre-viremic virus growth. But, obviously, we are dealing with different systems, different viruses often and the time course of this can't be directly extrapolated to humans, and probably also needs to be evaluated with respect to route and dose of exposure.

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But it does leave us with the principle that Robin summarized, that there is a period of the early phase, the so-called eclipse phase when the virus is replicating in tissue in the absence of systemic blood viremia. We don't believe people are probably infectious during this phase. Then there is the phase where there is detectable viremia, be it by culture methods, by lookback methods or by laboratory detection with amplification assays. The amplification assays have become so sensitive that we can now detect exceedingly low levels of virus in plasma, and the question has to be raised whether, in fact, even these very low levels are infectious -- how many infectious units are required to transmit, and there is also the effect of blood storage that reduces the infectivity of components. So, we will talk about this. Most important are units that do not have detectable viremia -- are they infectious, these units that might come from this eclipse phase?

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In terms of HIV, the best data that we have in terms of exposure to antibody seroconversion comes from an analysis by Glen Satten of 52 cases of healthcare worker HIV transmissions that have occurred over the past decade in the U.S. These are situations where an accident occurred in the hospital or clinic setting. HIV-infected source patient --

blood from that patient -- was through a needle stick injury and transmitted to a healthcare worker. That healthcare worker was monitored over a period of months and very rarely, about 1/1000, these health care workers became infected.

This is data from the infected cases that have been observed. Again, these people are tested every few weeks or so and, unfortunately, in most of these cases the samples aren't saved. But the data was available after they were determined to be infected, and compiled in terms of the dates of testing and whether the results were negative or at what point the person seroconverted.

What Glen has done is to model this, as shown here. This is data, again, over the last 10 years so a variety of antibody tests were used, relatively less sensitive to those in donor screening. But the bottom line here is that about half of the people were estimated to have seroconverted by about 50 days following the exposure.

The disturbing part of this curve is out here though because there is sort of a tail to this curve and, in fact, there were 2 people documented to seroconvert after 6 months from exposure. In those 2 cases sequencing work was done that verified that the virus that did infect these people was the same virus as was in the source patient. So, unequivocally these were delayed seroconversions out at

about 6 months. There were other cases that occurred here, but the upper 95% confidence interval of that is 6 months. So, it does mean we have to retain the recommendation that people should be tested up to 6 months following an exposure to essentially rule out infection.

Now, the question is whether these unusual delayed seroconversions -- whether these people were viremic for these prolonged periods. In several published cases of similar healthcare worker accidents from overseas samples were available and were tested and, in fact, the individuals were negative for virus by RNA and antigen until just before they seroconverted. In other words, these samples earlier were probably negative for infectious virus. Virtually all of these cases, including these delayed healthcare worker infections in the U.S., developed symptomatic primary infection just in the week or so before they were documented to seroconvert, and that primary infection really is a manifestation of the high titer viremia.

So, although it is disturbing in terms of these rare cases of delayed antibody seroconversion, the data is consistent with the probability that delays represent delays during which the virus was probably replicating in these regional draining tissues at a very low rate, and that the viremia probably occurred only during a brief, transient phase prior to seroconversion.

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In terms of the estimate of the infectious window period, there was a study that Lyle Petersen from CDC, coordinated, published about 6 or 7 years ago that looked at the probability that a transfusion would transmit HIV if that transfusion was given from a donor who subsequently seroconverted.

In this study of 700 seroconverting donors the records were reviewed. The recipient status was investigated, and overall it turned out that there were 182 cases where a prior donation from a seroconverting donor was transfused into a recipient for whom recipient infectious status was determined. Overall, 39, or 20% or so of these recipients became infected by the blood transfusion.

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It was, again Glen Satten at CDC with Lyle who modeled this data and looked at the probability of transmission relative to the time period between the seropositive and the prior seronegative unit that was transfused. What it showed was that the rate of transmission dropped profoundly as this time interval between the donations increased, essentially from a 75% transmission rate if the unit was given in the prior 3 months to essentially zero after a year.

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By modeling that data, Glen derived a model based on an estimated 45-day infectious window period, which is shown in green here, in parallel with the observed rate of transmission relative to the donation interval, shown in blue. You can see that these 2 curves overlap --

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-- such that the conclusion of the analysis was that for the overall period of March, 1985 through December, 1990 in which these lookback transmissions were occurring there was an estimated 45-day infectious window period. But in a separate analysis in the paper that looked at the period before and after we shifted from the first to the second generation of antibody test which we knew reduced the window by an estimated several weeks, what the lookback data showed was that the window period was reduced from an estimated 56 days to 42 days. So, it is this 42-day infectious window period in the late '90s that we have built on in terms of how the improved antibody, antigen and RNA test can reduce the window period further.

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The data that is the most accurate in enumerating a further reduction in the window period and the ramp up of RNA comes from these seroconverting plasma donor panels. In a study conducted a few years ago we characterized a large number of serial samples from 51 seroconverting donors, with

a variety of antibody, and antigen and RNA assays, we defined and estimated the duration of various stages of viremia, the RNA only, the p24 positive, RNA positive through the various antibody evolution phases. So, we have an understanding of the duration of these. We have also modeled the viral kinetics from this data.

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These are just representative panels. Again, these are source plasma donors, collected at about twice weekly intervals. These people were found to seroconvert way back here. These are just arbitrary bleed rates, extending from the first available sample through the sample that was determined to be antibody positive by the early generation assays.

What you can see, as you test these back now over time, is the rise in RNA followed by the rise in detectable p24 antigen, and then with evolving antibody detection by the newest third generation antibody tests which detect IgM with high sensitivity versus the less sensitive IgG antibody assay for that test. These panels are really quite consistent from one to another.

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It led to the definition of stages, if you just focus on this part, here. So, there is this phase during which we only detect RNA, and that is estimated at about 3

days. Then the levels of virus ramp up to where we can detect p24 antigen in addition to RNA. That is about 5 days, before finally the antibody screening test, the IgM sensitive assays detect antibody. Then there is actually a brief period where the screening tests are reactive but the most sensitive Western Blot is negative. That is about 3 days. Then there is a period where the Western Blot is indeterminate. Then there is a period where the Eastern Blot is technically positive but it is continuing to evolve serologically.

So, we have an understanding then of the duration, quite accurate estimates of the durations of positivity of virus prior to antibody. You can see that it is really very brief, only about 8 days. With the current sort of 100 copy sensitivity RNA tests there is only about 8 days before the antibody tests become positive, and only about 3 days before the antigen tests become positive where the current licensed assays can detect RNA. So, there is a very brief viremic phase.

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This slide shows the distribution of the RNA levels during these progressive stages of dissemination and seroconversion. So, during the RNA only stage, which is about 3 days, you can see that the levels of RNA range from the limit of the sensitivity of the assay, which is only

about 100 copies to levels around 5 X 10^4. Once virus levels get up above that level you almost always detect p24 antigen. So, this is the distinction between these first two phases where there is no antibody in either of these stages but the question is whether p24 antigen is already sensitive enough to pick these cases up. Then, finally as antibody evolves, you can see that the RNA levels drop off.

[Slide]

To try to get more understanding of the dynamics of virus during this ramp up phase and then projecting back as to when theoretically the first detectable virus would have hit the blood stream, we have done analyses on these panels looking at estimation of the doubling time of virus. Of those 51 panels, there were 24 where we had 2 or 3 RNA-positive samples before antibody was developed. For those panels, we were able to estimate, through regression analysis, the slope and the doubling time of virus with a very simple formula.

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This is the distribution of doubling times estimated. The average was about a day. There were some rare outliers that took 4 days for virus to double.

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This slide just sort of illustrates how this is done and how we used that to back-estimate when some

theoretical minimal copy number would hit the blood. So, basically there are 2 RNA data points here prior to any antibody. We did a simple regression line. If there are 3 you fit a regression line to the data, and then derive from that the slope. In this case it was half a day. We can then back-estimate from that slope when an individual would have had a theoretical 1 copy/mL of virus. Again, the assays we were using were only sensitive to about 100 copies, and often the first data point might have had 5000 copies. So what we want to do is to back-estimate for each of these panels when they would have had a theoretical 1 copy, and then from that we can actually reset the time scale to day zero for each panel when each person would have had 1 copy.

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Based on that, we derived this figure which has now reset these 24 panels to a single time line, setting day zero as the day at which each of these seroconverters would have been estimated to have 1 copy of virus per milliliter of blood based on the slope of the RNA ramp up and the data for each panel.

So, you can see that we estimate that there would be 1 copy/mL about 20 days prior to peak viremia, which is when antibody seroconversion occurs. The fundamental question really is when, during this progressive slow

theoretical ramp up phase, do people become infectious. But it certainly is consistent with our estimate that there is about a 20-day potential infection phase, of which we actually can only detect virus by current assays for about half of that 20-day period.

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This is a slide Susan Stramer put together based on this data and sort of summarizing it. So, we have this theoretical period from exposure to seroconversion which, on average, is about 50 days but sometimes is out to 6 months. But when we look at the lab data for not only these panels but from other data sources, from cohort studies, and the lookback data etc., that supports that the duration of infectious detectable viremia really is only a fraction of that total period from exposure, and is much more consistent and, in fact, there is really only a brief period of really 5-10 days prior to antibody during which current assays can detect RNA. Even if we extrapolate back, we would only say there are probably another 5 or so days during which there might be theoretical levels of virus in the blood, but the question is, is that material potentially infectious? But for HIV the bottom line is that the detectable infectious days prior to antibody are really very brief, probably no more than 10 to theoretically up to 20 days.

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So, in terms of the relationship between infectivity and transmission and detectable virus, there is really not perfect data. We will come back at the very end to some newer data, but where we do have some data is actually from historical studies before we started screening.

In the Transfusion Safety Study, we were able to go back to repository samples that were collected back in 1984, before the HIV test was available. The recipients of these units had been enrolled and followed, and we identified the seropositive units and then traced the recipients. In this analysis we went back and looked at the levels of RNA in the donations and the relationship between RNA detection in these units and whether or not transmission occurred.

In this study, which was just published, there was a total of 80 cases where the donation sample was available for RNA analysis. In 72 of these, the recipients seroconverted and in 8 the recipients did not. What we found was that all of these donations were RNA positive but that the transmitting units had significantly higher viral load than the non-transmitting donations.

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In addition, there was another variable that explained the non-transmissions, and that was the storage of

the blood in the refrigerator. The open circles here are the non-transmitting units. The bottom line is that the non-transmitting units were all in the lower half or third of the viral load distribution, plus, they were significantly associated with prolonged refrigerator storage of the component. So, it is a combined effect of relatively low viral load in these seropositive units and refrigerator storage reducing the infectiousness of the virus that is there that explains the fact that about 10% of transmissions of HIV antibody positive blood do not transmit HIV.

[Slide]

Now, we are going to go to hepatitis C. We have been doing a lot of work recently, going back to the transfusion-transmitted viruses population that Jim Mosley and, I think, Blaine was involved with a long time ago. The samples were collected back in the late '70s in post-transfusion prospective cohort studies. We have been looking recently at a lot of these panels and data to understand the distribution of time from transfusion to seroconversion, as well as the virus levels.

In this, what we have been looking at is the serial bleed data. These are people were observed prospectively in a large post-transfusion cohort study involving cardiac surgery patients, and these people were sampled at approximately weekly intervals, and a subset of

these people developed post-transfusion clinical hepatitis and/or subclinical documented ALT elevations. Over time a number of papers have been published where these samples were tested for surrogate markers, and HCV etc., and have demonstrated that HCV is the causative agent of virtually all of these hepatitis cases, and that the antibody tests have accurately picked up essentially all of the infectious transmitting donations.

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What we have done here is to go back to the serial samples from these recipients and from the donation samples that went into these recipients, and characterized viral load and then looked at issues such as the timing of detection of RNA following transfusion and prior to ALT or seroconversion. Also, we began to look at questions such as the relationship between the HCV RNA load in the donation or ALT levels in the donation and recipient transmission and recipient characteristics of infection.

[Slide]

Just to show you some representative panels and point out an important problem with these data, this shows a typical panel and, very impressively, within the first or second bleed following the transfusion, this is day minus 1 so this is the pre-transfusion sample, and in two-thirds of the panels the very first bleed collected post-transfusion

already has sky-high viral load, 10^5 to 10^7 copies, and the virus RNA remains highly positive really through evolution of ALT and antibody.

This panel is a relatively straightforward one because the antibody tests remain negative until out here, at day 51. So, in this panel we can talk about time from transfusion to antibody detection, and the antibody kicked in just shortly after the bleed after ALT kicked up and about a month after RNA was detectable.

But what you can see in this panel is that by RIBA analysis there were low level antibodies detectable on the first post-transfusion sample. This is passive antibody because the unit included antibody. So, in this panel the EIAs were clean negative until active seroconversion but the RIBA test shows high level passive antibody that declines over time before active seroconversion.

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The problem is that actually the majority of the panels show passive antibody by the EIAs as well. So, you really can't discriminate when the people lose passive antibody and seroconvert actively because of the enormous passive antibody that is transmitted with the blood transfusion.

This presents a problem in terms of these transfusion cases estimating time from exposure to

transfusion to antibody seroconversion. For that reason, what we have done in the analysis from the larger sample set is to characterize time from exposure to elevated ALT. I will show you separately that elevated ALT always occurs about 1 week to 2 weeks before antibody seroconversion, based on data from seroconverting plasma panels in hemodialysis patients. So, in a larger population distribution of the distribution of time from exposure to evolution of seroconversion, that is going to be based, as I will show you, on time from exposure to ALT greater than 90.

[Slide]

Just a few other examples, here is another one where, again, the EIAs are reactive due to passive antibody immediately post-transfusion and never seroconvert. The RIBAs are strongly positive and slowly evolve down. And, you can try to draw a line here. I will show you Harvey Alter's analysis based on the EIA ODs and the RIBA patterns. He has tried to estimate when these people developed active antibody but it is relatively difficult. In this case you can see a shorter period of active RNA before ALT kicked up, in this case out at about 27 days.

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There are rare panels where actually RNA does not become positive until after ALT comes up. In the vast majority of panels RNA comes up early and stays very high

within the first bleed or two, but this is a rare exception where RNA wasn't detectable until late, the caveat being here that these are samples from 25 years ago that have been stored in freezers, and frozen and thawed on several occasions. So, stability of RNA is a concern although, for the most part, the results were surprisingly clear.

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This is a very recent summary of the distribution from time of transfusion to elevated ALT in 113 HCV-infected transfusion recipients. This is analogous to that healthcare worker data I showed earlier. Time from exposure to ALT, and then ALT would be followed about a week later with antibody.

You can see that it is somewhat similar to the HIV healthcare worker data. On average, 50% of these people have developed their peak ALT and would have seroconverted a week or so later by about day 40 following transfusion. There is a tail but it is much less impressive, with rare cases extending out about 3 or 4 months but virtually all of these people have developed their clinical hepatitis and have seroconverted within about 3 months for HCV. So, it seems as if for hepatitis C the timing for exposure to symptomatic ALT elevation and seroconversion is relatively more consistent than for HIV.

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This is just a summary of the distribution analysis. Again, you can see that for about half the people the median is about 40 days, but there are several outliers that took about 4 months before they developed elevated ALT and seroconverted.

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The other thing we did then was to test back the RNA in all these panels. This is a little confusing. We completed data on 30 of these recipients where all of the serial bleeds have been characterized for RNA. This slide only summarizes the first 15 but the other data is consistent.

What it shows is for each recipient, numbered on the X axis, the time to first RNA detectability and then the time to first ALT elevation. So, in this case you can see that RNA was detected about day 8 and ALT kicked in about day 41. In this case similarly about day 8. You can see that virtually everybody developed RNA within the first 10-20 days of the transfusion, and the levels of RNA were very high. That was followed somewhat more erratically by development of hepatitis, as evidenced by ALT elevation greater than 90.

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So, overall in the first 15 panels there were 14/15 that developed high level RNA, very high titers, and

in 13 of these cases the RNA was detected prior to ALT with an average 12 days time from exposure transfusion to elevated RNA, and an average of 35 days from elevated RNA positivity to ALT elevation.

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So, fairly long for HCV then viremic pre-antibody phase, unlike HIV where it was very brief, perhaps 10 or at most 20 days. For HCV it is probably more in the range of 40-plus days, as I will show you in more detail in a moment.

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Again, this is just a summary from some literature that emphasizes that the timing from ALT to reactivity on the third generation antibody tests is about 2 weeks, and is quite consistent. So, I have been focused on the time from transfusion to ALT because in these transfusion cases the problem is that passive antibody precludes really accurate enumeration of when antibody kicks in, but this points out that ALT really is an early marker, about 2 weeks before antibody.

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This is a summary from Harvey Alter of his analogous work in his cases from the NIH clinical center. He also estimates that by about 3 weeks following transfusion RNA is detectable; about 5 weeks during which RNA is detectable before ALT kicks in; and then, similarly,

about 2-3 weeks from ALT elevation to antibody seroconversion. So, independent sources of data from Harvey really give very similar estimates for the periods. So, again, we have a problem with HCV in that time from transfusion to markers is relatively consistent in about 12 weeks, but the problem is that the vast majority of that period of time is viremic, and very high titer viremic.

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Now, that was all data from transfusion settings. This is data from Sue Stramer's work with NGI, looking at seroconversion panels, the plasma donor panels. Again, we don't know when these people were exposed. What we are doing is testing back on stored donations prior to the detection of antibody on a subsequent seroconverting plasma donation. What we can see is very similar to what we see in the transfusion setting, very high titer viremia, extending back in this case 26 days prior to antibody.

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In this case, it is spread out more because there are lots more bleeds here, but there was a 40-day interval between antibody detection and RNA detection with, again, a very rapid ramp up. So, unlike with HIV where there is a moderately slow ramp up of viremia in the blood detected first by RNA and by antigen, in HCV just a blast of virus hits the blood stream and you go from completely negative to

10^6, 10^7 copies/mL between 1 and 2 bleeds.

[Slide]

This just summarizes data from Sue's analysis of 19 of these seroconverting plasma HCV panels, and the important data is really right here, the estimate of a 41-day viremic phase prior to antibody from all of the analyses of all of these panels. Again, the titers here are exceedingly high, with very few outliers that have a lower level copy number.

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So, the question of the infectivity of these donations and relationship between viral load and infectivity is not easily obtainable or addressable. Again, we have gone back for the TTVS sample, as we did for HIV, and we have tested for RNA and gotten RNA viral copy numbers on the donation samples. Now, in HCV antibody positive units transmit HCV about 80% of the time. That was the case in the TTVS study as well. In this study, there were donation samples available for analysis from a total of about 75 or 80 recipients, and 67 of these donation samples were associated with recipients who did become infected, and in 16 the recipients got antibody positive blood but didn't get infected.

Now, of the 67 cases where transmission did occur, 63 of those had detectable RNA, and the RNA distributions

for these 63 cases are shown here. In the 16 cases where transmission did not occur, only 7 of them had RNA. So, the point here is that if you got an antibody positive unit that was also RNA positive, there was 90% probability of transmission, whereas, if you got an antibody positive unit that was RNA negative the chance of transmission was only 10%. In the cases where RNA was not detected in the donations that did not transmit, you can see that the copy number of virus was much, much lower than in the cases where transmission occurred. So, it is not an absolute cut-off but it is the same story as with HIV, and we still need to look at the issue of unit storage, but there is clearly a very strong correlation between detectable virus and quantitative level of RNA and transmission of HCV.

[Slide]

Now we are going to move on to hepatitis B. For hepatitis B the data, again, is coming from several sources. The data from transmission by blood transfusions is again from the Transfusion-Transmitted Viruses Study. This is, again, a survival analysis, time from transfusion to hepatitis B surface antigen detection. This is for the 12 documented HBV transmissions that occurred in the Transfusion-Transmitted Viruses Study.

Importantly, in a paper published by Larry Mims and Jim Mosley from TTVS, they demonstrated that the timing

of HBV seroconversion, time to surface antigen, and probability of persistence of surface antigen was very different for these recipients who got HBV only versus cases where the recipient developed both HBV and was co-infected with or had a preexisting HCV infection.

What the analysis that was published showed was that the people who had concurrent HCV had a more delayed time from transfusion to surface antigen, and had a higher and prolonged phase of surface antigen positivity compared to the people who got HBV only.

So, this first curve shows the analysis for all the cases, and you can see that the average was about 60 days from transfusion so, about 2 months from transfusion to surface antigen. In contrast, down here are just the cases that were HCV negative. You can see that it is shorter. It is about 50 days on the average. So, most of these delayed seroconversions to surface antigen were associated with concurrent HCV infection. So, perhaps in the REDS analysis where we projected the window period for HBV, we used the exclusive HBV only basis because, obviously, we are screening for HCV in the donations. So, anyway, we think it is about 50 days on average for seroconversion from transfusion to surface antigen positivity, and it is a fairly consistent drop-off. It doesn't have a long tail, based on the limited data that we have here with some

delayed seroconversions. Everybody was documented to seroconvert by about 3 months.

[Slide]

This is just the distribution of those 2 analyses, the overall cases versus the HCV-negative cases. Again, an average of about 60 days. That is the time from transfusion to seroconversion. The question is how long are these people viremic before they become surface antigen positive.

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To look at that, the REDS group, Rawal and my group have been looking at a large number of seroconversion plasma donor panels, doing viral load analysis and characterizing how long before surface antigen we can detect HBV DNA and what the kinetics are of ramp up of HBV DNA.

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I will focus on this first part of the analysis which is looking at a number of panels, characterizing them for HBV DNA quantitative levels and working back to look at the relationship between HBV DNA and surface antigen, estimating viral doubling time, and then projecting back again, if we were to go to even more sensitive HBV assays, how much further could the window period theoretically be reduced.

[Slide]

The assay we used in the initial studies was a

commercially available EIA licensed HBV quantitative assay from Roche, which has only a 400 copy sensitivity in terms of HBV DNA and genome equivalence, and based on titration against the chimp infectious dose panel that is approximately 9 chimp infectious doses. We will come back to this relationship between infectivity and detectability in a moment.

[Slide]

This one is upside down. I will just go to the next one. That was just an example of a relatively brief, rapid ramp up of DNA prior to surface antigen.

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This is another example of the extreme slow ramp up phase. So, here is the HBV DNA copy number and the 3 different HBsAg assays. What you can see is that HBsAg doesn't become positive with an STCO of 1 until out here, and we, in fact, set as day zero in our analyses the first HBsAg positive donation. In this case, we actually had 5 or 6 prior donations in which we could detect HBV DNA with a very slow ramp up phase of HBV DNA. In fact, there was 23 days between the first HBV DNA positive and the first surface antigen positive. So this is an extreme example of a slow ramp up HBV infection.

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This compiles all the data from the 17 panels,

again, setting day zero as the first surface antigen and then looking at the levels of HBV DNA. We can see that once surface antigen appears, the levels of HBV DNA are generally quite high. In the cases where we detect HBV DNA prior to surface antigen the levels are really quite low, less than 1000 to 50,000 copy numbers.

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When we then try to estimate with this assay, with a 400 copy sensitivity, and the Abbott HBsAg assay with 0.5 ng/mL sensitivity what is the duration of DNA positive pre-antigen window, we had 10/17 panels in which we detected HBV DNA on an average 11.5 days. So, if we simply multiply the proportion of panels in which it was detected times the average reduction, we could estimate that there is about a 7-day period prior to surface antigen, as detected by this test, that we could detect HBV DNA by this test.

The question, though, becomes how much further could a better test detect it. In looking at that, the first thing we needed to confirm was that there is a good relationship between surface antigen and HBV DNA after seroconversion, and that was the case. In other words, most of the virus that is present before and after detection has appropriate representation of DNA to surface antigen.

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Then what we did was analogous to what we have

done on the other viruses, to estimate the doubling time based on the slope of the DNA ramp up phase for each of the panels. So, this slide lists all 14 panels and then derives a slope estimate, and then a doubling time for the virus based on the DNA data points before and after surface antigen positivity.

You can see that the doubling time ranges from about 4 days to long doubling times of around 17 days, with an average of about 4 days. So, on average, it takes 4 days for HBV to double in the circulation in concentration. So, unlike HIV where it was 1 day, the rate of ramp up of HBV in plasma is much slower.

[Slide]

This slide shows if we then extrapolate from the assay that we were using, which has a 400 copy sensitivity, and we estimated with that test about a 7-day pre-surface antigen DNA positive phase, if we start to estimate what the sensitivity and window period would actually be if we pushed the sensitivity of the assay down to 100 or 10 copies, basically, as the assay sensitivity increases 2-fold the doubling time adds to it. So, you would add 4 days in each of these intervals.

So, the bottom line here is that we would theoretically estimate that there would be 1 copy of virus/mL in plasma about 38 days prior to surface antigen

positivity. So, this very slow doubling time translates into a theoretically very long potentially infectious window period. So, the question is what the relationship is between copy number and infectivity; when would these very low detectable DNA levels be associated with probable transmission by transfusion?

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That has been addressed. For HBV there are some very nice chimp infectious dose pedigreed panels, and this is just one example from work by Paul Ulrich and Girish Vyas' lab where 2 different chimp infectious dose pedigreed panels were assayed against 2 different DNA PCR assays. Both of these panels could be diluted out in chimps to 10^{-7} level and still transmit to chimpanzees.

What this study showed is that they could detect HBV DNA by PCR at or 1 log lower in concentration than one could demonstrate infectivity in chimpanzees. So, that suggested that for HBV our PCR assays are actually potentially more sensitive than is infectivity.

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This is a summary of that relationship in chimp infectious dose analyses between infectivity and detectable copy number. This is a table Nico Leli put together. So, from various studies for HBV in chronic surface antigen positive carriers, when these are diluted out into

chimpanzees and the endpoint titer of chimpanzee infectious doses is compared to the endpoint titer sensitivity of PCR, a number of studies have demonstrated that you can detect that there are between 1 and 30 genome equivalents per chimp infectious dose. So, in other words, if there are 30 that is saying that the PCR assays are more sensitive than chimp infectious doses. We detect 30 copies in a sample that has 1 chimp infectious dose/mL. So, this is another issue obviously, the volume infused in a blood transfusion may be 100-fold greater than the 1/mL infectious dose as assessed in these assays.

For hepatitis C, the most relevant data is related to the acute phase, where there has been some pedigree work in chimps. Those data would support about 1-20 HCV RNA equivalence per chimp infectious dose. Interestingly, once people seroconvert the infectivity of the virus drops profoundly, to the extent that you actually detect hundreds to thousands of viral equivalents per chimp infectious dose, suggesting that there is immune complex neutralization.

For HIV, the data would support, with some additional extrapolations, that there is probably about 1000 to 10,000 viral particle equivalents per infectious dose.

[Slide]

The final slide on this topic is a slide I think I showed a few meetings ago, which is a study that Harvey

Alter has primarily done with Chris Murphy, which really are the critical experiments that we are trying to extend now that involve actually transfusion of an animal and collection of large volumes of blood from that animal at weekly intervals. The initial animal was documented to develop viremia and seroconvert beginning at week 5. Then donations that were obtained and stored from several weeks prior to seroconversion were transmitted into second animals.

The question was asked when, during this so-called eclipse phase or predetectable viremic phase, did these animals become infectious? Were these units that had undetectable virus by nucleic acid and isolation methods actually contain enough material to transmit? Fortunately, the answer from this initial experiment was no. The units collected prior to virus detectability by nucleic acid tests did not cause infection. Only when we detected RNA did transmission occur to the second chimp.

These studies are being extended now, and there is work in progress to try to extend these studies to many more seroconversion panels, using actually human source plasma panel material and infusing them serially into chimpanzees to get a much better characterization of the relationship between infectivity during seroconversion to detection of levels of RNA as the RNA evolves.

[Slide]

So just to put this into perspective, we have been focused exclusively on understanding the window period. Now, how does the window period duration translate into understanding of risk? Really, the window period duration only plays into one source of risk, which is the window period pre-seroconversion units. And, you will hear a lot of discussion about this in the next two days, the way we derive risk of window period units from window period estimates is using the incidence rate, the rate of new infection. One can either reduce risk by selectively collecting blood from donors who are at low risk and, therefore, have low incidence of seroconversion, or by trying to reduce the window period either by making better antibody tests, adding DNA and RNA tests, or by effectively interdicting the window phase units through inventory holds or quarantines. That is really what all the focus is about, and that will be discussed at length.

The other point I want to make is that, again, the window period risk is only one component of the overall risk for each virus. For most of the viruses it is by far the predominant contributor to risk. For HIV, for example, in this analysis, and I think you received this review, 93% of the total risk for HIV is believed to be due to window phase, with only minimal contributions from immunovariant

viruses, from rare non-seroconverters or from test error.

For hepatitis C it is a little bit more controversial. There was some data suggesting that there may be a moderate number of non-seroconverting viremic donors. I think you will see data at this meeting that supports that this is not true and that, in fact, for HCV, as HIV, probably 80-plus percent of the risk is due to window phase units. For HCV test error becomes more substantial because the prevalence of HCV in the donor base is so much higher. So, rare errors on positive units can potentially sneak through.

For HBV virtually all window phase and for HTLV also. Now that we have a bona fide HTLV combi test, we believe that most of the risk is window period.

This is shown here to emphasize that although window period risk is the major contributor to risk, there are other sources of risk. So, whatever measures are being done here in terms of potentially interdicting inventory, they will not necessarily eradicate risk.

I will stop there. Thank you.

DR. HOLLINGER: Thank you very much, Dr. Busch. I think right now we will get the reading of the questions. Then we are going to take a short break and then we will come back with the three other presentations. So, we are going to have Dr. Biswas read the questions for the

committee on the FDA proposal on plasma inventory hold.

Presentation of Questions to the Committee

DR. BISWAS: These are questions hat the FDA would like the committee eventually to consider.

[Slide]

Question 1, does the committee agree (a) that FDA should recommend that a unit of source plasma should not be used until the donor of the unit returns to the collecting center after a designated period of time, and continues to meet suitable donor criteria, and (b) that the duration of quarantine for source plasma should be based on the window period for HIV, HCV and HBV?

[Slide]

Question 2, if the committee votes yes to questions 1(a) and 1(b) above, should the same recommendations be applied to recovered plasma?

Question 3, does the committee agree that if the donor of the plasma unit does not return to the blood establishment for requalification, the unit could be used for manufacture of non-injectable products?

Thanks. That is it.

DR. HOLLINGER: Thank you. We are now going to take a break for 15 minutes. So, we will reconvene at 10:48.

[Brief recess]

DR. HOLLINGER: This is the open public hearing. There are five people who have asked to speak in the open public hearing. The first speaker is Dr. Susan Stramer, from the American Red Cross. Susan?

Open Public Hearing

[Slide]

DR. STRAMER: I have prepared data to discuss the impact of both a plasma hold period awaiting host determination information, which I am abbreviating PDI, and then I am also going to show you data showing the impact of a plasma quarantine until donors return for subsequent donation.

[Slide]

This slide displays the cumulative information received reporting post-donation information for sampling of categories related to transfusion-transmitted diseases. So, what you see here is times of collection on the X axis and the amount of information we accumulate over time.

So, over a period, for example, following 6 months we may have 30% of additional information, that is, from call-backs or from subsequent donation information provided from the donor. By 6-12 months, or actually up to a year, we will have less than 50% of information based on post-donation factors.

[Slide]

To show you the categories that I picked so there is no bias included in these data, they are listed here. So, you can see over time, for example, for a history of contact with a person with hepatitis or IV drug use, these fairly well aggregate to the information being collected greater than 1-year period of time. So, plasma hold periods and these times really allow very little information to be collected.

[Slide]

So, in summary regarding a plasma hold period, the way the product is processed, first plasma is collected and then not pooled for a period of 4-6 weeks. So, if we do receive post-donation information we can act on that within the period of 4-6 weeks but, again, that only includes 5% of the subsequent information. The pooled product then is within Red Cross control for an additional 10 weeks, and it is actually 16 weeks if you include the time for manufacture of matched albumin for the product. But even over this period of time of another 4 months or 16 weeks we only obtain an additional 12.5-30% of post-donation information.

So then, in summary, we would have less than 50% information received by 1-year period of time, such that the benefit of the 60-90-day plasma hold beyond that which is currently happening from these time periods up here, the benefit of that is truly minimal. Then as we talked about

earlier at this meeting, the benefit of an additional plasma hold must be considered relative to product shortages.

[Slide]

Now, I turn to the next topic which has a greater impact, which is related to plasma quarantine. Before I show the data for this, I am going to talk about the conclusions and then show you one slide of data.

So, issues related to plasma quarantine include the fact that currently all collected plasma from volunteer donors is used to treat patients. I would like to emphasize that the plasma used for fractionated products is all inactivated by validated processes including ST treatment or pasteurization, and these processes have a proven track record of safety. In addition, 21% of donations are from first-time donors, and it is truly unknown what percent of the product would not be available because first-time or repeat donors did not return for subsequent donations.

We have some projections of this, and Chris Lamb, the vice president of our plasma operations, will show those data, followed by a statement from Brian McDonnough, the responsible head of the Red Cross.

[Slide]

The data that I will show will show the impact of plasma quarantine as the 50% of plasma from donors who subsequently donate would not be available for 6 months with

initially no product availability during the first 56 days of implementation. Another 6 months would be required to release the next 25%.

One must consider alternate approaches to decreasing risk, such as discussed by Dr. Busch in the previous presentation, such that window period donations from seroconverting individuals, which this practice is aimed to interdict which will include donations from both first-time and repeat donors, would be detected by pooled genome amplification testing for both HIV and HCV RNA that we plan to implement under IND.

[Slide]

Let me show you the data for interdonation intervals. If you follow along on the Y axis, this is the cumulative percent of donors returning for subsequent donation. The mean of these data are 364 days. So, the mean of our interdonation intervals is 1 year. The 50th percentile, the median, is 168 days. So, if you follow along here, you can see how much product would be available, only 25% after 3 months, 50% after 6 months, 75% after 1 year, etc. In fact, interestingly enough, 99% would be released after a period of 7.7 years.

I am now going to turn over the data on product availability to Chris Lamb, and I believe he has three overheads.

MR. LAMB: Good morning. My name is Chris Lamb. I am the Vice President for Plasma Operations with the American Red Cross, and I apologize for keeping you waiting.

[Slide]

Basically, what I wanted to show is the impact of a quarantine if we waited to retest donors prior to use of the plasma for fractionation or further manufacturing of the plasma for derivative products.

If we look here, there are three major product lines, which are IGIV, albumin and Factor VIII. Currently, the Red Cross makes available, or plans to make available in the next year as, for example you can see here, on the left, 3.4 million gm of IGIV, and grams is the common denominator that we use. This represents approximately 20% of the U.S. market. What we see is, because not many donors would return during the first 6 months, that in essence we would lose all of this capacity or supply to the marketplace. So, in essence, certainly for a 6-month period, and I think this is probably conservative, we would go from an annual rate of about 3.4 million grams, again, 20% of the market, down to about zero. Then, about a year later, we think we may be able to get back up to about half of that, which is about 1.7 million grams.

This data is from the American Red Cross in terms of the plasma it processes or has processed on a contract

basis. In addition, there is other non-Red Cross recovered plasma that is processed, that primarily is processed by the Swiss Red Cross. So, this 3.4 million grams would probably go up at least 50%, and I think you would see a similar impact where that would go down to about zero for a 6-month period and then go down to about half of that. So, probably you would take between 20% and 30% of the available supply off the marketplace during an initial period of time of 6-plus months, and then the available supply would be reduced substantially over the long term.

The same is true with albumin. Again, the American Red Cross provides about 2.4 million grams -- I am sorry, 12.5 equivalent units, again about 20% of the market and, again, this would dramatically go down during a 6-month period and then level off to about 50% of our current supply.

With Factor VIII, we currently provide about 93 million units, which is about 15% of the market and, again, this would diminish down to zero and then tail off to about 50% of what we normally supply.

Again, with both the albumin and the IGIV you need to add about 50%, at least, to cover the product that is manufactured by the Swiss Red Cross of recovered plasma from non-Red Cross blood centers.

I would add that all these products are in short

supply currently. The IGIV, I think you heard about the shortage. While there may be some lessening of the impact in the last couple of months, we certainly have not seen that. We basically live on less than a week inventory at any one time, and it is basically just based on what we can have produced for us. So, we get emergency orders, a couple each day and certainly 10-12 a week, and at any one time over the last 6 months we have had back orders where we simply have not been able to supply the product.

Albumin, again, has been in extremely short supply over the last 6-8 months and this would only further exacerbate the problem. Factor VIII, although there hasn't been a situation, I don't think, where people were unable to get product, certainly in our experience the supply has been very tight.

So, to summarize, I think the impact of this proposal would essentially be rather severe over the next year or two and would exacerbate an already bad situation. I know this committee doesn't get involved with cost, but the cost of product to the patients, I think, has already increased substantially over the last couple of months and would also increase as well. Thank you very much.

DR. HOLLINGER: Thank you.

MR. MCDONNOUGH: Thank you. I am Brian McDonnough, the Chief Operating Officer and Responsible Head

for the American Red Cross Blood Services.

Red Cross plasma, which is derived entirely from voluntary donors, is used for transfusable components such as red cells, fresh-frozen plasma and others, but also for derivative products, AHF, IVIG and serum albumin. The safety record of voluntary-derived plasma derivatives is extraordinary. There have been no documented cases of disease transmission from Red Cross IGIV since the introduction of the solvent detergent process in 1993. More than 1.2 billion international units of ARC HAF have been transfused since 1988 without a single documented case of transmission. There has never been a disease transmission from ARC albumin.

The solvent detergent treated plasma, when licensed, will add yet another layer of safety to the plasma for transfusion. Pooled gene amplification testing, soon to be introduced for plasma derivatives and all other products, will result in a further major reduction in the window period donations for HCV and HIV. This attention to safety and our success in achieving it, we believe, for the entire blood banking industry is extraordinary.

We propose that the key issue now is one less of safety and more to be one of supply. The nation currently has a critical shortage of IVIG, albumin and HAF. Emergency triage of these products is necessary to meet essential

patient care requirements. As you have heard from Dr. Stramer and others, the requirement to quarantine plasma and retest the donor pool prior to release will devastate this already marginal supply.

We estimate that as much as 25% percent of Red Cross volunteer plasma will be discarded because first-time donors do not return. In addition, 25% of the repeat volunteer donors do not return within the first year, resulting in a further loss of plasma. We believe the quarantine process is essentially redundant to the solvent detergent process, with no increase in safety but a very significant diminution of supply and a very significant increase in cost to patients.

The Red Cross believes that this proposal will have an extraordinary negative impact on the supply of essential blood products and derivatives which are already in critically short supply. The Red Cross urges that the committee regard this proposal to quarantine and retest recovered plasma as being detrimental to the clinical needs of the American people.

The Red Cross is further willing and prepared to discuss other proposals that may improve the safety without jeopardizing the supply of these essential blood products. Thank you.

DR. HOLLINGER: Thank you. The next presenter is

Mr. Jason Bablak, with the International Plasma Products Industry Association.

MR. BABLAK: Good morning. My name is Jason Bablak, and I am Director of Regulatory Affairs for the International Plasma Products Industry Association, the international trade association representing the commercial producers of plasma-based therapies. Our members produce approximately 80% of the products for the U.S. market, and include the four largest commercial fractionators: Alpha Therapeutic, Baxter Health Care, Bayer Corporation, and Centeon.

Continual improvement in the margin of safety of plasma-based therapies is a priority to our industry. As part of this constant examination, IPPIA developed a series of voluntary initiatives to further improve the margin of safety for these products. These initiatives, presented to this committee last September, include the exclusion of one-time only donors, a 60-day inventory hold for source plasma, and the implementation of PCR testing. These initiatives go beyond the current regulatory requirements and further reduce the potential that the so-called window period donations could enter the manufacturing process.

The American Blood Resources Association will present data later this afternoon that will provide some preliminary evidence of the success of our current voluntary

initiatives in further increasing the margin of safety. It is important to realize, however, that these initiatives just focus on the quality and safety of the starting material, and that validated viral elimination techniques initiated during processing contribute to the removal or inactivation of any remaining virus particles that may ve been sub-detectable and evaded other safeguards.

While the ABRA presentation will show the effectiveness of our programs, we must advise the committee that the data is still preliminary and our investigation is still ongoing. We appreciate the serious review the FDA and others have given our efforts to further improve the margin of plasma-based therapies, however, we request that the FDA, and all interested parties, allow us to complete our current data collection and evaluation of these initiatives before adding any additional requirements. Our industry has always responded to the scientific evidence for improvements in the safety and efficacy of our products, and we believe that the evidence will show that these voluntary initiatives further increase the margin of safety.

This morning, the agency proposed the addition of a quarantine period for all source plasma units that would require the retesting of a donor after a certain period, based on the window period, before that unit could be released for further manufacture. While we have not had

very much time to review this proposal, we believe the reasoning behind the FDA's recommendation is to close the window period. We support this reasoning. However, we believe this proposal may present certain logistical problems, and could also have a substantial impact on the supply of source plasma and, therefore, on plasma-based therapies that we produce.

As a consequence of this proposal, the last several donations from any donor who stops donating would always be discarded. While the impact is unknown at this time, we believe roughly 1 million of the 1.5 million donors cycle through our centers in any given year. If we assume that the quarantine period will be somewhere around 30 days, and that each donor donates once a week for some period of time before the donor stops, approximately 4 million donations could be diverted from the production of these life-saving therapies each year.

While our industry adheres to the highest safety standards and supports continual improvement, we cannot support any initiative that could destroy such vast amounts of this precious resource. To put this into perspective, each year under this proposal we could destroy as many as 4 million donations, each completely tested and nonreactive, to improve the possibility assessment that a window period unit might enter the manufacturing process by a fraction of

a percentage point.

As I stated earlier, we believe the reasoning behind the FDA's recommendation is to close the window period. This same logic was used to develop our current voluntary initiatives. We believe that the data will show that the combination of these initiatives have achieved substantially similar results to those expected to be achieved by the FDA quarantine proposal without disrupting the supply or exponentially increasing opportunities for documentation errors.

We commit at this time to come back to this committee in June and present data to both further substantiate our achievements and review the FDA's quarantine proposal in more detail. If at that time the data shows that our initiatives need adjustment, we will respond to that data and propose a method to further close the window period.

Thank you for the opportunity to respond to this proposal. Our industry is dedicated to the continuous improvement in our efforts towards increasing the margin of safety in plasma-based therapies so that the people who depend upon them for their health and their very lives will know that these therapies are as safe as possible, effective and available. We look forward to returning in June to discuss in more detail the results of our current voluntary

initiatives.

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

DR. LINDEN: What is your total number of donations per year, i.e., what percent is that 4 million that you are saying would be lost?

MR. BABLAK: We haven't estimated it, and ABRA is actually going to present some data on this, but about 13 million.

DR. LINDEN: Thank you.

DR. KOERPER: And when did all the manufacturers institute these voluntary plans?

MR. BABLAK: The first-time donor exclusion began in July of last year. The 60-day hold was bumped up from a 30-day hold at the beginning of this year. PCR testing currently is under IND and each of the manufacturers is working with the FDA to implement that as quickly as possible.

DR. KOERPER: So, in June you will have data from about 6-9 months on the elimination of first-time donors?

MR. BABLAK: Yes, and later this afternoon ABRA is actually going to be presenting some of that data. Like I said, that collection is still ongoing; it is in the middle of it.

DR. KOERPER: Exactly. And on the 60-day inventory hold you really won't have much information even

by June.

MR. BABLAK: Like I said, we started out with a 30-day hold and it has been bumped up to a 60-day hold, and ABRA, later this afternoon, will present some data on what would have been removed under a 60-day hold.

DR. KOERPER: When did the 30-day hold begin?

MR. BABLAK: I think that was initiated in July of last year as well.

DR. HOLLINGER: I still don't understand the 4 million donations that you are going to lose. Are these actually lost donations and destroyed, not used?

MR. BABLAK: Yes, what the FDA proposed would be an actual quarantine where, if the donor does not come back to be retested after the period of time, the units within that period would not be able to be used. Because each donor eventually stops donating, any donation in that period would have to be destroyed.

DR. HOLLINGER: I guess I never really understood that logic, you know, if the person comes back and they find something you are not going to use both of those bloods, but if he just doesn't come back in 60 days you are going to use it. I don't understand the logic behind that.

MR. BABLAK: What that does, our donors typically donate on a regular basis for some period of time, and it allows us to track and monitor those donors as they come

back and are retested throughout their donating history. Obviously, when they stop, you stop getting data on them. But that doesn't mean that those units are any more risky. It just means you don't have any data to follow up.

DR. HOLLINGER: Yes, but my understanding is that if you are a first-time donor that comes in and he doesn't show up again for 60 days, or comes in, in 90 days, or doesn't show up at all, you will use that --

MR. BABLAK: No, no. The first-time donor is never used --

DR. HOLLINGER: This is somebody who has been a qualified donor in the past --

MR. BABLAK: Correct.

DR. HOLLINGER: Okay, sorry. Thank you.

DR. BOYLE: Could you now, or will you tell us the various elements behind how much you lose under the different options that are being discussed here? I mean, your 4 million, is that the difference between the 60 days that you are basically putting in effect versus the window period, or is that the total in terms of any deferral?

MR. BABLAK: The 4 million is just an estimate. We haven't had a whole lot of time to put any real data together on this, and so what we have done is just tried to estimate based on some ball park figures. ABRA will present a little more detailed data right after me and also this

afternoon on that. But to answer your question, that is what we are asking the committee to do, to come back in June and present a more detailed presentation on our voluntary initiatives and compare them to what the FDA has proposed with this quarantine.

DR. BOYLE: And when you come back in June you will show it in terms of the various elements that are being proposed, because there is more than one piece to the FDA proposal?

MR. BABLAK: Correct.

MR. DUBIN: How about the issue raised in the FDA report in terms of a donor coming back, but a donor coming back 48, 72 hours later vis a vis the window period? And then you have that donor back but you are way within the window period so the second test really doesn't mean anything in terms of solving the window period problem.

MR. BABLAK: The voluntary initiatives that we put together -- there are four of them -- are to work in conjunction with one another. No one is sufficient by itself. That is why we put four out. The first one that you are talking about is the applicant donor standard, and the people from ABRA can actually explain this more because it involves them. But that is based more on the donor's ability to come back and willingness to come back. I think the data that was presented in September showed that about

95% of the positives are in one-time only donors. So, what we looked at with this data is what we can do to eliminate that risk, and that is to not use first-time donors. So, it was not originally used to close the window period. That is what the 60-day hold is for. So, when you use them in conjunction you have someone who comes back on a repeated basis and you have that time period of 60 days to then evaluate that donor and you can see that they start to work in conjunction as opposed to each one looking at that individual.

DR. HOLLINGER: Thank you. The next presenter is from American Blood Resources Association, Mr. Chris Healey.

MR. HEALEY: Good morning. My name is Christopher Healey, and I am the Director of Government Affairs for the American Blood Resources Association. ABRA, as you probably all know, is the trade association that represents the nation's source plasma collection industry. ABRA members own and operate nearly 400 source plasma collection centers that supply the U.S. market through roughly 11 million liters of plasma annually.

We appreciate the opportunity to comment on FDA's proposed plasma quarantine, and we support the objectives that underlie the proposal. The source plasma industry is committed to increasing the margin of safety wherever feasible. This is borne out by a number of programs and

initiatives, notably the Quality Plasma Program, QPP, and its certification requirements for source plasma collection centers. In addition to the safety initiatives that Mr. Bablak mentioned, including the qualified donor standard, the inventory holds PCR testing and the viral marker standard.

In a presentation this afternoon, Dr. Toby Simon will speak on behalf of ABRA and present data that demonstrate the effectiveness of the qualified donor standard in the 60-day inventory hold. You will also hear more about the effects PCR throughout the day by presentations by ABRA members and IPPIA members. I would just like to take this opportunity to briefly address quarantine proposal.

As we understand it, the quarantine proposal is aimed at reducing the probability that a potentially infective but nonreactive donation may enter the manufacturing pool, the so-called window unit. This is an important objective to which the source plasma industry has already committed extensive resources. However, it is important to realize that this is not the end of the safety chain. During manufacturing, source plasma fractionators implement validated viral elimination steps that inactivate or remove virus that may have been below detection levels prior to pooling.

Let me now address the industry's efforts directed toward elimination of possible window unit donations. Two current industry standards have a substantial effect in reducing the potential for a window unit to enter the manufacturing pool. These are the 60-day hold and PCR testing. The 60-day inventory hold permits interdiction of nearly all window units suspect for HIV and HBsAg prior to pooling. With the addition of PCR, the inventory hold will permit interdiction of nearly all window units suspect for HCV.

In contrast, at least for HBsAg and for HBV, a 30-day quarantine may actually increase the probability of a window unit entering the manufacturing pool. While the quarantine has little or no effect on HIV and HCV when compared to the 60-day hold with PCR, the window period for HBsAg is such that seroconversion may not occur within the quarantine period and window units may not be an interdiction.

[Slide]

This slide shows the comparison of the probability of a window unit entering the pool. You can see, on the left, for HIV with just the 60-day hold the probability is 0.6 donations per million. With the 60-day hold and PCR it is at 0.2. These are, as you can see, negligible amounts. Under a quarantine that number would be zero. For HCV with

PCR it is 0.7 and under a quarantine, again, zero. Once again, virtually no difference.

In contrast, for HBsAg with the 60-day hold our probability is currently 34 units per million. But under a proposed 30-day quarantine, for example, that number would shoot up to 160 because of the number of seroconversions that would occur outside of that 30-day period.

Any marginal safety increase that may result from a quarantine must be weighed against its effect on the source plasma supply, and the logistical and resource issues associated with managing a quarantine. Although ABRA has not had sufficient time to fully evaluate the impact of a quarantine on the industry or consumers, we have made some general assessments and preliminary evaluations.

For example, we can estimate that roughly 15,500 donors will be deferred on the basis of repeat reactive tests annually. Under the current 60-day hold, this necessitates tracking roughly 150,000 suspect window donations for the purposes of interdicting them prior to pooling. By contrast, under a quarantine, each of the roughly 13 million negative donations given every year would have to be tracked back to more than 1.5 million already qualified donors. This could have a dramatic effect on the industry and consumers.

[Slide]

It is important to note that the systems necessary to adequately manage this kind of increased tracking in unit release requirement, something of this magnitude, are not currently in place.

This is just to give you a rough idea of what is currently done under the 60-day hold. For donors, you can see that we track 15,500 donors. Under a proposed 30-day quarantine it would be all donors, which is 1.5 million. You can see the exponential increase in tracking requirements. For donations it is even more dramatic. It goes from 150,000 to 13 million.

Although the logistical complexities associated with a quarantine may be staggering, the source plasma supplies are also likely to be significantly impacted. You heard Brian McDonnough speak to this issue in detail. While we have not been able to collect conclusive data, we have been able to make some preliminary estimates for the projected source plasma loss that would result.

The loss of product from a 60-day hold is easily estimated based on seroprevalence data. This number turns out to be roughly 1.15% or approximately 11 million liters of source plasma collected annually.

[Slide]

By contrast, under a quarantine the loss occasioned would be somewhere between 25% and 40%. You can

see on this relatively simple chart that the 2 bars go up to 100% because they reflect the total collection. So, the number of collections made every year are going to remain constant under a hold or a quarantine. We will still be collecting roughly 11 million liters. But under the hold, you can see that we interdict roughly 1.15% suspect window units, and that is what we destroy or interdict prior to pooling.

In contrast, under quarantine that number would shoot up to 25% to 40%, and those are all test negative, nonreactive units that we would simply have to let go. So, that would be a dramatic impact on the supply.

It is important to note that these estimates are preliminary and we simply haven't had enough time to put together any conclusive data but, like IPPIA, we would like to come back to the committee and give further evidence as to the impact of our safety initiatives that are already in place, and address this or any other proposal. Thanks.

DR. HOLLINGER: Yes, Dr. Stroncek?

DR. STRONCEK: Long-term, what limits the amount of product that is produced by your industry? Is it the availability of donors, the availability of manufacturing plants or the demand for the products? What I am getting at is would this be short-term? Are we donor limited, or given time would you just recruit more donors and increase your

production back to current levels?

MR. HEALEY: My understanding is that there would probably not be a dramatic change in the numbers of donors, that that has been relatively constant and will likely remain so. I don't have any detailed data.

DR. BOYLE: We have been concerned about the availability of certain information, and you are going to go about obtaining some information for us to make certain determinations. Is there an ability to do an independent review or that information by the FDA or someone else to basically verify the assertions that you are going to make in June?

MR. HEALEY: Are you asking then if basically our data on effectiveness of our programs will be available to the FDA?

DR. BOYLE: Exactly.

MR. HEALEY: I am sure we would be happy to come forward and discuss our data collection methods, and go through them and give a full exposition of exactly what we did, and how we got our numbers. Sure.

DR. KHABBAZ: You mentioned that your estimates of the source plasma loss with the quarantine would be 25% to 40%. Can you estimate for us what percentage of nucleic acid positive donations would be of those lost? What percentage might test positive?

MR. HEALEY: What percentage of those would test positive?

DR. KHABBAZ: Yes.

MR. HEALEY: Well, the chart that I put up earlier shows the tracking between the number of window units interdicted and, again, those are test negative and nonreactive. So, I don't know how I would go about estimating the number of the lost units that would actually test positive. Presumably, none of those would test positive because they would be interdicted if they were. The donor would be deferred and the units would not be used. So, none of those lost would actually be test positive.

DR. KHABBAZ: Nucleic acid test positive.

MR. HEALEY: I am sorry, we haven't put those data together. Others may have data on that this afternoon.

DR. HOLMBERG: Does your organization or the IPPIA deal only with source plasma, or are you also representing recovered plasma?

MR. HEALEY: ABRA is the trade association for the source plasma.

DR. HOLMBERG: Just source plasma?

MR. HEALEY: That is right.

DR. HOLLINGER: Can you tell me again if you have a first-time donor that comes to you, and that donor comes back in a week and he checks out okay, those two units can

be used.

MR. HEALEY: They are held for 60 days, based on the bleed date, and if additional information becomes known during that interval, any basis for deferral, those units are interdicted. Otherwise, they are used.

DR. HOLLINGER: Otherwise they are used. Even if they come back in 48 hours, 72 hours, the units are used, even if it is a first-time donor.

MR. HEALEY: Not a first-time donor.

DR. HOLLINGER: No, I am saying if a first-time donor comes in and you have tested, and then he comes back 72 hours later --

MR. HEALEY: Right.

DR. HOLLINGER: -- the units are then held for 60 days and then you can use them.

MR. HEALEY: That is correct.

DR. HOLLINGER: Even if it is a first-time donor. I want to make the distinction between somebody else that comes in who has been a donor for a long period of time, been tested for a long period of time, and then comes back in 72 hours or a week. I think there are big differences between those two.

MR. HEALEY: They are treated the same.

DR. HOLLINGER: They are treated exactly the same? Okay.

MR. HEALEY: An easy way to think about the effects of the quarantine is a typical college student donor who hits final exams and goes home for the summer, and stops donating June 1st or whenever exams kick in, and doesn't come back to the program, well, those whole months of donations then, if you have a 30-day quarantine, would be lost. That is sort of the perspective that the industry is looking at it from.

DR. HOLLINGER: Is that the understanding about what the 30-day quarantine does, that the unit would be lost, or just that that is the quarantine time, that you have to have a period of time before they can come back, a short period of time.

MS. HEALEY: As I understand it, there has to be retesting.

MS. BISWAS: Remember that in my presentation I didn't give any time. I just said it would be based on a window period. So, when Chris Healey said, you know, a 30-day quarantine, that is his estimation of something that we haven't really thought about.

DR. HOLLINGER: No, I understand that. I guess it is a minimal time I was looking for. My understanding of the quarantine, whatever window period one would choose, is that they would have to wait at least that long before they could come back. But then, like the college student, who

leaves and comes back at 50 days, or 60 or 90, you are not going to lose those units. They will still be there for use at that point, but you would have to have at least a period of time, 30, 60, 90 days, whatever period of time is chosen.

MR. HEALEY: So, we took a conservative estimate in our data and chose a 30-day quarantine that would impact on a supply that was already somewhere in the neighborhood of 25% to 40%. So, we haven't run the numbers for 60 or 90 days which, obviously, would have a lot more dramatic effect.

DR. HOLLINGER: But that is assuming you would lose them.

MR. HEALEY: Right.

DR. HOLLINGER: And that is my point.

MR. BISWAS: Under the quarantine procedure the donor has to come back.

DR. HOLLINGER: Yes. That is right, but he can come back after that period of time.

MS. BISWAS: Sure.

DR. HOLLINGER: Those units are not going to be lost.

MR. HEALEY: Well, they could be held indefinitely, sure, but the point is at what point do you draw the line, and what are the logistical problems associated with managing that kind of tracking system,

holding those units from manufacture so you don't have them available for supply.

DR. HOLLINGER: Fair enough.

MR. DUBIN: Let's use your college student. If he or she leaves on June 30th and doesn't come back until September 7th, you haven't held those units that long. We are talking about 60 days roughly. So, you aren't going to lose those units because that college student is going to be back in early September when he or she comes back to school. That is 60 days, roughly. So, it is not a given that you are going to end up having to trash those units because that college student went home. True?

MR. HEALEY: That is potentially true but, once again, the issues are where are they in the manufacturing process; can they be released? One of the things that is different about a quarantine versus a 60-day hold is that quarantine actually become release criteria so that that unit of plasma cannot be released from the collection center or wherever until there is documentation that there has been a return of that donor. So, these units then would have to be released on a unit by unit basis, in contrast to an inventory hold where you can release larger numbers of lots of units, and then do the paperwork at the back end and track them to make sure that there is no deferral that made it.

DR. MITCHELL: Do you do anything right now to encourage people to come back and to redonate?

MR. HEALEY: Sure. They are the cornerstone of the source plasma industry. I mean, the redonors are what we base our donor --

DR. MITCHELL: And what do you do to encourage people to come back? Do you contact them?

MR. HEALEY: I don't know that we have outreach to them currently but, you know, we encourage them through a variety of means, and through participation in the program itself.

DR. KHABBAZ: I want to go back to Dr. Boyle's suggestion and endorse it. I think it would be actually very important to have the data reviewed by an independent group before it is presented to us. I think some of what we will struggle with in discussion is, you know, that at face value we tell you that there is going to be a shortage and, quite frankly, we are in a vacuum here.

DR. LINDEN: I guess I have to sort of bring up what I brought up at a previous meeting, which is that I think the analogy here is really for semen banks, which have repeated paid donations and then the donor must come back at least six months later only for a blood sample for testing, and what they do is withhold a significant portion of the payment which is then not given until that blood sample is

given. Have you done any work to investigate what type of incentive would be required to have your donors come back for a blood sample only 60 days later, or whatever? I mean, if you withdraw, like, $50, don't you think they would come in for $50? Granted, some people are graduating and students, as the example you gave, might physically not be able to come.

MR. HEALEY: I can't tell you that we have undertaken those kind of analyses and, frankly, we have been operating in a very short time frame even to bring you the data that we did today. So, we are working as hard as we can to bring you what we can, and that is why we have made a commitment to come back in June and give you more information about what this may mean.

DR. LINDEN: Yes, I think that would be helpful because I think we are assuming that the people who don't come back now would not come back but, in fact, you might be able to induce them to do so with money.

DR. HOLLINGER: Thank you. Dr. Verter?

DR. VERTER: Just to clarify something, when we are talking about this quarantine and the number of donations, is this kind of a rolling thing? If someone comes in every four months, every time he comes in the previous ones are okay but that one gets held until the next one? So, you are continually holding?

MR. HEALEY: Each donation has to be quarantined.

DR. VERTER: No matter what extensive history prior to that donation you have on the person?

MR. HEALEY: Yes.

DR. HOLLINGER: It is a big computer program! Yes, Dr. Buchholz?

DR. BUCHHOLZ: Some of the coag factors, for example, are fairly labile. Do we have any information on loss of coag factors in terms of ultimate recovery and yield in the final product as a function of storage time prior to processing?

MR. HEALEY: I don't have any of those data here today, but industry can see what we can do about that.

DR. BUCHHOLZ: Because that would seem to be another factor, or a potential factor in addition to just the material that would be lost.

MR. HEALEY: Part of the issue for a quarantine is that, if it is a release criterion that has to be done at the collection center, you are talking about having to increase the capacity for storage. The logistical issues associated with this are severe.

DR. EPSTEIN: If I could respond to Dr. Buchholz, there is 10-year dating for source plasma based on the frozen collection. So, the hold periods that we are talking about are negligible compared to the viability of the source

unit.

DR. BUCHHOLZ: Okay, but not the 7.93 years --

DR. EPSTEIN: Well, I think it is important to clarify that the situation is not the same for recovered plasma, where the conditions of storage are not defined under regulation. They are, of course, stipulated by the procurer of the recovered plasma, but where the material may have been held at a refrigerator temperature for a very long time, where there is no defined out-date where I think it has been quite clearly pointed out to us that the logistics based on the return of the donor are quite different. So, that is the reason that we separated the issue for the committee. We think that there is a set of considerations that should be examined for source plasma, and they may not be the same for recovered plasma.

DR. HOLLINGER: Source plasma is stored at minus 20 or minus 30?

DR. EPSTEIN: It is minus 20 for source plasma, or lower.

DR. HOLLINGER: Thank you. The next presenter is Dr. Steven Kleinman, of the AABB.

DR. KLEINMAN: Good morning. I have a short statement to make on behalf of the American Association of Blood Banks. I am Dr. Steven Kleinman, and I am Chair of the Transfusion-Transmitted Diseases Committee of that

organization.

The AABB is a professional association for approximately 2200 institutions engaged in the collection and transfusion of blood and blood components, including all American Red Cross blood service regions, independent and community blood centers, hospital-based blood banks and transfusion services, and more than 8500 individuals engaged in all aspects of blood collection, processing and transfusion. Our members are responsible for virtually all of the blood collected, and more than 80% of the blood transfused in the country.

The AABB was surprised to learn earlier this week about the FDA proposal before the BPAC to quarantine both source and recovered plasma collections until the donor returns and tests negative for all viral markers. We are disappointed that a proposal which would have such a profound impact on blood banking operations and plasma supply would be presented to the committee without sufficient time for prior discussions within the blood banking community.

We are also concerned about the precedent that would be established by the quarantine of recovered plasma vis a vis its possible extension to FFP for transfusion. We are not prepared at this meeting to provide definitive data on the impact of such a proposal on plasma supply.

Therefore, we respectfully request that the proposal be tabled or withdrawn until such time as the blood bank community can analyze the impact of the proposal and report its conclusions to the FDA. Thank you.

DR. HOLLINGER: Thank you, Steven. The final person who asked to speak today is Dr. Celso Bianca, for the American Blood Centers, ABC.

DR. BIANCO: Thank you. It is a very short statement. By name is Celso Bianco, and I am representing America's Blood Centers. America's Blood Centers congregates 72 independent community blood centers throughout the country, and America's Blood Centers collects about 45% of the volunteer blood donor collections.

We only learned about the proposal under consideration a few days ago, and did not have the opportunity to examine the full impact of quarantine, whatever the period is. However, looking at the limited data that was presented a few minutes ago by the American Red Cross, we can see that the impact would be absolutely devastating. If I could say in a more dramatic way, I believe that this is the death of recovered plasma or plasma from volunteer donors being used for further manufacture. Plasma from 85% of our collections is made into recovered plasma.

We request that FDA give us time to study that

impact, so that we can at least balance the benefits and the impact of such measures in terms of what we do and the availability of these products. It is hard to measure what the impact would be in terms of safety, but it is, I think, very easy to measure the impact that it would have on the volunteer blood donor collection system in the country. Thank you.

DR. HOLLINGER: Thank you, Celso. This concludes the formal open public hearing. Is there anyone else in the audience that wishes to make a statement before we close the public hearing and open it up to the committee discussion? If not, we are going to have the presentation of the questions again in a minute, but I asked Dr. Busch if he would summarize for us the window periods as we had them today, just in one transparency so we can deal with that.

[Slide]

DR. BUSCH: Dr. Hollinger asked me to try to capsulize what I presented. I have done that here. I sort of tried to discriminate between a window period estimate that is defined from exposure to seroconversion as opposed to the briefer period, subsequent to exposure where a person becomes viremic, detectable by nucleic acid tests or transmission studies and seroconversion.

So, we are kind of talking about this window period here, which is the longer total window period, and

for HIV from healthcare worker transmission studies, with older generation antibody tests the estimate was 40 days, with a range of 10-250. I think this would be cut probably in half, but we still have this concern with this delayed, rare individual who takes a prolonged period from exposure to seroconversion.

In contrast, the viremic phase prior to antibody is quite brief. RNA to antibody was estimated at about 8 days; RNA to p24 antigen at only about 3 days. Since we now screen with p24, we are really dealing with a very brief period during which we can detect RNA with current assays. If we project that, based on the analysis of the ramp up of virus when a person would have had a theoretical minuscule 1 copy/mL concentration, that could extend back as far as 20 days prior to antibody, or about 15 days prior to p24 antigen. So, that is HIV.

For hepatitis C, the data from exposure to seroconversion from transfusion studies is about 49 days, a range of 8-135 days. HCV RNA is detectable for the majority of that period, for 25 days prior to ALT, from the transfusion studies, and for 41 days prior to antibody from the seroconverting plasma donor studies. So, for HCV the vast majority of this pre-seroconversion phase is very viremic, and very high titer viremic. Again, there is no point in projecting back because the ramp up is so rapid.

For hepatitis B, from transfusion data the estimate is about 60 days from transfusion, with this range. DNA was detected about 7 days prior to HBsAg with the 200 copy sensitivity assay. Again, based on the ramp up data, we could project back when you would have a theoretical 1 copy, and that is quite a prolonged period, about 38 days, prior to surface antigen theoretically, although whether a person is infectious throughout this phase is unclear.

DR. HOLLINGER: Thank you, Mike, for that. I appreciate that. Just a historical note, Dr. Vyas and I were talking just a little while ago. You mentioned doubling times of about 3.9 days, I think. It is interesting, about 25 years ago the French and others have done studies with HBsAg that was injected into people, and found half-lives of about 4.6 days, very similar to the more sophisticated tests we have today. Yes, Dr. McCurdy?

DR. MCCURDY: Do we have any data on some of the viruses that are not inactivated? Each of these that are on here are inactivated by the standard procedures, and the concern is more about viral load in the plasma pool. How about those that are not virally inactivated, and is there any likelihood that any type of quarantine will let these illnesses come out to the point where they can be detected, and not tested for at this point, of course?

DR. HOLLINGER: Hepatitis A and parvovirus B19

would be the two I could think of right off the bat that have the most play in terms of window periods, and so on. Anybody have any data? That is a good point, Paul. I don't think we have that data right here.

We were going to present those questions again, just briefly, and then we will open it up for committee discussion. Let's just have the first two questions for right now, please.

Open Committee Discussion

DR. BISWAS: Question 1, does the committee agree, (a) that FDA should recommend that a unit of source plasma should not be used until the donor of the unit returns to the collecting center, after a designated period of time, and continues to meet suitable donor criteria and, (b) that the duration of quarantine for source plasma should be based on the window period for HIV, HCV and HBV?

DR. HOLLINGER: And number 2, of course, has to do with the question of recovered plasma. So, they are both being described. Thank you, Robin, for that.

Well, now opening this up for committee discussion, I think there are some important issues here, and we need to decide whether there is enough information at this point to make a decision, or whether one needs to have this tabled and discussed when more information is available. Dr. Boyle?

DR. BOYLE: Could I ask the FDA who have given us this proposal on the plasma inventory pool, earlier today they told us that there was a shortage in IGIV. They told us the shortage is likely to continue under present conditions. What they haven't said is what they estimate is the impact on availability with this proposal of theirs and, consequently on the other side, what they view as the safety benefits that would counter a reduction in the availability of IGIV and other products. Can we have somebody comment on that?

DR. BISWAS: I think in regard to the availability at this point in time, we don't have the data and we would be very glad to look at the industry data that they have. They just presented it, just now, and none of us, as far as I know, has seen this data. So, we would need to go back and pore over the figures that have been presented by industry.

What was your second question?

DR. BOYLE: What is the counterbalancing safety improvement as a result of this proposal?

DR. BISWAS: Well, I think that for the quarantine, if the quarantine really covered the window period, the infectious window period -- if it really covered it, there would be very few, or hardly any or no window period infectious units, contaminated units going to the

pools.

DR. EPSTEIN: I agree with what Dr. Biswas just said. I think perhaps a little bit of general orientation is needed. Why is the FDA doing this? As has been explained, industry put forward a set of proposals, and we understand that there has been some voluntary compliance with those proposals, although that has not been assessed by FDA. These proposals have not become FDA recommendations or requirements. What FDA is trying to figure out for each of the proposals is what is the scientific bases, and is it effective, and to what degree, and what should be the regulatory expectation?

I think that what we are saying between the lines here is that if the goal of an inventory hold is to interdict window period units, the gold standard is really a quarantine and retest. We are not saying, therefore, that should be the only possible strategy for managing donations. We are saying that we challenge the industry to explain to us, against that standard, how effective are the measures that they are putting in place. And, we don't know the answer to that question. I think we were hoping that that data would come to this meeting, and I think that what you have heard is that a declared commitment to gather pertinent information and bring it to us in June. So, I would not consider it unreasonable to table the question because we

haven't seen those data.

On the other hand, I think that if you ask, well, what would be the benefit of that system, Dr. Biswas, I think correctly, said the goal is to limit viral contamination of fractionation pools. We know that most of the contamination which occurs today is due to so-called window period units. We know that they occur. Now, the hold or quarantine is, as has been said, not the only strategy. We have also had many prior discussions on the development of PCR as a way to interdict at least detectable viremias which, as I think Dr. Busch has explained to us, probably for most of the agents cover most of the infectivity period, although there may still be small windows.

So, what we are talking about then are a set of strategies, each of which is designed to limit the viral burden of a fractionation pool. Now, why do we care, given viral inactivation? Well, we care because although we believe that the effectiveness of viral inactivation has been validated, we are concerned because there can be breakdowns of good manufacturing practice resulting in failure to carry out these procedures absolutely perfectly every time. And, the FDA has been faced many times with the question of figuring out a safety assessment in the face of some breach or deviation.

To date, I think it is fair to say that we have not had breaches with respect to viral inactivation of these agents which have raised serious concerns. But that is not to say that it couldn't happen. So, we think that limiting the viral burden of the input pool is an added safeguard and has a safety meaning. That is the goal here. But the quarantine or inventory hold is not the only strategy, and I think that one could conclude that it is not needed in addition to either the existing system or the addition of PCR when that transpires, and I think that these are all thinkable outcomes which the committee ought to consider.

But to put the matter in a nutshell, we are saying, okay, there is a voluntary inventory hold; it is not a regulatory position. We think the gold standard would be a true quarantine and we submit to you, you know, should we be seriously entertaining quarantines as opposed to inventory holds?

Now, you raise a very good point that they should not be considered without at the same time considering the impact on availability. I think that point is very well taken. I am glad that you made that point. But the truth is that we have not really heard what that impact would be, and that is the problem. I think that we have heard, with respect to the recovered plasma side, that the impact is likely to be disastrous, and we have heard that from

multiple independent speakers. I think with respect to the source plasma side, I have not yet heard data that I would accept as valid assessments, and we are waiting for those data and that is part of the problem.

I think it also has to be factored in that you have to distinguish short-term impacts which could be mitigated by phasing in of a policy, as opposed to long-term impacts which won't be reversed. I think that several speakers hinted at that, and that is also highly pertinent.

So, my answer to your question is there is good meaning to trying to interdict window periods at the level of determining suitability of collections; that that meaning is to limit viral burdens; that it is not the only strategy; and that FDA is not wedded to this proposal. We are simply asking should this be seriously considered.

DR. HOLLINGER: Thank you, Jay. Yes, Mr. Dubin?

MR. DUBIN: A couple of things, I think it is a rational approach for us to put direct review of this question off until the June meeting, but I think we can only do that if we are going to get the kind of data that we seek.

DR. HOLLINGER: Well, if this is the case, then we should talk a little bit about what kind of data you would like the source plasma group and the recovered plasma group to obtain for you so that we can say when you come here,

this is what we ask for; these are the things we expect.

MR. DUBIN: I guess I think over the two years I have sat here we have been asking for this data. We get generalized statements from the trade organization that represents all four of them. We don't get specific numbers from individual manufacturers. For example, we got a graph from the American Red Cross. They said here is our market share, and it was laid out. But we don't see that from the fractionators. We see ABRA and IPPIA giving general numbers and we can't get specifics and, again, we are being asked to make specific decisions, and we are hearing they will have a devastating impact.

Well, I keep sitting here saying, show me the meat. What is the impact? I don't want to make a decision where I will have to go back and explain to people with hemophilia why they are not going to be able to get a certain product that they happen to like because I made a poor decision. And, we have battled this, and debated it, and danced around it, and I hear staff saying -- I think, if I heard you correctly, Jay, I just heard you say the staff are challenging them to come up with the figures. We sit here and challenge them. Is it regulatory or are we doing this dance? I mean, who has the power to say these numbers need to come to the table so we can make intelligent decisions?

I agree with what has been said. It would be wrong for us to move on this policy fast. It is a potentially high impact that people have not had a chance to look at and review, and that would be a mistake. But I would hate to fly back across the country in June to sit down and talk about this and have the same kind of situation we have right now where we don't have specifics.

DR. BUCHHOLZ: Being a new guy on the committee and just having access to this material for four or five days, could I ask a question as to when industry was contacted as to preparing information to present at this meeting? I got a thread that seemed to go through all of the presentations that seemed to be, "golly, we heard about this last week, or a week and a half ago and we got together the information we could but, you know, we haven't had enough time." That would seem to me to be a pertinent part of the issue here. Has this information been requested in a time period that makes it reasonable to expect data that the committee could evaluate?

DR. HOLLINGER: Dr. Biswas, could you tell us when the various groups were contacted about this particular agenda item?

DR. BISWAS: Well, the agenda was published in the Federal Register. Linda Smallwood would know the precise date of that.

DR. SMALLWOOD: All of the trade organizations were sent an announcement of the BPAC agenda prior to the publication of the Federal Register notice, but essentially they were sent the agenda items at that time, and that was done very early. It was probably in February when that went out. It was faxed.

DR. BISWAS: But I should add that the precise proposals weren't transmitted to the industry until a few days ago. But the inventory hold agenda was sent out quite early on.

MR. REILLY: If I could just make one point? This is Jim Reilly with American Blood Resources. I think there are a couple of things that are worth noting. One is that the agenda being proposed 30 days ago doesn't necessarily enlighten us to what data would be specifically addressed because the proposal that came forward was not about inventory hold; it was about quarantine. There is a night and day difference in data that we need to deal with that.

The second point is even if it had been communicated 30 days ago, this is relatively complicated data to collect. It is not the kind of thing that you can do overnight, which is why we put some caveats around the data that we presented that it was preliminary, because it was done in a hurry in an effort to be responsive. So, I think there is a question of time limits here.

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

DR. STRONCEK: We could get more data, and we could wait three months; we could wait six months. I doubt that it is going to change a lot on how this committee could vote. I think we have had a lot of data here. I agree that with the recovered plasma industry it would probably be devastating to have a quarantine period, and it is probably not the right way to go.

But with the source plasma, the whole plasma proposal, it doesn't make any sense. It takes a long time to figure out what they are doing. There is plasma that they collect and then the donor doesn't come back -- I am not comfortable with that policy at all. I think it looks like the standard is going towards some kind of quarantine but they are just not biting the bullet to do it. I think this committee should really be worried about safety, and I would encourage us to vote for a quarantine period.

I know we have to be sensitive to the supply issues, but the source plasma industry is quite different than the recovered plasma industry and, you know, I think they have the ability to be entrepreneurial. They pay their donors. I would suspect someone will come up with a way to increase the recruitment and, in the long-run, make up for the losses they have based on the quarantine period. It would be unfortunate in that we would probably have more

shortages of product in the long-run, but in the long-run I think things would take care of themselves.

DR. HOLLINGER: Could you respond to the question though, since recovered plasma and source plasma are often made into the same products, could you have a double standard? Because, basically, that is what it would be. You are going to allow one group to do one thing and the other to have perhaps more stringent criteria. Could you deal with that?

DR. STRONCEK: Well, that might be difficult, but I think the problem if you go to a quarantine period with both is that you would really hurt the recovered plasma industry, and that would be another huge loss in product. That would probably be devastating to patients around the country.

MR. REILLY: I think the fallacy that seems to be emerging about source plasma is that you can just keep getting the donor back endlessly. The truth is that every donor at some point stops donating. Under a quarantine system, if it 30 days, 60 days, whatever it is, all of the donations that are in that period when the donor stops donating will be garbage basically, regardless of their test status. The data that Chris tried to present is that, if collections remain stable at 11 million liters or about 13 million donations, we will lose 25% of the donations, as a

very conservative estimate, on an ongoing basis. We know that 1/4 that we actually collect will be destroyed, ongoing, not just one time hit but permanently. You can try and get the donor back but there comes a point at which the donor just doesn't come back.

DR. VERTER: I have a couple of things to say. One, I actually agree with ABRA -- I forget where he was from, the gentleman that just spoke. This was a very short period of time for anyone to put together a solid presentation. Some folks may thing that with the computers that are available, and whatever, you should be able to get all this data together and present it in a coherent manner in four weeks. I would question that, and very seriously. So, I totally agree with the last member of the panel who spoke, that the main issue is safety and we shouldn't worry about other things, other than secondarily to supply. I think that is an issue.

However, I am kind of in support of tabling this for a couple of reasons. I don't feel like I have the data other than a knee-jerk reaction to vote for anything at this point. If I could have just a couple of minutes, I will tell you some of the things that I would like to see. But I think probably what needs to be done is maybe a subgroup of this committee should sit with FDA, or whatever, but someone needs to focus the people who will present in June as to

what we want. They may give ideas in addition to that but there should be some uniformity of the people presenting in what they present so that we can look from one group to the other as to how much they have done; what contribution they have to each of the various product sources; what the potential impact is.

Having said that, I don't today, for example -- and this may be because I haven't read enough, although I try to read most of it -- have the sense of exactly what the issue is for the viruses we do know about. For example, over the last five years on a yearly basis, how many people have become infected from the use of albumin IGIV or Factor VIII or IX from products?

DR. HOLLINGER: Zero.

DR. VERTER: Well, we have not been told that. I don't see how we can make an intelligent decision without knowing at least something about that. If it is other than zero, what is the relationship, for example, of the time between the donations for those that became infected, or the time since the last donation?

In addition, we have been presented with a tremendous amount of data today which tries to look at window periods and time to the infections. Some of the models that were presented may be fine, but from the data presented I have serious questions about the estimates. For

instance, I do not like extrapolation beyond the data and there were serious extrapolations to go backwards in time assuming a linear model. There could be an exponential model which would increase the time, not decrease it. So, I think we need to have someone present this, when they do modeling, what the assumptions are that they made in those models. There were kind of pseudo-survival curves that were presented to us a number of times. I don't think they were really survival curves. I think they were estimates from specific cohorts that were tested only at one point, and put together as if it was a cohort followed over time. If I am wrong, I apologize to the presenters, but that is the implication for the estimates we saw.

Finally, I would like to say that whereas I have absolutely no expertise or experience in how badly the actually supply would be reduced, I was playing around with a little model here and it is not, as I understand it, a static situation; it is dynamic. People today come into a blood resource center and donate. At some period of time, some of those people are going to come back; others are going to leave and never come back. But at that second period new people enter in and give, and it keeps on going. So, there is a flow here which may actually, after some period of time, if there were a quarantine catch up and maybe even exceed. I don't know, I doubt that. But with

some reasonably sophisticated computer programming you could do a lot of modeling with this kind of model to see under what conditions -- if there was a 20% dropout, 50%, if the number coming in next time was 50 or the same number that came in the time before, just what the impact would be.

So, I think there is a lot of work that could be done here to help us by the FDA and the community to make a rational decision that we don't have right now.

DR. HOLLINGER: And along those same lines too, to deal with the comments you are making, if the goal is to interdict window period units we need to know how many units are being interdicted. That is another thing we would like to have information on.

But, as I said, this has been just a short time when they actually started this. I think it was September, October that there was this voluntary thing going, so there is not a lot of data yet. Yes, Dr. Boyle?

DR. BOYLE: I just want to begin by reiterating that we know that in November, December, January thousands of immunodeficient patients were unable to get immune globulin because of a shortage. We don't know the causes of the shortage. We would certainly like to know them. But they were unable to get that. If the issue that has been put on the table, raised by several people, is that the charge of this committee is to deal with blood safety and

not availability, do recognize the consequences. There are 5% of immunodeficient patients who can no longer get their gamma globulin, or 10% or 15%. But take 5% or take 1%, the health consequences are substantially greater than what we have heard today about the actual consequences, not the potential benefits but the actual consequences of moving to a window period.

I don't disagree at all with what is being proposed here, which is to look at the potential benefits of changes in the current model, and that we need more information to know how that could be implemented in a fashion that is consistent with improving the safety of the blood and, at the same time, the safety of the patients who are using the blood. So, I would like to reiterate what Corey said, or I will expand upon it. These are serious decisions and we need some serious information, and we don't have that serious information.

I would also like to endorse what Joel said, and that is, you can't walk into these meetings with some stuff dumped on you because we don't even hear the two sides necessarily because the two sides haven't discussed whether they agree with these numbers or not. So, something has to be done in the interim period to make sure the kinds of information presented to us in June are consistent with our information needs.

DR. MCCURDY: I have a couple of comments. I agree with Joel that we need additional data, and one of my questions, I guess, is what kind of data would ABRA or IPPIA provide. They have talked about additional data. I don't have any idea what they have in mind. It seems to me that Jay Epstein said a few minutes ago that quarantine and retest is the gold standard and, therefore, I don't think it should have taken a rocket scientist or a rocket surgeon, or whatever you want to call it, to determine that an inventory hold would need to be defended against this gold standard. There may not be data yet to do that, but it should come as no surprise that one would need that type of thing.

The final question that has been bothering me for more than 20 years is why 60-plus percent of whole blood donors donate only once a year. Why can't they come in, maybe a smaller number, come in twice a year or three times a year, and then this might not be as devastating on the recovered plasma section of the group as it would be with the one-time a year donor situation.

DR. KHABBAZ: I agree with Dr. McCurdy, Dr. Verter and Corey regarding the need for data. Our charge here, as I understand it, is to look at proposals that increase the margin of safety, and I think taken at face value as Paul said -- the gold standard, I mean, it really is obvious that you would endorse something that would close the window

period but, as Jay told us, this is one of a number of strategies that are coming down the line to increase the margin of safety.

I understand that we are not supposed to address cost on this committee, but it kind of bothers me. I mean, we cannot ignore that any strategy has some cost associated and, you know, cost associated with a strategy is going to impact what you can do in other areas. Is it unreasonable to request or put on the table that the relative benefits or effectiveness of all these strategies that are coming be examined or addressed, rather than look at each one of them separately because it becomes an impossible task? I mean, sure, we are going to endorse anything that says it is going to be a little safer but is that reasonable?

DR. HOLLINGER: Is there an additional motion that someone wants to make in regards to the questions that are put up there now about what to do? Yes, Dr. Koerper?

DR. KOERPER: Well, if you are asking for a motion, I would move that we defer the vote until June to allow time for more information to be presented to us.

DR. HOLLINGER: Is there a second to that?

DR. BOYLE: Second.

DR. HOLLINGER: Discussion? Yes. Joel?

DR. VERTER: I certainly support that, but only with one proviso and that is that there is some concerted

effort, involving perhaps FDA, the industry and maybe even some of us, to putting together some format, a minimal format. They can go beyond it.

DR. HOLLINGER: And I will reiterate what you have mentioned so far, and others have mentioned here, the question about risk of disease in recipients of products; the number of window period units being interdicted with the various test for HIV particularly and HCV, and with PCR testing or genomic amplification technology; problems with extrapolations, looking at different models and making sure that survival data occurs or are important and appropriate; and looking at the impact of donor availability, particularly with flow with new patients coming in, old patients leaving etc.; about shortages; and data on non-envelope viruses, and so on.

DR. STRONCEK: I would like some explanation of how they recruit their donors, how they reimburse their donors, what kind of incentives, and have people tried different incentive plans to increase the number of source plasma donors.

DR. HOLLINGER: And also I think to deal with the question about standards. If one is going to have to have a different standard for recovered plasma and source plasma.

MR. DUBIN: And I want to underline something I think Joel said and, John, I think you seem to say part of

the same thing. We have gone down this path before. Let's involve the committee somehow, whether that is you, Blaine, as chair, or a few people, but let's make sure we get down to it and do it, and assist FDA in the way we need to, and keep the process directed because we have made some very specific requests. We almost have a consensus of knowing what we want. Now we need to see that we get it, and maybe there is a way the committee could be involved, not the whole committee but a subcommittee or a small group with the chair, something of that nature.

DR. HOLLINGER: I would like to call a vote on the motion to table this question until the June meeting of the committee. All those in favor of the motion to table, raise your hand, please.

[Show of hands]

And all those opposed?

[No response]

And the consumer and industry agree?

MS. KNOWLES: Agree.

DR. BUCHHOLZ: Agree.

DR. SMALLWOOD: The vote to table was unanimous among the voting members of the committee. The industry and the non-voting consumer representative agreed with the unanimous vote to table.

MR. DUBIN: With that motion to table, is there

going to be some language so it doesn't just look like a motion to table?

DR. HOLLINGER: Yes, I think there should be.

DR. MITCHELL: I think that we didn't recognize what the industry has done as far as the inventory hold. I mean, I think that we should commend the industry for having taken that step on a voluntary basis and, you know, saying that we want more data is not to imply that we don't appreciate what they have done voluntarily.

DR. VERTER: I just have one other request, and I know that Dr. Smallwood and her band of cohorts at FDA tries as hard as they can, but I really think that there should be a policy that the information is sent to us -- I would get shot if I said a month but no less than two weeks before the committee meets. No less. I mean, it was a tremendous amount of data to try to read. I didn't get through half of it.

MR. DUBIN: I get through it but frequently I am up half the night getting through it, and then I have to drink six cups of coffee to stay awake in the meeting because I was up half the night getting through it.

[Laughter]

So, which option do you take? Do you not get through it and then come in feeling like you are not prepared, or do you do it and then hope enough coffee will

keep you going?

DR. HOLLINGER: Okay, thank you. We are going to take a one-hour break. It is 12:25. We will reconvene at 1:25.

[Whereupon, at 12:25 p.m., the meeting was recessed, to be resumed at 1:20 p.m.]

Afternoon Session

DR. HOLLINGER: Before we begin, for those of you who are keeping score, on the window period that Dr. Busch showed us initially, there was an error. In the HCV WP-1, the window period-1 which comes from exposure to detection, that HCV should have been 70 days instead of 49, with a range of 25-150 instead of 8-135.

With that change, we are going to begin this afternoon on the topic of comparison of infectious disease marker rates in paid versus volunteer donors. We are going to start with a background and introduction by Dr. Ruta.

Comparison of Infectious Disease Marker Rates in Paid Versus Volunteer Donors

DR. RUTA: Thank you, Dr. Hollinger. This afternoon session is on comparison of infectious disease marker rates in paid versus volunteer donors, and specifically we are looking at marker rates for HIV, hepatitis B virus and hepatitis C virus. Today, the FDA is seeking advice from BPAC on its current efforts to obtain information on comparing infectious disease marker rates in paid versus volunteer, that is unpaid, donors.

Today we have invited members of industry with relevant information to present their data. We will also talk about how to model the data and, hopefully, a CDC person will also be talking about that.

There are some differences in paid and volunteer systems that make the comparisons difficult. So, today we are seeking advice from BPAC about whether we are asking for appropriate information, and whether the analytical approach we are using is sound.

The underlying issue that we are addressing is whether there is a difference in safety of plasma derivatives made from paid donations, and I am generally going to refer to this as source plasma obtained by apheresis, but probably more properly it should be commercial plasma, versus that made from non-remunerated volunteer donations, and by that I primarily mean recovered plasma from whole blood donations.

The last time we looked at this issue was in 1993, and we decided to revisit the issue of marker rates in paid versus non-remunerated donors because of some of the changes that are occurring in plasma collection and manufacture, and these include changes in donation management practices, implementation of PCR testing, and we are trying to take a look at the effect of lookback retrieval.

[Slide]

The FDA believes that there are four issues that should be evaluated: the prevalence of infection in the donor populations; the incidence of new infections in the donor populations; the risk of viral contamination in plasma

pools for fractionation; and, finally, the risks of the products after viral inactivation.

We have asked for information on marker rates incidence and effectiveness of lookback retrieval from industry and other sources. We have asked that the plasma industry, represented by the American Blood Resources Association, or ABRA, the American Red Cross, and Dr. Ron Strauss of the University of Iowa present the information that they have to the advisory committee. In addition, the FDA has invited IND holders for genetic tests to present their information to the BPAC. We think that is important because PCR testing provides a direct measure of the current state of window period collections, and we think we may have to take into account the effect the PCR testing will have on lookback retrieval.

Now, approximately 20% of the plasma used in the manufacture of plasma derivatives is derived from recovered plasma, from non-remunerated donors, and the remaining 80% is derived from paid donors. There are some difficulties in trying to compare marker rates from paid versus non-paid donors, and I am going to try and point out some of those difficulties.

[Slide]

First, there is a difference in donation interval in which donors can donate. Non-paid donors, by regulation,

may not serve as a source of whole blood donors more than once in 8 weeks. In contrast, apheresis donors can donate plasma twice a week, with an interval of at least 48 hours between donations.

There is also a difference in the volumes that can be collected from the two donors. Whole blood donors can donate, as I said, every 8 weeks and give approximately 450-500 mL, which yields about 250 mL of recovered plasma. In contrast, the apheresis donors can donate up to about a liter of plasma for collection.

Now, there have been a number of recent changes in industry practices regarding donor management, and we have heard about that this morning and I will briefly repeat some of that because we think it adds some complexity to the comparisons.

As the committee has heard, last year the plasma industry instituted a 60-day voluntary inventory hold on units of plasma that they have collected. In addition, they adopted the use of donations from "qualified" donors.

[Slide]

In the source plasma, commercial plasma sector, suitable donations are not used unless the donor becomes a "qualified" donor. So, there are two categories of donors. One is an applicant donor. An applicant donor can either be a first-time donor or a previously qualified donor who has

not donated within the last six months.

[Slide]

To become a qualified donor, the donor must pass 2 history interviews and have 2 negative sets of screening tests within a 6-day period, and that is in the absence of any other information that would disqualify the donor during that 60-day period. Now, in order to remain a qualified donor, the donor must have donated at least 1 time in the prior 6 months.

[Slide]

In contrast, for non-remunerated donors all suitable donations are used, and there are again two categories of donors but they are slightly different. There is the first-time donor, and that is a donor who has not donated previously, and a repeat donor is a donor who has donated previously.

Now, we think that there have been some problems or limitations in some of the data that has been previously presented to the advisory committee, and I want to try and explain what we think some of those are.

[Slide]

One of the problems can result from over-counting of marker-positive donations. Last September, September 18, ABRA presented information to BPAC on marker rates in paid donors for HIV at a rate of 1.9 per 100,000 donations; HBV,

5 per 100,000 donations; and HCV, about 11 per 100,000 donations. We think there may have been over-counting in some of these donors.

[Slide]

What I would like to do is try and go through a hypothetical example of a seroconverter and try to point out a couple of things from this example. One of the things this example is meant to illustrate is that in the apheresis system where a positive donor might donate several times before the establishment learns the test results and excludes the donor. In contrast, this is not likely to happen in the volunteer system because of the 8-week interval between donations.

[Slide]

So, what we have here is a hypothetical seroconverting donor who has donated 10 times within about a month and a half period. I will explain in a few minutes how I classify these donations. The donor is an HIV seroconverter. The first 5 donations test negative for p24 and the 6th donation become reactive. The p24 may stay reactive for a while and then disappear. The antibody profile for these donations would, again, be negative for the first 5 donations, because p24 may come up earlier the 6th donation may be negative for antibody and, subsequent to that, all the other donations from this donor should test

positive for antibody.

We have observed that for some of the plasma collectors and fractionators there can be a 2-3 week delay between the time that the donor comes in and gives this first reactive unit and the center gets the test results and learns that the donor was actually positive. So, because the interval of donation can be as short as 2 times a week that donor can come back in and donate several additional units.

Now, this can lead to over-counting when you are counting positive donations in the numerator over total donations, and we think that can be a complicating factor if you are trying to look at seroconverters because we have one seroconversion event here that can be represented, for example, in the antibody by 1, 2, 3, 4 antibody positive donations. So, that is one of the points I wanted to bring up from this example.

What this unit will do, in addition to triggering a response to not using that unit and not using any subsequent units collected from that donor, to defer that donor, is to trigger a lookback. So, at that point the plasma center should go back and look for prior collections and quarantine those collections. Again, because of the short interval, there may be lookback units and those may be available to quarantine. Now, if all these units are

interdicted then none of these units actually go into the pool.

I wanted to mention about PCR. PCR testing may now occur under IND, and let me remind the committee that this is still an experimental system which is currently being validated, nevertheless, we think it is important to try to calculate incidence and looking at the marker rates because, again, you can represent this donor by 6 positive PCR units. In addition, PCR testing should, as we have heard earlier, detect the seroconverter earlier in the time period. So, that should trigger deferral of this donor earlier and, again, trigger a lookback at an earlier point in the infection process.

If this were a whole blood donor, one would expect that you could eliminate rows 2-9, and there might be a single unit which was negative for each of the markers and then a subsequent donations which tested positive. But the interdonation interval would be much larger, at least 8 weeks and we think it may be as large as one time per year, but we will hear more about interdonation interval later.

One of the points of information that FDA doesn't know very much about is the interdonation interval for plasmapheresis donors, and we have asked the industry to provide us with information on interdonation interval. Obviously, the shorter the interdonation time interval is

the more likely, in the case of a seroconverting donor, that window period units could be donated.

So, we think that because of the complexities in the over-counting of positive units it may be more useful to calculate incidence, which is the number of seroconverting donors divided by the person years of observation in the donor population. We have asked both ABRA and the ARC to try to calculate those numbers.

In addition, we think that the actual risk for the plasma pool is represented by window period units that are not intercepted by the lookback retrieval procedures. Therefore, we have asked industry to provide information to us about the efficiency of lookback retrieval.

As I said earlier, we do not have very much information on the interdonation interval for the source plasma industry. Last September, ABRA also presented information that there were 1.5 million donors who contribute approximately 13 million donations, for an average of about 9 donations per year, which comes out to about once every 40 days. But we think, and the industry tells us that donors are likely to give in clusters. They are likely to give their 9 or 10 donations during a short interval and then go away for a longer period of time. So, that makes comparing the two systems a little bit more difficult.

[Slide]

So, what I want to explain now is the type of information that we have asked for from both ABRA and the ARC. We asked for information on first-time donors because we think it may be a useful measure the prevalence of infection in the donor populations, as well as indirectly a partial measure of the effectiveness of donor history in excluding high risk donors.

[Slide]

We have also asked both ARC and ABRA to provide information on incidence in donors residual risk remaining from window period units for each of the viral markers, and the impact of lookback retrieval on the pools used for fractionation.

[Slide]

Incidence, as I said before, can be defined by this equation, the number of seroconverting donors over the person years observed in the donor population.

[Slide]

The theoretical risks for plasma pool can be calculated by the following equation, which is the number of seroconverters divided by the number of donations times the duration of the window period divided by the average time between donations. Now, the number of seroconverters over donations is close to the marker rates that we have seen

presented by both ABRA and ARC. We are lacking information about the average time between donations, and we heard this morning about what new estimates for the window period would be for these markers. But we think that this is a theoretical risk to the pool because a number of things can prevent those units being used in the pools for fractionation. Also, this equation will only give you the risk for those people you know who seroconvert. So, if a donor donated a window period unit and didn't come back after 2 years, those units go into the pool and you don't really know about it until possibly 2 years later.

[Slide]

Some of the things that may reduce the theoretical risks to the pool are, for example, confidential unit exclusion, and I give this example because it has been cited in the literature as an example of an event where the donor, after going through all of the testing, said, you know, "don't use my unit of blood," and that donor was actually positive for p24, I think -- did I get that right?

[Slide]

A second thing which may affect the theoretical risks to the pool is lookback retrieval, and that is retrieving prior window period donations from a donor who subsequently tests positive. And, we are trying to measure lookback retrieval. Now, the FDA has required or

recommended the implementation of lookback retrieval in regulations. At 21 CFR 610.46, for HIV the FDA requires that blood and plasma establishments take appropriate action when a donor of whole blood, blood components, source plasma, source leukocytes tests repeatedly reactive for antibody to HIV, or is otherwise determined to be unsuitable with tests in accordance to 61045. What they have to do is, for units intended for use in further manufacture, they have to interdict the units collected within the past 6 months and to quarantine those units. They have to notify consignees so that they can also quarantine previous collections.

[Slide]

Similarly, the FDA has issued a memorandum, in July of 1996, that recommended the exclusion from use in either transfusion or manufacture into injectable products prior collections of whole blood, blood components, source plasma, or source leukocytes from a donor who subsequently tests repeatedly reactive for HBsAg or HIV. The recommendations are directed at in-date on pooled units that are in the blood establishments and consignees' inventories.

So, this example is meant to illustrate the impact of lookback unit retrieval. There is a delay between time of infection or infectivity and when the donor becomes antibody positive. These are estimates from Dr. Schreiber's

paper. We heard new estimates this morning. I think the 22 days for HIV antibody is actually from infectivity, and the 82 days for HBV may be for infection. I left HBV out but we heard this morning that it is about 60 days for HBV. Now, what lookback retrieval does is that it allows interdiction of prior collections from the donor so it, essentially, shortens the window period.

[Slide]

In trying to calculate lookback retrieval, I came up with this equation. Because we are trying to get an estimate here, I would appreciate comments on it. One way of looking at it is that you can measure lookback retrieval by the window period units interdicted over either the window period units or the number of units collected during a lookback period. What I ama trying to do is get a number estimate for lookback retrieval.

[Slide]

Now, we think that that impacts on the risks to the pool in the following way, and I came up with this equation so I will take comments on it too. That is, the risk equation that we have seen earlier with a new factor in here, 1 minus the window units interdicted, divided by lookback units. So, how this works out is that if you don't have lookback, there are no units interdicted. That is a zero. The zero drops out, and you end up with the risk

equation that we had before. Now, as you start to interdict the window period units this number becomes greater than zero, and as you interdict all of the window period units it approaches 1, and 1 minus 1 becomes zero. So, the risk becomes zero. That is for known seroconverters. We have asked that industry provide us information on lookback retrieval efficiency so we can try and include it in our calculations of what is the actual risk to the pool.

[Slide]

One other topic that I want to cover is PCR testing. PCR testing is currently being done under IND. It is not validated yet. But I think it is useful to look at because these are incident infections, and it may tell us something about incidence in the donor population. We have also asked the industry to give us information on lookback retrieval for PCR.

So, again, in a simplified version, here is a donor who becomes infected and 22-82 days later becomes antibody positive. The lookback may take you back a certain distance. PCR will identify the donor earlier than the antibody test, and if you do lookback from PCR you come closer to collecting all the units that may be window period units.

At last year's BPAC there was some discussion of should we treat donors who are identified under PCR IND

protocols. Even though there wasn't a vote by the BPAC there was discussion that we should treat these donors the same as a serologic positive, and there was discussion about possibly a 3-month lookback period for PCR positive units. So, that is why I have put that up there, but that is not yet a recommendation by FDA, although I believe we have asked all the IND holders to do lookback for any of the donors right now identified as PCR positive.

[Slide]

I wanted to also begin talking about viral load and the impact of PCR testing on viral load. A viral load in the window period unit remaining after antibody testing can be as high as 10^7 and 10^8 HCV copies per mL, and I put HCV because I think that is one of the higher viral loads. Now, this is I think the more extreme example. I think that from the seroconversion panels I have seen they may run 10^6 and 10^7 so I tried to give you the extreme examples.

Currently, there is PCR testing going on in pools of 100 to 1000 samples in a single pool. We have set a limit that the IND holder must be able to detect 100 copies in a pool, no matter what the size of the pool is. So, if you have a pool where you detect 100 copies and the samples are diluted 1:1000, that is where the number 10^5 comes up. If the pool is 100 and you detect 100 copies, the window period unit could have been 10^4. So, this sets a level for

the HCV copies, or copies of the other viruses that above that should be detected by PCR.

Now, you may hear from some of the IND holders that they think they may be able to go below that. Again, those studies are under way and have to be validated. So, what PCR testing should do is it should eliminate units from donors greater than 10^4 to 10^5. In looking at seroconversion series, I think it is possible that PCR may eliminate a lot of HCV positive units, and I have probably overstated this here, that PCR testing, when fully validated, may result in the exclusion of almost all HCV or HIV window period units. I think we would have to see that demonstrated by the IND holders during the course of validation of their studies. So, as we have heard earlier this morning, it is possible that PCR testing may have an impact on the viral load for HCV and a lesser impact on HIV. I think we have heard that it may reduce the window period by a few days.

[Slide]

I want to talk about HBV for a minute. I think you saw Mike Busch present this earlier today, and there is indication that the viral load in HBV seronegative window period units may be about 3 X 10^3 copies per mL. So, that may be below what pooled PCR tests could detect. So, the benefit of pooled PCR testing may be less.

Again, we have asked the IND holders to work with the FDA on calculating both incidence and lookback efficiency because we want to see the impact of PCR testing on both identifying donors earlier in the donation, and how well the lookback retrieval works under the PCR setting. Again, the PCR needs to be validated. There are some problems or potential limitations that were discussed this morning, including genetic variations. As always, tests and manufacturing process have to be done under GMP. They have to be done right in order for them to, in practice, meet what we think they should theoretically do. So, the manufacturers have to follow good manufacturing practices.

Another point that I would hope to get feedback from the committee on is, as we are looking at marker rates, if the committee could give some thought to what the risk is that donors at high risk for one of the markers that we are looking at, HIV, HCV or HBV, may be at risk for an unknown agent that may not be inactivated by current technology.

This finishes the part of the presentation dealing with studies that are under way. I wanted to spend a few minutes reviewing a talk that was given to the BPAC last September by Dr. Lynch on viral inactivation removal.

[Slide]

Viral clearance is inactivation removal. There are individual manufacturing steps that may either be

specifically designed to remove viruses, or they may be intended for purification purposes but serve to remove or clear viruses. Each of the clearance steps must be separately validated, and the production methods and practices must perform to the validated methods.

[Slide]

These are two of the clearance methods that have been approved for inactivation, heating -- and these are different heating methods that have been approved. I think this is for albumin and PPF, This method has been approved, heating in solution 10-11 hours at 60 degrees. Chemical inactivation, which is a solvent detergent, ethanol, or low pH.

[Slide]

Virus removal can occur by partitioning during fractionation, which would be either ethanol fractionation or chromatography. There are also methods approved for nanofiltration, which can remove particles between 15 and 100 nm, or some of the filters may absorb viruses.

[Slide]

A manufacturer selects the clearance method they want to use. This method must assure that product quality and potency is uncompromised. They do a scale-down production method to the laboratory model. They spike the starting material, and that can either be the actual virus

or model viruses, and they perform the operation and compare the titer in starting and ending material. These methods must perform according to GMPs to ensure consistent effectiveness.

[Slide]

You measure proportional reduction in virus concentration. You don't always demonstrate complete elimination of a virus but the multiple clearance steps can be combined, and each is independently validated and each is based on a mechanism different from other clearance steps.

[Slide]

I wanted to show you a couple of examples of product. The committee members have all the slides in the package, and I just picked two to show you examples of but you should have the full presentation. This was presented last summer to BPAC.

For albumin and PPF, there has been no transmission of HBV, HCV or HIV since the initiation of heating, which is 60 degrees for 10 hours in the final container. There can be removal of 1.5-5 logs reduction of the different viruses by partitioning during fractionation. There also can be reduction by inactivation during heating.

Another example I want to show you us clotting factor, and for this particular product the manufacturer uses affinity chromatography, solvent detergent and dry

heat. They have demonstrated for HIV 2 log reduction by chromatography, and greater than a 10 log reduction by solvent detergent, or greater than 12 log reduction in the final product.

[Slide]

So, the conclusions are that viral clearance is important in assuring the safety of plasma derivatives. The effectiveness of all clearance methods is shown by validation and clinical experience. Of course, the methods must be done according to GMP in order to assure that they are effective.

At this point, my part of the talk will end. What I have done is to ask Dr. Tabor if he would talk about some epidemiology associated with these viruses. Then, if the Chairman likes, we can have the questions for the committee. So, I am done for now.

Presentation

[Slide]

DR. TABOR: I have been asked to give a short summary of the of the presentation I gave at the June, 1997 BPAC concerning the epidemiology of the transmission of certain viruses by plasma derivatives. For those of you who are interested in seeing the other data from that talk, I am in the process of preparing a review of the entire data.

This presentation was limited to the epidemiology

of transmission of HIV, HBV and HCV, that is, the viruses for which we currently have tests available and for which inactivation processes are applied to plasma derivatives.

[Slide]

This is the cascade by which plasma derivatives are manufactured, which are comprised of methods of Cohn and Oncley, and the results of products, shown here in yellow, and hemophilic factor, Factor IX complex, immune globulin, PPF and albumin.

[Slide]

Over the years, we have thought of these products as falling into certain risk categories, and those risk categories have changed slightly with the introduction of inactivation processes to the products for which there were no inactivation processes originally. Now I think it is reasonable to consider them in these three categories. First of all, there are those products which are inactivated have been inactivated for many, many years and have a very long history of safe use. This group comprises albumin and plasma protein fractions. The second risk category are those products which are currently inactivated but have a much shorter history of use in their inactivated forms, most notably antihemophilic factor and Factor IX complex, but also alpha-1 proteinase inhibitor and antithrombin 3. Finally, immune globulins really fall into a separate risk

category. They have a very long history of safe use, but the reasons why they are safe are not completely understood, and I will explain more about that later.

[Slide]

Albumin is in the category of those products with a very long history of safe use. In the entire 45-year history of albumin use in this country there has been no transmission of hepatitis B virus. This is due not only to the manufacturing process, but also to the fact that it is subjected to heating at 60 degrees for 10 hours. There were also volunteer studies conducted in the 1950s, which I will describe in a few minutes, which show clearly that the inactivation process can kill any hepatitis B virus that might be present.

Hepatitis C virus is also killed by the inactivation process that albumin is subjected to, as shown by chimpanzee studies.

With regard to HIV, there has been no known transmission of HIV by albumin, even in the years before screening for anti-HIV was introduced, and it has also been shown that heating at 60 degrees for 10 hours could clearly inactivate any amount of HIV that might be present. Experimental studies have shown that heating at 60 degrees for 10 minutes, 1/60th of the time that albumin is heated, can inactivate 5 logs of HIV infectious doses per mL, and

that is 1 log greater than has ever been documented to be present in human plasma.

[Slide]

In the early 1950s, Robin Murray, who was director of the agency that was the forerunner of CBER, conducted studies in human volunteers. The plasma and serum sample from the individuals in the study were saved, and they were reanalyzed when the tests became available several decades later. In some of those studies, Murray took an infected plasma pool containing 7 logs of HBV infectivity and prepared albumin from this material, and subjected it to heating at 60 degrees for a variety of different time intervals.

This summarizes for you when the albumin preparation contained 7 logs of HBV and was heated at 60 degrees for 10 hours, it did not transmit hepatitis to any of the volunteers inoculated. Whereas, heating for a shorter period of time or albumin which had not been heated did transmit to some of the recipients and, of course, the unheated plasma also transmitted.

[Slide]

With regard to immune globulin, there has essentially been no transmission of hepatitis B virus by any lot of immune globulin that has been made from screened plasma, and that is over a period of at least 25 years.

That goes not only for the IG preparation but also the intravenous preparation. In addition, there were volunteer studies, similar to those for albumin, which also showed that again, using an infected plasma pool with over 7 logs of infectivity, an immune globulin preparation using the Cohn method 6 and Oncley method 9, the methods used by all manufacturers in the United States today, the material, without any further inactivation processes, did not transmit hepatitis to recipients but the unprocessed plasma did.

[Slide]

It is not really known why the processing of plasma to make immune globulin removes hepatitis B virus infectivity but, clearly, it does. It may in part be due to the presence of antibodies in the preparation that can combine with any virus that happens to be present, or it could be due to the process of fractionating material.

[Slide]

The situation with regard to immune globulin and hepatitis C virus is somewhat more complicated. The intramuscular preparation, when it was made before the introduction of second generation anti-HCV screens, often contained hepatitis C virus RNA but there has been shown to be no transmission of hepatitis C by any of the lots in people who have received frequent injections of the IM preparation in either of two studies, and there as no

transmission by the intramuscular preparation of immune globulin from the same donor group as the intravenous preparation that had transmitted hepatitis C virus in the Gammogard outbreak. Those are not the exact same donors but the same donor group.

The intravenous immune globulin, in an outbreak in 1993, a lot made by one manufacturer transmitted hepatitis C virus, and in a very elegant series of studies, Dr. Finlayson, Dr. Hu and Dr. Tankersly at CBER showed that that was the result of the introduction of even better anti-HCV screening. Subsequent to that outbreak, viral inactivation procedures have been introduced by all the manufacturers and there has been no transmission of hepatitis C virus by any lot of intravenous immune globulins since 1994.

[Slide]

With regard to HIV, there were no seroconversions to anti-HIV in any of the recipients of lots of either the intramuscular or intravenous preparations of immune globulin, or HBIG made in the years from 1982-1985 when HIV had already entered the donor pool, but before the introduction of donor screening.

In addition, it has been shown that the fractionation process itself to produce immune globulin removes greater than 10^{15} infectious doses. As I said earlier, the highest titer of infectivity ever shown in the

plasma of chronically infected humans is 10^4 infective doses. This slide is incorrect; it should say 10^4. So, there is a great margin of safety there with regard to inactivation of HIV by the manufacturing process itself for immune globulin. In addition, HIV has never been cultured from lots of immune globulin that contain anti-HIV made in the year before screening was introduced.

[Slide]

Antihemophilic factor and Factor IX complex did not have inactivation procedures until about a decade ago. However, since the introduction of those procedures there has been no transmission of hepatitis B virus by any U.S. licensed product that has been made from properly screened plasma and with properly conducted inactivation procedures.

[Slide]

With regard to HCV, the same thing is true. There has been no transmission since 1987 by any lot of AHF or Factor IX. In addition, CDC surveillance during the years 1993-1996 show that there were no confirmed seroconversions in any of 71 hemophilia centers around the country. These represented approximately half of the hemophilia centers in the United States, and this information was kindly provided by Dr. Michael Souci.

[Slide]

It is true that HCV RNA could be detected in some

of the AHF lots that were made from pools that were positive, but none of the lots made after the introduction of second generation testing, and now the introduction of PCR testing of final product, have been positive.

[Slide]

With HIV as well, there has been no transmission by any lot of AHF or Factor IX since the introduction of inactivation processes when those processes were conducted according to protocol. In addition, the CDC surveillance study showed that there were no confirmed seroconversions to anti-HIV in 71 hemophilia centers.

[Slide]

So, in summary, there has been no transmission of HBV, HCV or HIV by any U.S. licensed plasma derivative, except for intravenous immune globulin, since 1987 when properly screened plasma and inactivation procedures were conducted, and there has been no transmission by intravenous immune globulin since 1994. Thank you.

DR. HOLLINGER: Thank you. Rima, do you have some comments to make on this from the perspective of the CDC surveillance?

CDC Surveillance Systems

DR. KHABBAZ: Yes, I was asked to make some comments regarding the surveillance systems at CDC and what they might contribute to the question of transmission of

these agents by effective inactivated products.

With regard to the surveillance systems, CDC has a number of systems that allow us to address current or potential risks related to the transfusion of blood and products. Relevant to this really are a few systems. A number of them are disease based, and there are a couple already mentioned, namely, the hemophilia surveillance system. The National AIDS Surveillance System contributes some information in that this is the national reporting of AIDS cases, and included in that are AIDS patients with no identifiable risk factors, and these are pursued via interviews for risks. Also, there is a special focus on patients with hemophilia and no other risks that may be reported for AIDS and looked at for possible association with product received.

In terms of hepatitis, the Sentinel County Surveillance System, in effect since the late '70s, is an active system that also collects risk factors. We interview patients with hepatitis. It is 7 counties representative of the population of the U.S.

Then the recipient-based systems were mentioned. There is the Hemophilia Surveillance System, that is 6 states based, population based, all the hemophilia patients seen in those states. Then, the Universal Data Collection System that is being implemented, which includes all

hemophilia treatment centers.

As Ed mentioned, through these systems or through any other mechanisms, we are not aware of any cases of HIV or hepatitis associated with receipt of effectively viral inactivated products, the exception being hepatitis C virus transmission associated with the IVIG product in '93. Gammogard.

DR. HOLLINGER: Thank you. The next presentation is by Dr. Glen Satten, a statistician from the Centers for Disease Control, in Atlanta.

Presentation

DR. SATTEN: Before I start, I would like to say that this talk is directed to sort of a number of audiences, so there is material at a number of different levels. For panel members though, probably the major message is that I was asked to think about the question of what effect did the 60-day hold have on a number of potentially infectious units.

[Slide]

I think that we have such a model at this point so that is some information there. There are some interesting ideas as well.

Because this is sort of work in progress and we realized we wouldn't have risk estimates ready, this is also sort of directed to my colleagues in the FDA and industry so

that they can look at this model for the first time.

[Slide]

I would like to give a few reasons why sort of a fairly mathematical treatment is required to address this question. The first is that the outcome that we are trying to learn about is really inherently unmeasurable since we can really only determine is potentially infectious by actually transfusing it, unless you are willing to believe that PCR detects every infectious unit, which I am not quite sure is true. So, right there we are stuck with some mathematical modeling.

But there are also additional reasons. There are a number of systematic sampling biases at work and the need to be properly accounted for.

In addition, using a mathematical model it is often possible to based estimates that are based on the properties just of seroconverting donors with estimates that are based on the properties of all donors. So, you increase your effective sample size by many thousand.

Finally, a mathematical framework sometimes helps you define what data you need to be thinking about collecting and, in the very best cases, it helps you really think about the problem in a new way.

[Slide]

I would like to start right away with the first

mathematical complexity or mathematical assumption that goes in, which is the role of a steady-state approximation which comes right up in the question that we are trying to answer. The real question we want to answer is, given some time period, let's say a year, how many potentially infectious donations are made during that time period. Again, since the window period donations aren't identifiable, you can't answer this question. Instead, what we usually try and answer is a surrogate question; how many potentially infectious donations were made previously by donors who were detected in the time period of interest, over the year we are studying?

Those two are not the same questions, however, the answer is the same on average only if you have a steady-state approximation. So, specifically, you need to assume things like the disease incidence is constant over time among repeat or qualified donors; that the donor characteristics are constant over time; and the third one we will make a lot of use of, that donors that drop out are replaced by new donors on average at the same rate, and these new donors have on average the same characteristics as the ones that dropped out.

[Slide]

Like I said, there is going to be material at a number of levels, and I hope that some of you who aren't

mathematicians will bear with me. I think there are things to be gleaned from this.

I would like to start by introducing the mathematical object that I have found useful for looking at blood safety questions. It is called the renewal process. A renewal process is just a model for recurrent events in which the times between events are independent and identically distributed.

So, what I have drawn on this transparency is sort of a hypothetical realization of a renewal process, and it has fairly regular increments because I used the "tab" key.

[Laughter]

So, the first interval here is t_1. The second interval is from t_2 to t_1. That is the next gap. It has the same distribution and is independent of that gap. This long one, 3 tabs, is also another independent random variable, and so on. These times between events are independent and they follow some distribution, f, with some mean, mu.

This is a fairly simple but pretty general framework that can be used to model repeat donations of plasma donors or whole blood donors as well. Of course, each donor's times of donations follow a different renewal process. So, the f_i donor would have a mean of mu_i. I will deal later with the question of what happens when donors

drop in or drop out of the system in some detail.

[Slide]

When we start a renewal process, especially when you use your "tab" key, you are pretty sure that the next event doesn't occur right after the very first one. So, we have something called stationary renewal process. That is one that has either been going for a really long time, or one where the time where we start watching it is random with the uniform distribution. Statements in general are more true if you use Greek letters!

[Laughter]

There is something called a renewal theorem, and I will give you the version for stationary renewal processes. That says that the expected, and the word expected means the same as average or mean -- so, the average number of events which occurs in some interval, let's say from tau which is when we started watching, to some T is simply the length of the interval, divided by the average time between events. This is just sort of a mathematician's quantification of an intuitive result that says, you know, if you have a donor who makes donations on average 10 days apart, then in 30 days they make 30/10 or 3 donations. So, that is what the renewal theorem is.

[Slide]

So, the first little complexity that I want to

talk about is the question of the difference between sampling donors and sampling donations. So, suppose that we take, let's say a 3-month period which seems to be typical of the kind of data that is lying around, and in this time period we gather information on all donations made in this time period, and I want this information to include the time of the previous donation, I will call this kind of data per-donation information. The reason I am calling it per-donation is that it doesn't represent donors equally. So, donors with more frequent donations -- the people with the smaller values of the mu's -- are represented more frequently in these data than donors with less frequent donations.

I just want to point out that that is a sampling bias that we know how to deal with. If you further restrict to donors who have made at least 2 donations in this interval, you get a serious sampling bias that really can't be dealt with whatsoever analytically. That is why I said that I want this information to include the time of the previous donation to get around that.

[Slide]

Now, the T's are times of donations made by individuals. Now I am going to define a symbol for the time differences. So, $delta_{ij}$ will be the intervals from the i_f donor. For those of you who don't plan to follow all the

details of the math, just remember that delta's are intervals and t's are actual times. N is the number of donations made by the i_f donor in this little experiment that I am conducting. Because of my renewal theorem that says that the expected number is the length of time divided by the mean, there is this relationship between the per-donation average that is the average of all of these interdonation intervals, even though it contains too many intervals from frequent donors and too few from infrequent donors.

It turns out that there is a relationship between this and per-donor information. That is, this quantity here is the harmonic mean of the mu's for the donors. So, this is a relationship that we get from this renewal theorem that allows us to relate this simple gathering of information experiment to something that has to do with just individual donors.

Before describing the model for the effect of a hold period, I want to show you how these simple ideas lead to the result that Martin showed you on what he called the theoretical risk.

[Slide]

I am going to use this model backwards in time because I like to think of time zero as the time we catch the donor, and then we look backwards and we find that there

are first, second, third, fourth and fifth donations before seroconversion. Now, the time of seroconversion we are assuming is not related to the times that the donations are made. So, it is one of these random times. You can start your renewal process there. That seroconversion, looking backwards, if omega is the length of the window period, then tau to tau plus omega is the window period. By the renewal theorem, we know that the average number of potentially infectious donations made by the donor, whose average window period is omega, whose average time between donations is omega/bar.

[Slide]

So, now we assume that each person has a window period that is independent of everything else when they make their donations, and that the average window period is omega/bar. So, that tells me that the average number of infectious donations made by a seroconverting donor is omega/bar times -- this sort of looks like this harmonic -- so that tells us that we can replace this thing that looks like a harmonic 3 by the average interdonation interval, the average of the delta's.

Now let's just suppose that we detected n plus seroconverting donors in a year out of n_{don}, total donations. Then the proportion of potentially infectious donations would be simply the number of seroconverting donors times

the average number of infectious donations each one of them makes per n_{don}, donations. I am going to flip this delta/bar into the denominator, and then we recognize that the number of donations times the average time between new donations, that is just the person time of observation. Okay? So, we have here the number of seroconverting donors detected divided by person time, which is incidence, times window period.

When we first started talking about this, there were some questions about whether or not this would hold for people who made lots of potentially infectious donations, and the answer is yes, that is the proper equation.

[Slide]

So, why did I go through all that?

[Laughter]

Well, first, to show that the elements that I am going to use are reasonable. You always check to make sure that you get a familiar result in a case where you know at the end what the answer is.

What can we come up with now for the model for the effect of the T-day hold? Now I am going to start simply with long-term repeat donors, and what I mean by that is people who have been donating for a lot longer than T-days.

Well, here is our picture, the same picture that we had before, except that what I have done here is that I

have stuck on a big arrow, telling me the T-days before time zero. Okay? Well, I have my renewal theorem and that works just as well for this time, t as it did for this time, tau plus omega. So, the number of units I am going to get from this person -- if this t is to the left of the start of the window period, well, then I am going to have t minus tau over mu. That will be the expected number from my renewal theorem. Of course, if the t happened to be bigger, to the right of the tau plus omega, then I would get this.

[Slide]

Again, I will say that the window period, omega, now follows some distribution, and I will define Pt, which is proportion of individuals whose window periods is greater than some time t. That is a survival function, for those of you who recognize that object. Again, assuming that each individual's window period is independent of other characteristics, we get this rather nice, compact expression for the proportion of potentially infectious donations that are interdicted for the $_i$ donor. H, this quantity, is simply the interval. I know all of you doctors had to take calculus --

[Laughter]

So, if I now get the expected value of this, overall donors, basically I can just slip that into the interval here. Here is the proportion of potentially

infectious donations that are interdicted averaged over all donors.

[Slide]

Just like we were able to convert the harmonic mean of the per-donor that we used, we can convert this into per-donation intervals. It is done in pretty much the same way. We would replace this average by the survival function of all interdonation intervals that I get from my per-donation experiment. So, S/bar is the proportion of interdonation intervals which are longer than some time, tau. Remember, delta/bar was the average. So, that allows us to estimate this overall proportion of potentially infectious units.

[Slide]

Martin raised the question of the donor who makes some window period donations and then disappears and never comes back, or maybe comes back two years later. So, what is the effect of donor dropout in recruitment?

First, i will consider the case Martin was considering with no hold. We can only calculate the number of potentially infectious donations made by donors who are detected by making a seropositive donation. So, with donor number 1, let's say that this donor makes some donations and then seroconverts at some later time but we never see that event so we don't ever count these window period donations.

But here is donor number 2. The diamond there is some series of qualifying donations, whatever series you want to make it, it really doesn't matter. That person neatly sort of takes up where donor 1 left off, makes a seropositive donation there. And, we made a mistake with this person too by using omega over mu-i. We over-counted that person's donations. Right? They have a short series and we have some that are missing.

In steady state, because people drop out and drop in, with exactly the same characteristics and exactly at the same rate, the over-count in donor 2 is exactly made up for the under-count in donor 1. So, in steady state this exactly cancels out and our equation is exactly correct, even with people dropping in and out.

[Slide]

What happens when we have a T-day hold? Here there is actually an idea, if you have not been paying attention --

[Laughter]

What happens when we run the same experiment with a T-day hold? Let's say that this is T-days, here. Well, the hold period effectively ends right here for this donor. We don't have an actual link between donor 2 and donor 1. That was a way of doing some bookkeeping that was handed to us by our steady state assumption. Okay? When we are

looking at real donors, you know, these donations really aren't there. Donor 1 really is missed, and it is exactly the same as if we had said we are going to put a hold period here and then we will release all those previous donations. Okay?

[Slide]

So, what we can do is we can define a fraction, and r is essentially the proportion of long-term donors. So, for the long-term donors I get the expression that I derived before. For the short-term donors, a fraction 1 minus r, I get the same expression except that the hold period is a round number that is uniformly distributed throughout the length of the hold period. So, that is what happens with donor drop-in an dropout.

Martin is correct, the proportion of potentially infectious units you get simply by multiplying the original proportion, multiply the proportion you interdicted, and t here are population-based estimates for this quantity r.

[Slide]

Even I couldn't give a talk on only equations to an audience like this, so I had to come up with some kind of numbers. One of the things that you get out of that equation is sort of the bad news that the effect of the hold period is going to depend on the actual shape of the distribution of window periods, which is something we have

some knowledge about.

But let's just make some simple assumptions about where we can do the intervals. I just assumed that the distribution of interdonation intervals was exponential and the distribution of window periods was also exponential. Okay? If you do that, things start to simplify. You get a simpler equation. F of T is the proportion of people whose window periods are less than T days, and if we pick our window period large enough that F of T is essentially 1, we actually get a pretty simple equation.

So, some wild guesses. I have no idea what r is, but sifting through some randomly faxed documents that I used to receive almost daily, I am going to guess that r is about 3% --

[Laughter]

-- and for HIV a window period of about 5 days, 60-day hold, essentially all of the potentially infectious units are interdicted. Over lunch, with a calculator I just plugged in what would happen with the same assumptions but a 90-day window period, and there you would only pick up 48% of them.

[Slide]

So, in summary, there is mathematical model now for the effect of this T-day hold on the number of potentially infectious donations. The quantities required

to estimate the effect of this hold can be obtained using the per-donation data that we talked about. So, to conclude, I guess we can really start to answer the question of what effect that has. Thanks.

DR. HOLLINGER: Somebody want to summarize that?

[Laughter]

DR. SATTEN: There will be an exam!

[Laughter]

DR. HOLLINGER: The FDA has a statistician that wants to discuss this also. This is Cornelius Lynch.

Presentation

[Slide]

DR. LYNCH: I am going to address really the following problems that are basically summarized here. If we are given a data set from plasmapheresis donors and estimate the number of window period donations from donors who subsequently test positive -- that is all. So this is a very focused problem that we are looking at, and the solution is about 3 orders of magnitude less than complex than what Glen just described to us.

[Slide]

The overall solution, which I will explain in a little more detail, is sort of summarized here. Basically, we considered all possible window period intervals for each donor who subsequently tested positive. There could, of

course, be several possible window periods with different intervals for each positive donor.

For an individual donor then we would identify the number of donations given within each interval, for all possible intervals get a mean value or an expected value of the number of donations for that positive donor, and do the same thing for the other donors, and we would combine them all to get an overall estimate of the number of window period donations.

I want to point out that we are not, at this point, talking about safety in any sense. We are not looking at the 60-day hold or things like that. Also, let me just point out that we are looking here at the positive donors, not the negative ones. If we have a particular data set, once you truncate it you lose follow-up for all the individuals, but we are not really addressing that in this particular situation.

[Slide]

I am going to explain our solutions in terms of a simple example, which is shown here. What this represents is that we are talking about one particular plasmapheresis donor, and we have time along here and these represent the days of donations. On day 1 there was a donation, 5, 8, 13 20, and so forth.

In this simple example we have 4 negatives and

then all of a sudden a positive donation. A window period occurred. When did it occur? Well, it could have ended, say, no earlier than the window period shown here. Why? Because if it ended prior to this time, then this particular donation would have been positive, not negative. So, this donation was given during a window period. On the other hand, it had to end sometime before we got here to the positive one. So, this would sort of be a boundary for when the window period ended. If it had ended afterwards, then we would not have had a positive donation here. You know, we could have various window periods.

For the simple explanation here, I have considered sort of a sequence of possible window periods that would shift over 1 day at a time and it would look something like the following overhead.

[Slide]

In this simple example we have just these 6 possible window periods. These are sort of boundaries of the extremes. But if we are talking about 1 day at a time, it could be any one of these intervals in here.

What we have done then, we have looked at the various possible window periods, starting, say, at this very first one and identified how many donations were given within that possible window period. In this case there were 3, on day 5, 8 and 13. So, if the window period did occur

for this individual during that time period, then we would have had 3 window period donations.

But what happens if instead of that one it were this window period? Well, we would also count the number of donations given within that window period. In this example there are also 3 and they turn out to be the first 3 that we had above. On the other hand, if we go down here to this third one, then there would be just 2 donations during this window period, day 8 and day 13. Well, we can continue in the same way for all possible window periods.

[Slide]

So, once again, I am just continuing on with the example we started with. We had 6 potential window periods. The first began on day 4 and ended on day 14. As you recall, it could not have ended before day 14. In that one there were 3 donations. In the second one there were also 3 donations. We shifted over a day. So, we begin on day 5 and end on day 15. We go all the way down to the last possible window period, and it would be one that started on day 9 and ended on day 19, and there were 2 donations there.

Well, we don't know which of these 6 possible window periods actually occurred. So, what we can do is sort of a uniform distribution. That is, any one of them could have occurred and they are all equally likely to have occurred. If that is the case, in this example there were 6

of them so we give each the probability of 1/6 occurring. We add up the number of donations that were given within each one of these, multiply by 1/6, and we end up with a mean value, or an expected value, or an average value of window period donations for this particular donor. Recall, we are talking right now only about donors who ultimately are positive. When I say positive, it does not necessarily mean with PCR or antigen or antibody. We are talking about positive by one or more tests. Well, this is for one individual. Overall, what we are going to do is make this type of computation for all the positive donors in the data set. Recall that we are still talking about a plasmapheresis data set.

A simple example is on the next overhead of what we would be talking about if, say, there were 5 positive donors in the data set. We would do those types of computations for each donor.

[Slide]

The first one in the example said you had an average of 2.5 donations, and so forth. Well, in this particular case, to get the overall mean we simply add up these. In this example there are 5 of them. Add them up and so we have 7.8. That is the expected value of the number of window period donations in this particular data set. If it happens to represent, say, 100,000 donations,

then the rate, of course, would be 7.8 X 10^{-5}, something of that nature.

[Slide]

The next overhead gives a general expression for what I have just covered. This expression right here, this is what we have just covered now for each individual. N_i is the number of possible window periods for our donor, i, in the example that happened to be 6. These would be the sums of the window period donations over each possible window period. This would be the sum of what we had before, plus 3, plus 3, plus 2, plus 2, plus 2. So, this would be for 1 individual. We just add all these up for all the individuals. In this case we are assuming we have N positive donors.

Now, I have shown this particular expression for two reasons. One is, this is just preliminary and this is sort of the first step of what we have at this point, but at least it is completeness in that sense. Another is that it also indicates or helps us if we are going to pursue this line of reasoning. It suggests to us what kind of data we need. You can see from here, if we do have the date of donation for the donors, whether positive or negative.

[Slide]

I have some general comments on this particular approach, shown right here. First of all, up to this point

we have done some of this: Account for donations given subsequent to the first positive donation. Of course, it is cut off at the first positive donation. If we are talking about plasmapheresis, it could very well be that an individual has come in and donated, say, 2 days later, or something like that, before the first results come in. I did not incorporate that in the material I have presented thus far.

We also didn't talk about the 60-day hold, although you have heard quite a lot about that. In the little example I gave at the beginning, for example, none of those donations would have gotten into the blood supply precisely because of this 60-day hold.

And, we want to express units. I gave you the example per 100,000 donations or person years of observation. This is what Glen likes and epidemiologists like to express, person years of observation, or whatever unit is meaningful depending on how the data might be useful.

There is a little problem here, where we have an overlap of a donation day where it begins and a donation. Is that given during a window period time or not? For example, if a donation is given at nine o'clock in the morning and the window period starts at two o'clock, that is too fine of a distinction for us to make. So, at this point

I think when you have that type of overlap then, yes, you add to the count. That is, you would add to the count of the number of window period donations.

[Slide]

This is my last overhead. An example I gave used a fifth window period. Well, the window period is going to differ, I guess, by each person. An average can be misleading. There are various possibilities. One is to use a whole range. I think Dr. Busch, this morning, was telling us about some of the ranges for the window periods. That is one way of doing it. We can look at 90 percentile, the range, or assess different lengths in distribution for the window period. So, that would be another possible enhancement of the model.

I also want to point out that these computations are supposed to be carried out separately for each type of event, HIV, HBV, HCV, or whatever we are talking about. There are a couple of reasons and, from my perspective, the main reason would be that the window periods are going to differ, I guess, significantly from one type of event to another.

One advantage is that here -- recall, we are talking about a particular data set. We are talking about data for individuals. So, we have an individual and we know what the interdonation intervals have been for this

particular individual. We have it on that basis. It can differ from one individual to another, but we are actually using individual data so that we don't get involved with the average interdonation interval, and the problem there. There has been some discussion earlier on that. So, if you have the individual data you can avoid some of those kinds of problems. I am fully aware that some people don't particularly like to use individual data, but I want to remind you that we are focusing on one particular data set, and that sort of is what we are looking at. It is not a more comprehensive type of approach at this point.

That is one advantage of individual data, but the disadvantage is also basically the same thing. Using individual data, you have to have a relatively large data base on this. Right now, I do not have a nice data base. I am told we may end up with a data base, but at this point we do not have it.

Anyway, that is basically the model. The whole purpose of presenting this is to, you know, give you the idea of the logic, whether it is reasonable or not, and whether we should pursue it. If we do pursue it, we will incorporate some of the other things I have. These are just general comments. As I have said, we have already done some of those other things.

At this point, that completes my remarks. Thank

you.

DR. HOLLINGER: The final presentation for this section is by Dr. Ronald Strauss, from the University of Iowa. He is going to talk to us about paid and volunteer donors, and some of the risks with those two groups.

Presentation

DR. STRAUSS: Thank you. I was going to say we are going to switch gears but that is probably an understatement. My comments are going to be very much of a practice-related type laboratory and clinical practice. My task really is to compare volunteer whole blood donors and the paid plateletpheresis donors that we have had at our institution for the past several years.

My understanding is that you received a copy of a reprint of an article that we published, and also a critique that was published in the same issue of Transfusion. In addition, I sent a number of materials to Dr. Ruta that I believe you have, which have all of my slides. Since the time is limited, instead of going over all of those in detail, I would rather spend the time talking a little bit about the way in which our studies were done; the rationale for the way we monitor our donors; and then to provide some data that are more recent than the published ones.

I did notice, looking through Don Buchholz' set of papers, that you have two sets of slides from me. The ones

that you want are the longer set. I sent some follow-up ones to him.

[Slide]

As people who both prescribe and provide blood, we really have some common goals, and one is to make certain that components and derivatives are optimally safe, and also available for the patients. We really have to meet both goals, and it goes without saying, without lowering safety.

Altruistic donors, obviously, are desired but, to some degree, all of us receive some sort of incentive of a personal value when we donate blood, ranging from those that obviously have value, like cash or equivalent to cash such as paid time off; recognition and prestige, like winning the blood drive contest; or the psychological gratification that directed and family donor members get.

I think that instead of sort of agonizing over what the relative values of these are, it would be much better for us to focus on what is the safest possible blood product, and what is the way that we can get the most units of this blood product? Obviously, these mathematical models that we heard are ways that one can approach it.

[Slide]

But also there are some clinical ways, and I am going to describe those in just a second. We are sort of in this balance of trying to keep safety and availability,

both, optimal. Anything that we do that might increase safety at the expense of availability we might argue about, like the CJD issue but, nonetheless, it is generally an accepted practice. On the other hand, anything we might do to increase availability if it impairs safety in any way is not an acceptable practice.

[Slide]

At the clinical level, we try to increase transfusion safety by at least two different ways. One is to try to limit allogeneic donor exposures. I think all of us know that autologous donation and transfusion is one way to do that. But it is really a very costly and wasteful way, and any overall scheme of allogeneic donors really doesn't solve much of the problem for us.

Another way to limit allogeneic donors is to use apheresis products versus pooled products. Platelets are the things we are most interested in, or at least most familiar with, but apheresis collection of red cells and plasma is also one way of limiting donor exposure.

To illustrate that, the recent TRAP study was reported in the Christmas issue of The New England Journal. Patients with adult leukemia were assigned to receive apheresis platelets as therapy during induction therapy had a median donor exposure of 11, with the range as shown, as compared to those that were exposed to pools of whole blood-

derived platelets which, as you can see, on median received 6 times more, with a rather alarming upper limit of 840 donor exposures in one of those patients.

The second thing we can do is try to collect blood as much as we can from repeat donors. All of us know that repeat donors are believed to be safer than first-time donors. Their infectious disease positive rates are higher, in first-time donors, than in repeat. So, presumably, their false-negative rates are also higher. And, we all know that donor source subjected to multiple infectious disease tests over time have a much lower chance of transmitting infection because of window period episodes.

[Slide]

One way of looking at that is with this rather simple-minded picture. These are negative units; these are positive units; these are units which are falsely negative, meaning that the donor is infected but the unit is not detected by the test. The positive units are all thrown away. Those that appear to be okay for donation are put into the pool. This separate donor group, which has a much higher rate of true-positive units -- of course, those are all pitched out, but the chance of getting a false-negative unit is increased in that group. Although we can quibble about the linearity of the mathematical relationships when you compare one group of donors to the other, I think we

still would all agree that you are much less likely to get infected if you pick from this as opposed to if you picked from this group. That is sort of the rationale for the studies that we have tried to do.

[Slide]

Just very briefly, the history of the apheresis paid donors -- our whole blood donors are obviously not paid, at the DeGourin Blood Center is that back in the 1970s or early '70s, we decided that apheresis platelets were superior to pooled whole blood platelets. At that time we had a contract from NIH to study plateletpheresis techniques, and people were paid $30 in order to be experimental subjects in that study. Obviously, the funding of that has lapsed for 20-some years or so, but we still maintain a pool of apheresis donors and they still get paid $30.

The idea at that time, when we first started, was that they ought to get $10-15 per hour for the 2-3 hours of time that it took. Since that time, for a whole bunch of reasons that you can see here, we decided that we wanted to stick with apheresis platelets and that we wanted to collect them at our own place for a number of quality issues. So, that is sort of the nuts and bolts of our program. Although the whole blood donors are volunteers, the apheresis donors are paid $30.

[Slide]

One of the things that is really critical for our program is to understand that is very structured and, I think, reflects the fact that it seems to work, as I hope I will convince you from the data, at our place. It may not always work at other centers or other parts of the country. But it is very regimented and it is not easy to be a paid apheresis donor at our place.

All of these donors have to meet the usual criteria for regulatory agencies. They have to have a permanent address and a telephone number. They attend an orientation which involves 2-4 visits over a 2-month period of time, during which they see a slide show. They give consent. Also, a very important part of that is that they must donate or volunteer a non-paid unit of whole blood. We say this is so we can check your veins. The real reason is because it puts them into a 2-month holding period during which they cannot participate in the apheresis program.

Once they have completed that, they have to meet scheduled, not drop-in times. They are scheduled to come in every 3-4 weeks, depending on the needs that our patients have. So they can't drop in. If they fail to show, if they miss appointments without calling us, then they are dropped from the program. As a consequence, they have to survive repeated interviews and donor testing over, hopefully, long

periods of time. Once they have agreed to be in the program for at least a year or so, they are HAL typed and have leukocyte antibody studies. So, the point is that they are a highly educated, very committed and dedicated group, even though they get money.

[Slide]

This is a picture of some of our donors --

[Laughter]

It is supposed to interject a little humor, but it is also to emphasize the fact that the donors that we have in Iowa, and the way we treat them, are not necessarily the same as the donors one might have every place. And, we are very much in favor of an all-volunteer system but I think realistically that may not be possible.

[Slide]

So, just to very quickly go over the data that are in the published report, I just want to make two points on the slides. One is that these are two entirely separate donor groups. There is no overlap at all. They were either exclusively whole blood donors, and all of their whole blood donations were included in the analysis, or they were paid apheresis donors and all of the products they donated -- platelets, granulocytes or the whole blood unit that they gave to get into the program, were all considered part of that group because this whole blood unit was given with the

intent that they would enter the paid apheresis program.

We looked at all of the donors who were new to our institution during this period of time. Being new to any one institution does not always mean it is the first time they ever donated blood. We learned this rather painfully afterwards. So, I think attempts to look at first donors versus second donors, the data are sometimes not as clean as you would like it to be. But, nonetheless, there 917 volunteer donors, 1240 paid apheresis donors. Fairly comparable numbers. The gender breakdown is quite equal.

We looked at first and subsequent donations, again, at our institution, not necessarily the first they ever gave in their life, during that period of time. There were 757 whole blood volunteer donations and 8098 paid apheresis donations, including the whole blood.

So, you can see that the whole blood people donated about twice, the apheresis donors donated 6-7 times on average. So, the apheresis donors were, of course, tested many times more than were the whole blood donors.

[Slide]

This is a slide that summarizes all of the results. The paper has a breakdown in a variety of ways. But, these are the volunteer donors break down by gender; these are the paid apheresis donors break down by gender. These are the number of donors who were deferred during that

interval of time on the basis of history, some sort of infectious disease thing, or the number on infectious disease testing. You can see that the apheresis donors have markedly lower deferral rates.

If you wanted to express it per donations that they had rather than donors, then you would have to divide this number by about 2 and this number by about 6.5 or so. So, you can see if you express it per donors, the apheresis donors don't have infectious marker rates increased or actually statistically decreased but by donation there is a marked difference favoring the apheresis donor group in this particular way that they were looked at.

[Slide]

But I think it is more important than just that data to have an ongoing way in which you can look at these donors. As part of our quality plan, part of process control, we use data that we all have anyhow, and that is, we look at all whole blood and apheresis platelet donations studied for infectious disease screening and testing. For purposes of our quality plan, whole blood donors are equated or to represent volunteer donors. The platelet donors represent paid donors. And, we compare the percent of units discarded among all of those that are collected for infectious disease reasons, either repeatedly reactive infectious disease screening tests or some sort of recall or

use of the CUE.

[Slide]

You can see that over the years -- we look at this quarterly but I put this into a yearly thing so I could get it all on one slide, starting in 1992-97, that for the whole blood units, the number that were collected during those years, these are the percent of units that were discarded for some infectious disease reason. For apheresis platelet units the number collected and the percent decreased has, obviously, always been lower over those years.

The second thing you will notice is that here there is sort of a breakout where the units fall markedly in terms of the donor being discarded, and that was because of getting rid of the accursed ALT testing.

[Slide]

Now, to try to look at donors rather than donations, I went back for 3 years, '95, '96, and '97, and I will just show you the '95 data. These are the number of donors that were permanently deferred. So, during that period of time, 1995, you can see there were 5798 volunteer whole blood donations, 4878 paid apheresis donations, and these are the number of donors that were actually deferred. The reason they were deferred is in this column, here. This is HIV, HTLV, HCV testing. In the parentheses is whether they were Western Blot positive or Western Blot RIBA

positive. So, you can see that there is a sizeable number of whole blood donors that are deferred, most of them because of antibody to core found on more than one occasion. But there are a few with more of the sort of real infectious disease tests but almost never, in our donor group, do we have confirmatory test positive, with the exception of HCV. About half of them turn out not to be RIBA positive. The apheresis donors are markedly less.

The slides for '96 and '97, which are in your handout, look very much like this and so I won't take time to show them now.

[Slide]

I did want to show another set of data though, and that is trying to link donor frequency with deferral rates. So, we looked at all donations during one-year period of time, August, 1996 through August of 1997. We also then allowed a 6-month period of time for donors that were in that group to come back and be tested again, to try to take into account window periods. Six months is probably long enough to pick up most of them.

So, the way this slide is set up then, these are the number of donors -- this is whole blood -- that donated 1 time during that year's period of time, that donated 2-4 times, that donated 5-9 times, who donated 10 or more times -- obviously, none did but this column is on there because

the apheresis slide will show that there were some donors. These are the number of donors who were temporarily deferred, usually for a risk activity. As you can see, body piercing, malaria travel, hepatitis exposure or something like that. So, they were out for a 1-year period of time.

You can see the more frequently they donate, it seems the less we are deferring them for temporary reasons. We are probably selecting out some of the people.

Permanent deferral was usually based on repeatedly reactive infectious disease tests. You can see that the numbers also drop quite a bit the more frequently they donate.

[Slide]

Looking at exactly the same sort of slide set for the paid apheresis donor group, you can see that these are the number of donors who donated once, 2-4, 5-9. You can see that about a quarter of them donated more than 10 times during that year's period of time. The deferrals, both temporary for historical sort of things and permanently because of repeatedly reactive infectious disease tests, are so infrequent that it is kind of hard to pick up what the pattern might be. But it is obvious that they are strikingly less.

[Slide]

This slide sort of compares those data for you.

Whole blood donations, these are the number of donations; apheresis, the number of donations. These are the total number of donors that gave those donations. Total number of apheresis donors that gave those donations.

You can see that 2.9% of whole blood donors donated 5 or more times during the year, compared to 50% of apheresis donors. The frequency of donation, and the importance for us of having repeat donors for safety is what I am trying to emphasize. The percentage of donors temporarily deferred, 2.9 versus 1.9; permanently deferred because of repeatedly reactive tests, 1.6 versus 0.5.

[Slide]

The final bit of data I wanted to show you is, is this really necessary? Well, I don't really know. We have surveyed our donors on a couple of occasions to find out how important money is for them and it is always difficult to know exactly what the right answer is.

This is just to illustrate. They get $30, the same as they got back in 1972 or so. We feel it is really not so much payment as it is sort of reimbursement for the expenses that they incur by coming and spending a couple of hours with us. Maybe $13 an hour for a couple of hours missed from work -- they don't get compensated for time off from work, for parking, taking the bus, those kinds of things, child care, whatever happens to be involved. I am

not really trying to justify this; I am just trying to explain it, to sort of put it into the relative value of people who get 2-4 hours of time off from their job in order to donate platelets. I am not sure that there is a great difference here, even though this is cash that you get in your pocket.

Fifty-nine percent of the donors said that they would continue to donate even if they got nothing for it, about 60%. But I think very importantly, 48% said, yes, they will keep donating but it has to be fewer times; they can't come 10 or more times per year.

We have analyzed, or we have asked the donors a couple of times, in '93 and '97. We have looked at them to find out how many of them donate 10 or more times a year, and it has been, remarkably, about 25% of the donors. So, for purposes of safety and availability of platelets that we need, right now it appears that payment seems to be helpful.

[Slide]

So the conclusions, and I think they have to be viewed as working conclusions; they have to be modified as we learn more and as we continually monitor these donors. But past and present paid donors are not really the same. The derelicts and other people that were described back in the '70s are obviously not the same as the people that are in our program.

Cash, at least in our hands, the small amount that they get doesn't seem to be any worse than any equivalent for cash, just based on the low infectious disease marker rates. We don't have any comparative data. Based on infectious disease testing, paid repeat apheresis donors actually are deferred less than the volunteer whole blood donors at our place. Token reimbursement for time probably permits increased frequency, and we don't think it diminishes safety at all. Committed, educated repeat donors we need. We would all agree with that. And, I don't think it is unreasonable to reward them for exceptional service, or maybe to reimburse them for the time and expenses that they have.

[Slide]

The criticism of our study, and I should point that out, is that the paid apheresis donors seem to be selected. That is, we have more repeat donors in our apheresis group than we do in our whole blood group. So, it is unfair to compare as I have because the whole blood people have more first-time donors.

Well, obviously that criticism is valid, I think. If you are trying to study donor demographics, trying to assess the comparative risks of different donor risks, assuming you are going to do something with that data. For the plasma industry there is a way. Maybe you can do

something by holding plasma units. For the platelet and red cell people it is not as clinically relevant to test donors ahead of time and then have them come back, and draw them and test them, or do we throw out all of the first units? Right now there is no systematic way in which we are supposed to use this info. So, it is kind of a hollow criticism I think.

In a way, I would rather think it is goal to have more repeat donors. For the repeat donors, the reason it is a goal is that people getting blood want to have more repeat donors. It is the safely of the unit on the shelf that you are going to take off and give to me that really counts.

[Slide]

It sort of comes back to this picture that I showed you. If you are going to reach your hand in the refrigerator and get a unit out of there or a unit out of here, which one would you rather have, regardless of how you happened to get those units as long as it is reasonable?

[Slide]

Just to end up with a personal touch, this is a patient of mine, a young, desperately ill child with thrombocytopenia who needs a transfusion. Put yourself in my role as the prescribing doctor.

[Slide]

The blood center comes by and says here are a

couple of platelet units that you can pick from. I say let me get the parents. Let's look at these units a little bit closer. Do we want this one that says volunteer's successful donations past year one, lifetime one? Or, do we want this one that says remunerated, or paid, or whatever name you want to put, successful donations past year 8, lifetime 63?

Well, it is sort of hokey, I guess, to be showing this slide but I think there are some very practical reasons, and I think it emphasizes again that we really want to identify the safest units and then figure out how we can get more.

[Slide]

As a final slide in a regulatory way, I really hope that we think of allogeneic donors in the most scientific way that we can; to use data to try to assess the safety and to make decisions; and to critically analyze the data that we have, the data that I have and other people. It isn't perfect. There are flaws. So, critically look at it, but try not to be biased and have tunnel vision, focusing back on donors of 1970 or so.

I think it is very reasonable in a regulatory sense that all allogeneic donors undergo formal process control as part of our quality plan. We, obviously, rigorously interview and use infectious disease testing that

is identical for all allogeneic donor groups, but I don't think it is unreasonable at all to require that those institutions, facilities, centers, hospitals drawing blood should come up with a kind of data that I just showed you as part of their annual report to their transfusion committee, to AABB, FDA, whatever it happens to be, where you would compare the donor group safety in terms of discarded units or deferred donors, looking at the groups of donors that you draw -- true volunteers, those that get absolutely nothing; minimal cash equivalent, those that get T-shirts, those that get parking coupons, pins, whatever it happens to be; those that get paid time off. I feel very strongly that this paid time off is the equivalent of cash. And those that get psychological, emotional or ego things, these special donors like the directed donor group.

I think if we were required to do this and submit these kinds of reports, within a very few years, especially if they were set up in a structured and uniform sort of way, we could really begin to gather some of the data that maybe could be tested by these mathematical models.

Thank you very much. I appreciate your attention.

DR. HOLLINGER: Thank you. We are going to take a 15-minute break and we will reconvene at 3:45.

[Brief recess]

DR. HOLLINGER: Before we start with the open

public hearing, I have had one or two committee members ask if they could ask some questions of the previous speakers. Dr. Linden, you had a question of some of the previous speakers?

DR. LINDEN: Yes. I have a question for Dr. Satten and one for Dr. Ruta.

DR. HOLLINGER: Dr. Satten?

DR. LINDEN: Towards the end of your presentation you had donor 1 and donor 2, with donor 1 seroconverting but not during donation time that could be detected and donor 2 being picked up. I think you said you were assuming that they cancelled out, and I guess I am not clear on that. Donor 1, the interval during which he could have infectious donations would be equal to the infectivity period, slightly less actually, which is going to vary, as discussed by Dr. Busch this morning. The second donor, the interval during which there could be infectious donations is equal to the turnaround time for the laboratory until they find out the test results. And, that is not going to be the same as the infectivity period. Right? Am I missing something?

DR. SATTEN: I think I was imagining that we were just counting window period donations, and that the 2 donors were seroconverting at the same time. So, donor 1 was making some earlier donations and then dropped out before they seroconverted. Donor 2 starting making donations at

about the time that donor 1 dropped out and then seroconverted. So, the original expression that I derived said how many total window period donors would donor 2 make. But that is an over-count because he didn't really make all those donations because they started maybe in the middle of their window period phase. Donor 2 also made some window period donations but then dropped out before seroconverting. And, those are the two types of donors that, on average, balance each other. Does that help? No, it didn't? You don't look happy.

So, if a donor starts up during that window period, is recruited during the window period, then the standard formulas would over-count the number of infectious units they donated because they weren't making donations all through their window period. They started in the middle. Okay? Another donor who makes some window period donations and then drops out before their window period ends, they never get counted. The point was simply that the donations that donor 2 never made are balanced by the ones that the unseen donor made, on average if you have a steady state.

DR. LINDEN: Okay. Thank you.

DR. HOLLINGER: When you computed the data for the hold, you were really talking about a hold not a quarantine. Is that right? That was a T of 60 days hold?

DR. SATTEN: That was for a T of 60 days from my

understanding of what the hold is, which means that units are dated, and if there is no subsequent information that that donor has seroconverted, then that unit is released after 60 days.

DR. HOLLINGER: Thank you. That is why when you said 90 days, that was a lower percent?

DR. SATTEN: Yes.

DR. HOLLINGER: Okay. Thank you.

DR. LINDEN: A question for Dr. Ruta. Was your entire discussion an analysis purely of plasma donors, source plasma, recovered plasma, and nothing to do with blood components?

DR. RUTA: No, I think it would apply for both whole blood and source plasma donors, with my limited understanding of how these equations would apply but they should apply to both.

DR. LINDEN: Well, in whole blood donors then, you define the lookback interval as being 5 years for components and only 6 months for plasma for fractionation.

DR. RUTA: Yes. For right now we were talking about recovered plasma for the purposes of fractionated products for further manufacture. So, I thought when you said whole blood donors you meant in terms of recovered plasma that would be collected from a whole blood donor for use in fractionation. I wasn't dealing with components.

DR. LINDEN: So, you were only talking about source plasma versus recovered plasma?

DR. RUTA: Right.

DR. LINDEN: Thank you.

DR. HOLLINGER: We are going to go ahead and open up then for the public hearing. There have been six people who have asked to speak, and I have talked to them about their time commitment so they know how much time they are going to be given. We are going to start with Andy Conrad, from National Genetic Institute. Andy?

Open Public Hearing

[Slide]

DR. CONRAD: Basically, as an IND holder for PCR, I am going to try and examine just quickly the mechanisms and the effects of PCR in the paid donor system.

I think if we are able to look at some of the data that we have, we have now tested in real time about 1,600,000 donations for Alpha Therapeutics and Baxter. So, we are going to look at just brief flashes of some of this data. But this is real time, real data, real donors and real donations, and we will get some of the effects of PCR. I am also going to explain very briefly how we do pooled PCR.

[Slide]

Basically, what we do is we take 512 samples and

we organize them into rows, layers and columns. Those rows, layers and columns are called primary pools for the first pool we make.

[Slide]

Primary pools will contain 64 samples of a row, a layer and a column -- 64 times 8 is 512. Each pool is then tested twice for resolution.

[Slide]

We combine all those into one big cube, 3-dimensional cube on this device. So, that device has 512 samples. The argument is that where a row, a layer and a column intersect, right here, you would get a donation that is positive. That donation can be removed. If the whole pool is tested and it is negative, then all 512 of its members are at least below the limit of sensitivity. I am going to go over that briefly.

So, basically what we call the big pool of 512 is the master pool. When we do the automatic pipetting, we make two of those, and I will show you why. We have an algorithm that can resolve positivity.

[Slide]

Basically, this is the device that we do it on, a T-can Genesis machine. We pipette 8 samples at a time. That is why we chose 512, because it is immediately divisible by 8.

[Slide]

Pool size -- we can make it anything. We can make it 128. We set 512 as the maximum. There are some economic reasons for it. The bigger the pool, the less expensive the testing but there is less sensitivity.

What is interesting about this system is that it is the only system ever where retests are better than the first tests because when we retest, we move from a concentration from a 512-fold dilution to a 64, to an individual sample which is undiluted. Essentially, each retest is of a greater quality than the test previous, which is rare. Most laboratory retest systems are testing the same sample again, and then trying to referee between them. But, in this case, we learned early on with co-investigators that whatever the result of a more concentrated sample is, is the overriding result.

[Slide]

We basically have this algorithm. We test master pool number 1. If it is positive, we go to the row, layer and columns of the primary pools. If they are positive primary pools, then we test the positive implicated sample. The rest of the samples can be released. If we get some anomaly, there are some mechanisms to deal with anomalies. They are very uncommon now. At the beginning, we learned an awful lot and now the system is relatively smooth and it

runs quite simply.

Basically, in order to make a calculation of the true sensitivity, as Dr. Ruta showed a slide where we talk about 10^4 or 10^5, our sensitivity is validated by ICH3 limits tests.

[Slide]

For HIV, it is around 9 copies per mL. When you are centrifuging you can concentrate this stuff dramatically. We can concentrate these big pools. For HCV we get an average of 13 copies. So, HIV around 9 copies, HCV around 13.

[Slide]

Also very importantly, I notice Dr. Ruta talked about genomic variations or genetic variations in the viruses. This is a study we did where we took clones that we made of every subtype of hepatitis C, and compared its detectability in a series of dilutions. As you can see, there is a highly significant association or rho value for all the different genotypes, which means our system detects hepatitis C genotypes. We did the same study for HIV type O, M, outlier, and we did all the same studies for the genetic variations for HIV and HCV. This is critical because part of a window period donation can be a window period for multiple reasons. It can be because the genomic sequence is different or antigenically it may never develop

antibodies.

[Slide]

We use the Southern Blot system. This is what an actual membrane looks like.

[Slide]

These are positive controls. Every sample gets run multiple times. Fortunately, there are robots that do it all. Every sample gets done with multiple primer pairs in replicate, and this adds to the reproducibility and the success of being able to determine this. It also helps in contamination control in other ways.

[Slide]

Here is a sample. This is a positive sample. As you can see, it is actually done in quadruplicate because the primary pools are all done, according to the IND that we submitted, in duplicate of each of the 2 primer sets, primer set 1 and primer set 2. FDA wanted to see if there was true competitive inhibition between the internal controls. So, we actually ran everything in septuplicate for the IND, just to evaluate some technical components of what was happening.

[Slide]

So, basically, what you end up getting is that the next thing that happens is you take those 2 membranes and you rehybridize them for their internal controls. Every sample has an internal control. So, a negative can't truly

be called a negative unless the internal controls all show. A positive can be called a positive even if the internal control didn't show, obviously if the viral positive showed because of competing internal control, you would still call it a positive.

[Slide]

So, this is essentially what a master pool result can look like, either a negative, all 6 of the negatives show nothing and all 4 of the internal controls show positive, or positive with a band in each of these.

Just briefly, you can see competition, when the internal control can compete with one of the primer sets for false negativity. So, you have to be very careful about the amount and the type of internal control you use. These are just hard learned lessons.

[Slide]

The primary result pools are the same. The primary pool is called positive if the positives are positive by the internal control under this scenario where the internal control shows, and the negative are negative.

[Slide]

So, now to the data, the part you have all been interested in. What I did, I took a snapshot of what the formal IND component of this was. We agreed with the FDA that we would assay at least 300,000 samples before we

opened our trap and started talking about it.

So, these are the results of 344-some odd samples for both HCV and HIV. This, again, is in real time. It represents paid plasmapheresis donors. And, this is the rate of positivity. So, we tested 704 master pools, an average of around 512, and you know the total number of donations, 340,000-some odd donations. And, 103 of the master pools were positive for HCV, 18 for HIV.

Now, it is important to know that in the system the samples were sent from repeat donors to us before the antibody testing was done. So, we could test some of the samples that were, indeed, antibody positive. That does not mean that the antibody laboratory missed them. That just means they came to us before the antibody -- they would have been pulled out by the antibody data, and 24 of them we didn't get the data on. So, basically, 14.6% of the master pools were positive; 120 individual donations out of the 344,000 were positive. With Dr. Satten's interesting but complex discussion of some of the models now, this is the guide that should be used, the total number of donations, total positivity. This is independent now of window periods or anything because this is the PCR. It doesn't matter when they turn antibody positive, and the same for HIV. What we will do, we will go over some of the things that we took from this, some of the other surrogate markers.

[Slide]

We had some scientific questions to ask, questions like what would happen if we were to have looked at ALT is a surrogate marker. The answer to this could also have indicated whether hepatitis C in very high viral titers has a direct hepatolytic effect. The answer clearly was no.

What you see here is that we looked at samples less than 38, ALTs of 38, which was the laboratory normal; 38 is quite conservative in industry for an ALT value. And, 69 of the samples that we identified that were antibody negative had ALTs less than 38. Whereas, only 7 of them had elevated ALTs, and those 7 above 38 are shown over here. They are quite low actually. Only 1 of them would be over the traditional cutoff for ALT. So, this showed us that for hepatitis C in the window period ALT brings little or nothing to the test. You can't use ALT as a surrogate for hepatitis C infection. Once the antibodies came up in the antibody positive ones that fortuitously slipped through by sending them in, you see that the antibody rates are quite a bit higher but, again, not perfect or a good indicator. What this tells us is that markers like ALT are not a valuable, at least valuable in detection of hepatitis C window periods, and that the hepatitis C even in very high viral titers does not directly affect the liver as far as hepatocellular lysis.

[Slide]

More important is that we began to look at HIV. What happened is we detected 18 positive donations. If we go back real quickly, you can look at the antibody stats of those 18.

[Slide]

Six of them were antibody positive; 7 of them were antibody negative.

[Slide]

What we wanted to do in order to demonstrate to the FDA the utility or futility of the antigen testing, p24 antigen testing is they began to sense spikes or seroconversion panels through the system that were known to be either p24 positive or p24 negative, and they were all run at these 512 pool dilutions that we described.

What is important about this is that it is clear that p24 -- and I think Dr. Stramer, who is coming up later, probably has better data than I do on this -- but what is clear -- and she explains it better, because that p24 is a subset of the viremic samples.

[Slide]

I think this is best illustrated in this 2 X 2 table. Of the PCR positive samples, which are here, 59 of them were detected by both the p24 and the PCR where 32 of them were missed. Now, when you look at the inverse of

that, what would have happened if we would have left out the p24? You see that you would have missed zero. None of them were detected by only p24 and not in the 512 PCR pool dilution. I think that this is a significantly important finding, and that there is a lot of effort used on tests that may be yielding very little value.

[Slide]

Now, antibody is different. Antibody is very important. We still have to keep antibody. In no way to we play on using p24 to supersede the use of antibody. I will show you why. Towards the end the viral loads begin to drop as antibody titers come up, and there were definitely some cases --

[Slide]

-- three of them, to be exact, where we were unable to detect it by 512 PCR yet the antibody still found them positive. It is not a big number. What is nice about this is that it does check for antibody. I mean, they both sort of work hand in hand. Antibody and PCR work hand in hand.

[Slide]

Finally, keeping my promise of 12 minutes, I just wanted to say that we also tested some important points about frequency, the length of window period, viremia. These are from some Baxter donors. You can see that they

are viremic the entire time, and only quite in the late period does the antibody become positive.

[Slide]

This is just another seroconversion panel in HIV, where there is a large time when only the PCR is positive.

[Slide]

What we learned from this, and I was very gratified to see Dr. Satten talking about his modeling because what we began to suspect is that there really isn't a fixed ratio between the number of donors which are antibody positive, the frequency of antibody negative, PCR positive samples, and the frequency of antibody negative PCR samples that will be detected.

You can kind of get a good idea of what you are expecting to see about the sampling of people who did seroconvert. This is just a different form of seroconversion; it is conversion to viremia and there is a ratio between those. Basically, the thing that governs that ratio is dependent upon the rate of antibody positivity, the frequency of donations and the length of the viral window. We think we are now capturing data that gives you those variables, and sophisticated statistical analyses will let us really understand what the risk is. What we are suspecting, because of the high viral loads, is that the window period really will become a moot point.

[Slide]

So, my conclusions based on this data -- and we will be submitting the finalized BLA in the next 2 or 3 months, is that HCV window period donations are more frequent than we originally thought. They are frequent because of the length of the window, and final rates will soon be determined, and that is both donor and donation final rates.

Window period viral loads are extremely high. This is another important point. The rapidity with which virus is replicated is an important factor here. Pooled testing probably will be very, every efficient because there is not smoldering viral infections; they shoot up fairly rapidly.

Pooled PCR testing dramatically reduces the viral burden of the plasma and may almost eliminate the window period. I think that is a less ambitious statement than it may sound, and the data will eventually show that.

[Slide]

Finally, it looks like p24 antigen testing appears to be inferior to the PCR antibody mix testing. The interesting thing about this is that it is pretty economic because, remember, you are screening 512 samples with a single test. So, there is not a lot of big money. If you wanted to translate this into single donor costs, the real

cost of doing this is less than a dollar per unit. So, I think that the economic barriers aren't really that profound. That is it.

DR. HOLLINGER: Thank you, Andy. Andy has a plane to catch. Are there any questions from the committee for Dr. Conrad at this point?

[No response]

Thank you very much. The next speaker is Susan Stramer, from American Red Cross, who will discuss their data.

DR. STRAMER: Thank you very much. Could I have the first slide, please?

[Slide]

My topic is a little bit different, and I think it is consistent with the title of this afternoon, however. What I was asked to discuss by Martin Ruta was HIV, HBV and HCV incidence and prevalence in whole voluntary blood donations at the Red Cross. I did not present any data separately on CUE. CUE donors are excluded from this database. Also, I don't have any data on product withdrawal and quarantine or, as Martin called them, the lookback cases, because we basically act on repeat reactive results, and the frozen products that are interdicted are not tested. So, we really don't have any data to discuss for those.

I would like to acknowledge the help of my

collaborators, Roger Dodd and John Aberle-Grasse.

[Slide]

In order to go through this data properly, I need to prevalence and incidence. Although they have been defined previously today, I am going to repeat the definitions. Prevalence can be defined as the portion of infected persons in a population independent of time of infection. In populations with low incidence rates, as we believe whole blood donors are, the prevalent positives contribute to risk primarily or only by test error.

Incidence is the proportion of persons newly infected in the population during the period of time under study, or the rate of new infections. Incident positives contribute to risk by window period donations, as we have seen.

[Slide]

We also need to define risk, and risk in the case of my presentation is the sum of the frequency between test error, which we assume to be small, and window period donations, which are the major contribution, we believe, or risk.

The risk of window period donations is the product of the length of the window period times incidence. So, in populations with high incidence there is also high risk, or you can really look at that also by the length of the window

period. If the window period is shorter, the risk is lower. As the window periods increase, the risk is higher. We calculate incidence typically from seroconverting repeat blood donors.

[Slide]

We have seen this slide only twice today, but just to show it again, this is HIV seroconversion, and the point of this slide is really to show you in a repeat plasma donor the number of donations that occur. You can see seroconversion occur over a very short period of time. Here is the p24 antigen data and, as Dr. Conrad previously alluded to, you can really see, even if you are doing pooled PCR testing which just has a higher cutoff and a typical cutoff of single donation testing, that p24 antigen represents a subset of the RNA positive period. Here you would have a window closure of 2 days for HIV, which is relatively small.

[Slide]

In contrast, for HCV, as Andy just said, we have very high viral loads and long window periods. So, doing tests of increased sensitivity, like HCV PCR even in pools as high as 512, does have efficacy.

[Slide]

Now to get to the real numbers, and most of the rest of my slides just go through prevalence and incidence

of the Red Cross, and I will discuss how these were all calculated.

These are straight results from screening for HIV, HIV-I/II, HBsAg and anti-HCV using the 3.0 test. This column just displays the numbers repeat reactive or the repeat reactive rates, and then the confirmatory results. So, based on the number of positives for the number of donations, we can calculate number for positive per 100,000. These are typically the numbers displayed for the number of confirmed positive anti-HIV, that is 0.007%, HBsAg, 0.033%, and HCV, 0.11%. Those are our confirmed positive rates at the Red Cross over this period of time.

I should also let you know that this represents the subset of collected blood at the Red Cross. We don't have as good data throughout the entire system, as I will focus on through this talk. So, we focus on 19 regions in which we collect very good data, very detailed data, and that is our infectious diseases center regions, and they represent approximately 37% of the collected blood in the system for the period of time that I am covering.

[Slide]

Looking at each marker separately, again, this is prevalence but because I am dealing with a period of time that has an interdonation interval of 364 days, basically we are talking about each donation representing 1 donor. So,

the numbers in repeat here would represent incident infection, whereas, the numbers for first-time represent prevalent infection. Again, if you look at the total here of 7 for HIV, they break out into 3 per 100,000 for repeat and 23 per 100,000 for first-timers.

[Slide]

Looking at the data similarly for HBsAg, 33 total in repeat donors, which represents about 80%, 78.9% of the total population of donations, and then 21% of the donations come from first-time donors, and the number here is 143.

The other thing that I didn't discuss, this is our population of donations less than 60 years old because those are the donors who are used in fractionated products, and that is the emphasis of today's whole discussion.

[Slide]

Looking at the same display of data for HCV, we have 112 total positives per 100,000 donations over this period of time, and they break out into 29 per 100,000 in repeat donors and 425 per 100,000 in first-time donors. If you look at this number, which is 0.4% relative to the general population which is at about 2%, you can see even first-time donors have overall lower prevalence than the general population.

[Slide]

Putting this data together in one summary slide

again gives you the total by marker across the top for HIV, 7, HBsAg, 33 and anti-HCV, 112. I also wanted to point out the numbers that we have gotten for p24 antigen screening since its implementation, March 15, 1996. This database for this period of time includes 1 seroconverting donor, and then that number breaks into 0.03 per 100,000 or 3 per 10 million. Since this entire time of p24 antigen screening, our total yield for the entire blood system, and it is now March 19 -- today is a 2-year anniversary, and now I can say we have had 2 positives in 24 million for the whole blood collection system in the United States because the 1 positive that we did have was a repeat donor. But, again, these are the total numbers for each marker, a breakdown for the first time and repeat donations.

[Slide]

In contrast, talking about incidence or the rate of new infections, this is to define, hopefully, the same thing that Glen said but in terms that I can understand.

[Laughter]

Incidence includes the number of seroconverters, and in this case we are talking about 100,000 donations over the person time of observation, which in person years is defined as the number of donations times the interdonation interval factored for a year's period of time.

[Slide]

The way we use this data, we took a one-year period of time -- so we are going to look at incidence in repeat donors over the period of time from July 1, 1996 to June 20, 1997. I picked July 1 because this way for HCV it is internally consistent. That is, all the HCV data that I will show you is with 3.0 testing and 3.0 confirmatory. Within this period of time a repeat donor is defined as a donor who had at least 1 donation within the previous 365 days of their donations. Basically, because we are limiting the period of time per donor to 365 days, here the mean donation, instead of being 364, as I discussed earlier, in this case, for this particularly truncated period of time, was 154 days. So, applying the model that I went through, the number of seroconverters in 100,000 donations over the number of donations times the interdonation interval, adjusted per year, will give us incidence.

[Slide]

This slide shows the incidence numbers. Here I have included antibodies to HIV and p24 antigen. The number of seroconverters we had, using the model I described, is 12. The number adjusted for 100,000 donations is 1.09. The interdonation interval for the entire population was 154. Just for these 12, it was a mean of 194 days. Incidence per 100,000 person years was 2.59. If you multiply incidence by the window period you can calculate risk. So, in doing so,

we see our risk per million donations for the combined HIV in repeat donations at 1.1 per million donations.

Doing the same calculation for HBsAg, we come with a final risk of 10.1. Now, I did not calculate anything beyond 59 days for the HBsAg window period. In Schreiber a factor was included of 2.38 to calculate the fact that HBsAg is positive for only a transient period of time. But I did not use that adjustment factor. I just calculated straight HBsAg.

For HCV, we had 54 seroconverters during this period of time. That ultimately calculates to an incidence per 100,000 of 11.65, times the 82-day window period, which would give us 26. If we use a 70-day window period, as I probably should have done based on the third generation test or 3.0, instead of a number of 26.2 the corrected number should actually be 22.3. So, one could say this is the worst case number that I show on this slide.

[Slide]

The problem or limitation in all the incidence calculations that have been published is that they do not include incidence in first-time donations. So, using a model that you have probably heard about in previous advisory committee meetings, we used a model developed by Rob Jansen, Mike Busch and myself, called the "detuned" model. This is one way to estimate incidence from first-

time donations. It involves a serologic testing algorithm which depends on reactivity to a sensitive EIA as compared to the reactivity on an insensitive EIA. So, basically we always talk about closing the window. Well, in this case we open the window, and the period of time we increase the window period to be, rather than 22 days or 16 days, in this case a 129-day window period.

[Slide]

Just to give you a little detail on the "detuned" model, this basically shows you the sensitivity at post-infection, at time 1, the reactivity to the sensitive EIA, and then the elapsed time to detection by the insensitive EIA. This window period of 129 days represents the "detuned" negative period of time. So, you are basically an incident positive when you test reactive on the sensitive EIA and you test nonreactive or below the insensitive EIA cut-off, and we call these "detuned" negatives. Actually, I failed to acknowledge Glen Satten. He did all these calculations. So, I was negligent in omitting that.

[Slide]

Anyway, applying these to some HIV seroconverters, you can see the profiles in yellow on the sensitive test, and then on the insensitive or "detuned" test you can see those profiles in blue. So, really this difference means out at 129 days, but this ratio will tell us who long ago

the person has supposedly been infected, theoretically been infected.

[Slide]

This model as applied to Red Cross donations for a period of time between 1993 and 1996. The incidence number I showed you from the period of time that we calculated incidence in repeat donors, not using "detuned," was 2.59. Using "detuned" which basically is the same data but calculating it differently, we came up with the same number practically of 2.95.

Looking at first-time donors in this period of time, we had an incidence of 7.18, or 2.4 times higher in first time than repeat. If you look at the total incidence, and we know that repeat donors contribute about 80% or 78.9% to the population, first-time donors are 21% of the population at an increased incidence of 2.4 times, we can basically have a final factor of 1.31, which really means the total incidence, including first-time donor incidence, is 31% higher than the repeat donor incidence.

[Slide]

Applying this incidence model for first-time donations and combining that with our incidence in repeat donations, what we have tried to do in this slide is get an estimated total incidence, and then an estimated adjusted risk per million donations.

So, looking at incidence per marker for the combination of repeat and then first-time donors, applying the adjustment factor of 2.4, gives us an estimated total incidence of 3 for HIV, 8 for HBsAg, again not including a correction factor, and for HCV 14.91 as total incidence.

Then applying this time to the window period gives us this total risk, including both first-time and repeat donors for HIV. So, it goes from 1.1 in repeat donors only to 1.5. For HBsAg, using a 59-day window period, the risk is 12.9, and for HCV it is 33.5 using an 82-day window period, and 28.6 using a 70-day window period.

[Slide]

So, in summary, the data that I have shown you includes the fact that most volunteer blood is collected from repeat donors. Positivity in repeat donors represents new or incident infections. Using the HIV "detuned" model and calculated repeat donor incidence rates, overall incidence and risk may be estimated.

[Slide]

The combined first-time and repeat donor estimates of adjusted residual risk were within the 95% confidence interval of published estimates using only repeat donors. Let me go back because I didn't really highlight that two slides ago.

[Slide]

When I calculated total incidence and we applied those numbers to estimate total risk, these confidence intervals, here, are those published by Schreiber. So, we can see that these numbers fit within the confidence intervals calculated even though these were for repeat donors and this is for a total incidence in total donors.

[Slide]

So, again, this is combined first-time and repeat donor estimates adjusted for residual risk. We are within the 95% confidence intervals of the published estimates using only repeat donors. The inclusion of first-time volunteer whole blood donors does not have an overriding contribution to risk. I also showed you that to further decrease risk we can test by methods to detect window period donations, such as genome amplification testing. Thank you.

DR. HOLLINGER: Thank you, Susan. Questions from the committee?

DR. MITCHELL: Yes. Why did you use estimated numbers? Do you not have real numbers for the incidence rates in your population?

DR. STRAMER: No, those are real incidence rates. We estimated risk by multiplying those by the window period donations, window period length.

DR. MITCHELL: Okay, but do you not have the risk for the first-time volunteers?

DR. STRAMER: We don't have incidence in first-time volunteers, no. The only way we can do that is by applying some models to the data. Since the donors have only presented once and they are positives, we don't know when they in fact they seroconverted.

DR. HOLLINGER: I think, Susan, you have to admit that that is a fairly weak part of the argument here. I think one would have to stretch it to say inclusion of first-time volunteer donors do not have an overriding contribution to risk. Even though it is within those confidence intervals, it is still clearly at the end of those confidence intervals.

DR. STRAMER: Right, absolutely. But I think statistically when you are dealing with a number between a confidence interval, it is either significantly different or it is not. And, this is the only way to show approximate incidence in first-time donors. So, as soon as there are better modeling techniques available we certainly would like to refine those. But this is to give you a flavor of some point estimate of what we believe is perhaps happening.

DR. HOLLINGER: And part of that reason I suppose is because you only have 20% first-time donors pooling into that group.

DR. STRAMER: Right. Right, it is a weighted average.

DR. HOLLINGER: Any other questions of Dr. Stramer?

[No response]

Thank you, Susan.

DR. STRAMER: Sure.

DR. HOLLINGER: the next presenter is Toby Simon, for American Blood Resources. Toby?

DR. SIMON: It is my privilege to be here today, representing the American Blood Resources Association as Chairman of their Medical Directors Committee. I have had experience over a number of years with both the recovered plasma whole blood systems and the source plasma systems. And, I think what we have are two different systems, which are very different, and travel different paths to reach the same end, which is a highly safe and effective product.

As a result of my presentation today, you will have an understanding of the steps that we have instituted to continuously improve the safety of the source plasma product, and some of the preliminary data that demonstrates the effectiveness of those steps.

We work closely with the IPPIA, which represents the fractionators, although we actually represent technically the collectors. That represents 1.5 million donors per year, about 13 million donations of 11 million liters. These donors are men and women over the age of 18

in their communities. They have to be local residents in good health, and meet the standards of the FDA and the industry. These include people from all walks of life. As part of our quality plasma program, we have been moving to get the plasma donor viral marker rates as close to the community standard as possible, and we have relocated many centers. We have areas of the country, such as the Dakotas which never before had plasma centers that have them now, and we are also locating preferentially many of our centers near colleges and near military base where we find a lower viral marker rate.

We have brought many safety initiatives to the BPAC at the September meeting: the viral marker rate standard, the quality donor standard, the inventory hold and PCR. These products are used to treat patients and, due to the effectiveness of the viral attenuation procedures, as we have heard, have been very safe.

The source plasma industry operates under strict regulatory requirements from the FDA, and it is important to note that source plasma is a licensed product, whereas recovered plasma is covered under short supply agreements and is drawn in both licensed and registered establishments. So, there are very different requirements, which we will also go through.

[Slide]

This just describes briefly the differences in both the systems and some of the data that we will present. Due to the success of the REDS study, the recovered plasma has had the advantage of having longitudinal data, whereas ours is really a snapshot.

The donation interval for those in the recovered plasma system is 56 days or longer, whereas our donors can donate twice in 7 days. All donations are pooled in recovered plasma. For source plasma, only those qualified donor donations are in the pool. The unit size for recovered we estimate at 250 mL per donation. For source plasma we are estimating 825 mL, which gives you a significantly reduced donor exposure in the source plasma system.

Test error is always possible, but we have limited that by not considering a donor qualified until we have 2 sets of test results on 2 different occasions.

We have instituted an inventory hold. Both systems are looking at PCR testing and have INDs in place. These numbers indicate that about 80% of the product that patients receive comes from the source plasma system.

[Slide]

In order, hopefully, to answer some questions that have arisen about the procedures, we bring you this graph, which I will try to go through quickly, but clearly the

first-time donor presents to donate has a donor history; if the questions are satisfactory, then he goes through the requirements both of the FDA and the voluntary requirements which we have placed upon ourselves. There is a check of a national donor deferral registry to which all our members contribute. If the donor is in that registry, he is deferred. There is heroin testing, a physical exam as required by the FDA done by a physician or a physician substitute. If all of these are satisfactory, the donor can proceed to donate. If the donor is not a first-time donor, then this once a year procedure may be omitted. The donor, of course, has the viral marker testing done, and if the tests are negative the donor comes to this point. If the donor is not a first-time donor but is qualified by having donated in the past 6 months successfully, then the unit can pass on. If the donor is a first-time donor the unit is held until the donor returns.

Now, the importance of the hold in the qualified donor program is simply that we have experienced over years, very similar to that in the recovered plasma program, that first-time donors have higher marker rates than repeat donors. So, those donors who have not returned to donate a second time, in our experience, are those with higher rates of positivity and, therefore, are also at higher risk of having a window period unit. So, we eliminate those donors

to begin with, and then go only to a qualified donor program. If the donor does return and is not a first-time donor, then the units go to the fractionator, who then holds those units for at least 60 days.

This is where the inventory hold comes in. The inventory hold is based upon our knowledge from the past that we get a certain amount of post-donation information from the donors. It could be in the form of a positive test, new data on the donor interview form, becoming sick with a disease, and most of that will come within the 60-day period. Through this hold we can interdict the units and remove them before they are pooled into final product, and not be in a situation where we have information and have a final product that has been made. So, what we are dealing with in terms of the data we will present is the risk of those units which go into the pool which is made into final product.

[Slide]

We have begun collecting data in the 1991 time frame with our quality plasma program in order to have a viral marker rate standard. This collection of data was done by the individual centers, and was insured through our quality plasma program inspections but was not centrally managed. What we have tried to do in our second phase is to manage the data centrally and to provide data on those units

which actually go into the pool, and to provide a qualified donor standard for our centers to meet to remain in the quality plasma program. Our objective is to monitor the collection centers and develop industry-wide seroprevalence rates, which will be reported back to industry, consumers, regulators and the public. We are now in the process of doing that. So we are reporting to you preliminarily at a time when we are in the process of gathering the needed data.

[Slide]

The current data collection effort began in July of 1997, when we began phasing in the inventory hold. This data was collected from confirmed positive qualified donors, and the total number of qualified donations. The data collection was begun for the purpose of establishing a qualified donor standard, which we are continuing to work on to set, and need more data.

This time, as opposed to our previous effort, we are using confirmed positive rather than repeatedly reactive although, of course, units which are repeatedly reactive would not be allowed into the pool. During this effort, we are utilizing WESTAT, a contract research organization, to assist in the management of the data collection activities and data analysis. So, we are using an independent agency to work with us in this part of the effort. WESTAT, as many

of you know, is the group that works with the REDS study that is funded by the NIH. So this will, hopefully, bring us to a high level in terms of data reporting.

[Slide]

Initially, we obtained our data from the testing laboratories, and there is a relatively small number of testing laboratories in the source plasma industry, either connected to the fractionators or one of the independents. They reported the data to us and to WESTAT over the 4-month period, which will cover a total of 3.95 million donations and will give us a preliminary analysis. We do have data from 90% to 95% of the QPP plasma collection centers, and about half of this data comes from fractionator-owned centers.

[Slide]

This is the viral marker rate data among qualified donors. So, these are the donors who met the qualified donor standard and have returned at least once within 6-month period. If they don't donate within 6 months, then they have to start over again to requalify. These analyses were originally performed at the request of the Government Accounting Office, and were previously reported but these data are somewhat different because, as Dr. Ruta indicated, we did have a problem due to over-reporting and inclusion of applicant donors, as well as some donors repeated twice.

That was because we were taking the data straight from the testing laboratories. In this data effort, we are now going back to the source plasma collection centers themselves to get the information that we need.

The industry is moving towards computerization and automation, but it is incomplete at the present time. So, much of our data does come in paper form and has to be placed into a computerized data set. Because of that, we are incomplete on the data that we are presenting and we are still entering data. It also means that the one organization which provided us data on this would be totally represented. So, we still need to normalize that data for the entire industry.

[Slide]

The data on this slide shows the result of the qualified donor standard. In blue, here, we have our prior viral marker rate per 100,000 donations, which was for all donors. However, this is repeatedly reactive and we didn't have the confirmation information from that data set, so we have used published information on proportions that are ordinarily confirmed to get the next bar, which is the adjusted or the confirmed positives per 100,000 donations, also prior to our current qualified donor standard. The last bar here represents the data that we currently have. Though incomplete, it is going to be highly representative

of the qualified donors.

As you can see, the qualified donor standard has resulted in a lower viral marker rate in those units which could potentially go into the pool. This is the HIV rate, here; hepatitis B; and hepatitis C. So, the population that we now have due to the qualified donor standard does have a much lower rate, and there has been a significant impact on moving to that.

[Slide]

We have undertaken intensive data collection efforts to verify previously reported seroprevalence data and to respond to the specific requests. We are still targeting the same 4-month period, and we have gone back through corporate channels to get additional information so that we are not over-counting the same individuals.

[Slide]

As a part of this effort, we have requested lookbacks from all confirmed, qualified donors and then, in order to get interval information to do the calculations that we have been talking about, we have requested 4-month donation history for 25 random, nonreactive qualified donors from each collection center. We have input about one-third of the data, and so about one-third of the data is now available for analysis. Nonreactive involves histories for about 10,000.

[Slide]

This has permitted us to give a preliminary evaluation of the window unit interdiction rates under the inventory hold; so, to provide data on the effectiveness of the inventory hold, and the probability of a window unit entering the plasma pool using the incidence model that has been previously published for whole blood, one that has been published in The New England Journal.

[Slide]

This is that first data, which is the effectiveness of the whole period which reflects the percentage of suspect window units that would be interdicted under the industry's current minimum 60-day hold, or hold of 60 days or longer. The reason I say "would be" is because the hold was being phased in during this time period.

[Slide]

As this data shows, we are virtually at 100% for HIV with the hold, with HCV 54.7%, and HBV 91.4%. We have some preliminary data from some of our members on PCR, which suggest that we will get to 100% interdiction using PCR testing. So, this uses the 60-plus day inventory hold and indicates the ability to interdict units through that hold period. This is assuming a 10% non-return rate for donors.

[Slide]

This is the so-called incidence calculation, which

is a comparison of the probability of a window period donation entering the plasma pool. This was done using the previously published model. It is important to note that, of course, no seropositive units are used in the pool and viral inactivation and partition eliminate what viruses are there. But using the model that has been previously published, which we have not completely validated for the plasma industry, the source plasma group, indicates that source plasma with a 60-day hold -- then we also show adding PCR based on preliminary data on PCR, 0.6 per million donations, 49.5 per million donations, estimating 0.8 per million when we add PCR testing. Then for hepatitis B, 34 per million donations.

Now, a couple of caveats about this particular graph: Number one, of course, we are in the process still of entering data. Number two, we are using this previously reported model, which we need to rethink given some of the presentations here today. Thirdly, we are using a 3-interval data system which we feel is not entirely satisfactory. So we have a number of donations that seem to us are probably going to be shorter than the number that we wind up with. Our current average from the data that has been input is 5.3 days, but we have one company that is over-represented and we think when we have a full snapshot of the entire industry it is going to be longer than that.

So, these numbers will probably come down.

This number, as I did the calculations in my head quickly based on the data presented by NGI, seems to be higher than what is being gathered from PCR testing.

[Slide]

So, these data are preliminary and full data sets are not available, and the effects of PCR have not been fully realized but that is ongoing through the work you have heard and will hear about. The window unit probabilities are based on a model that has been previously published, which has not been completely validated but which we will continue to work on for the source plasma model, and look for other analytical models.

We are committed to return in June, if we receive an invitation to provide further information and update on the particular data sets that should have more information. We are also going to have continuous monitoring as we establish our standard. So, we will be putting in another 2 months. But we will continue to work on this.

[Slide]

The last slide just simply summarizes that this is all being done, within the context of a large number of initiatives, with the FDA and with self-regulation of the industry in terms of training workshops; continued upgrading of our national donor deferral registry, which is national

so that a person with positive tests or information cannot go from one location to another; the establishment of viral marker rate standard to get our centers as close as possible to the community standard; and, of course, continuing CGMP and quality assurance; upgrading our donor screening efforts and looking at increased validation there; expanded patient liaisons on our various committees and regulatory liaisons; and our continued location and relocation guidelines to get us to the community standard.

[Slide]

We believe that industry initiatives, in addition to those that we have through the regulation, make these plasma products safer; that the qualified donor standard has significantly reduced seroprevalence rates in those units; the inventory hold has permitted us to interdict a high number of suspect units, and we are committed to the continued scientific analysis of these initiatives through the use of data.

I do want to acknowledge WESTAT, and George Schreiber in particular who can answer any specific questions about the data, as well as Chris Healey and Bobby Whitaker from the staff of ABRA and, of course, all of our centers for hustling to provide us with this information.

DR. HOLLINGER: Thank you, Dr. Simon. Questions for Dr. Simon? Yes?

DR. MITCHELL: The data that you presented are impressive. I am glad to hear that. Do you have actual numbers of units that -- I am assuming that with the lookback you pulled some of the previous units that you had where the person didn't qualify. Do you have numbers on the actual number of units that you might have pulled?

DR. SIMON: The actual numbers of units that were interdicted?

DR. MITCHELL: Yes.

DR. SIMON: The problem is that we were phasing into the hold, which is why it was "would have been" interdicted. So, we don't have that yet, I don't believe, but we should have more data on that also as time goes on.

DR. MITCHELL: Is it possible to get copies of the slides that you presented?

DR. SIMON: Yes, we have given that to Dr. Smallwood.

DR. MITCHELL: Thank you.

DR. KHABBAZ: My question relates to the marker rates that you reported in 25 donors, qualified donors. Does that include the donors who might not have returned that might be pooled and used?

DR SIMON: If they were qualified and did not return they would be included. The ones that would not be included were first-time donors who never returned.

DR. HOLLINGER: When these are analyzed eventually will you have some way of looking at those particular donors to see what their window period positive rates are, and so on?

DR. SIMON: The donors who do not return?

DR. HOLLINGER: Yes, for the sample you have which you are going to pool. You will have the sample. Are you going to be able to look at those --

DR. SIMON: Oh, you mean the applicant donor samples.

DR. HOLLINGER: Yes.

DR. SIMON: Those samples would have been tested, so there is that data.

DR. HOLLINGER: By PCR?

DR. SIMON: Well, no. That depends, I guess, on the method of PCR the particular collection agency is using. The most common system I believe that is evolving is that the units are being EIA tested, and for those people who have negative EIA tests, then a sample is sent for PCR. At least one of the collection agencies that we know of is waiting until the end of the hold period. If they are interdicted, then those donors are not tested by PCR. So, there is a little bit of variance in our protocol in terms of PCR testing.

DR. STRONCEK: My understanding of the

presentation is that you make an assumption on how many people with rapid tests your hold period would capture, and the assumption was that 90% of the people come back and donate again. You only lose 10%. Whereas this morning, someone from your group estimated that if there was a quarantine period you would lose 20-25% of the donations based on people not returning. Am I misunderstanding something?

DR. SIMON: Well, 10% was within 60 days that did not return. I guess it would depend on the --

DR. STRONCEK: Well, I guess if you are right that 10% of the people don't return, then if somehow something changed so you had to discard these units, you would lose 10% of the units, not the 25% that they talked about this morning.

DR. HARTIGAN: I think it is because the people who don't return donate 2 or 3 times before they don't return, and those specimens would be quarantined and then be discarded. So, although only 10% don't return, 20% would be.

DR. SIMON: I guess I missed that point. We will have 2 samples often but the person may not come back. Thank you for your help.

DR. HOLLINGER: Thank you. The next speaker is Sue Preston, from Alpha Therapeutics.

MS. PRESTON: Good afternoon, ladies and gentlemen. My name is Sue Preston, and I am representing Alpha Therapeutic Corporation. I would like to discuss the potential impact of gene amplification on testing for HIV and HCV RNA and the IPPIA voluntary 60-day hold safety margin for plasma derivative products.

[Slide]

Alpha Therapeutic Corporation has been one of the principle investigators on two investigational new drug applications, sponsored by National Genetics Institute, to explore the efficacy of testing pooled samples of plasma donations for HIV and HCV specific nucleic acid sequences by polymerase chain reaction, commonly known as PCR.

The next few slides will depict the preliminary analysis of our clinical trial experience. I will then describe our post-clinical trial experience with continued testing for HCV RNA by the same method. Finally, I will discuss the impact of PCR testing in conjunction with the IPPIA voluntary 60-day inventory hold on deducing the number of window period units that may inadvertently enter a plasma pool for manufacturing therapeutic products.

[Slide]

The investigational drug applications were submitted on February 17, 1997 and were approved by the FDA on April 30, 1997. Samples from each patient collected from

approximately one-half of our license sites were sent to our central testing laboratory, located in Memphis, Tennessee, for routine serological viral marker testing. Aliquots from the same samples were pooled into a 512 cubic matrix for PCR testing. During the clinical trial the samples from first-time applicant donors were subjected to PCR only if the samples were negative for all currently licensed viral marker tests. However, for qualified or repeat donors, the PCR testing was conducted concurrently with the viral marker testing.

[Slide]

You have seen this before today, and I thank Dr. Conrad for describing what the test does, and I won't say very much about it, other than that each donation sample is represented in 1 layer, row and column in the primary pool, master pool as he referred to it. We employ this matrix to allow the rapid confirmation of the suspect positive individuals through triangulation to the positive primary pool. The pool samples in not more than a 512 matrix are sent to the National Genetics Institute where for polymerase chain reaction testing are performed for HIV and HCV genome sequences and separate reactions.

The results are returned to the Memphis laboratory for correlation with other test results and disposition of the individual units of plasma. The IND sets forth a

minimum of 300,000 donations, at least 10,000 donors for testing. Part of the investigation plan was to follow eligible subjects to seroconversion.

[Slide]

The clinical trial was designed to identify the HIV or HCV positive donor as early in the seroconversion period as possible. Any donor that was positive for HCV RNA and negative for HCV antibody is determined, in our hands, by the Ortho 3.0 ELISA, was asked to enroll in the follow-up clinical trial. ALT testing was routinely performed for all donations with Genetics Systems test, and donations are tested for the absence of HBsAg with the Genetics Systems 2.0 enzyme immunoassay. Once enrolled, the donor was asked for a sample to test for HCV RNA and HCV antibody weekly for 6 months until seroconversion.

[Slide]

For the HIV investigational new drug application, the clinical trial for confirming the HIV RNA positive donors had eligibility criteria for the subjects to include positive HIV RNA and/or reactive for HIV-1 p24 antigen. And, we used the Coulter HIV p24 antigen ELISA, with positive neutralization, again a Coulter test, and reactive for HIV-1, 2 antibody by the Genetics System second generation kit. When appropriate, the Cambridge Western Blot test kit was utilized to confirm repeatedly reactive

antibody samples.

[Slide]

The results of this clinical trial that ended in mid-September -- there were a total of 344,843 donations covered in the clinical studies. Of these, approximately 3500 donation samples are pending resolution. Of the 341,000 donations with finalized HCV RNA results, 76 donations -- let me stress that this is not donors -- are positive for HCV only. If we look at HCV, what those represented were 20 donors, 13 of which enrolled and 7 of which were eligible but did not enroll.

For the HIV clinical trial we detected 50 donations that were positive for HIV RNA. Of these, 6 were positive for HIV RNA only. This correlated to 2 donors, 2 of which were enrolled and 2 of which were eligible but did not enroll. All of the HIV RNA positive samples were nonreactive for HBsAg.

[Slide]

Now, because I always like to do things a little differently than anybody else, I thought I would plot this to try to indicate what happened with the 4 donors in the HIV clinical trial. So, each bar represents 1 donor. The way that this is plotted is that day zero, this time point, is the donation that is first positive for PCR. On the right-hand side of this graph are the days from that point

of being PCR positive. The blue color represents the PCR positive only; the yellow, here, was PCR positive as well as p24 antigen positive; the red color represents all 3 markers, PCR, p24 antigen and HIV antibody reactive.

On the left side of the chart, we have been able to look and see whether we had PCR negative samples for each of those donors or, in some cases, this was done during the study period and sometimes we took the samples from lookback samples and had them subjected to the same matrix. Each tick mark represents a donation sample, and you can then see that there are quite a few negative PCR donations prior to the first positive PCR donation.

The lower 2 bars are the 2 donors that did not enroll, and the upper 2 bars represent the enrolled donors. The data are somewhat consistent with what has been published and what we have heard today with respect to window periods for antibody seroconversion and for antigen seroconversion. As of today, in our clinical trial we have not found a confirmed HIV p24 antigen positive sample that, if tested by PCR, was not found positive for HIV RNA.

In conclusion, even with HIV where we have a relatively short window period, PCR testing of pooled samples appears to allow earlier detection of window period donations.

[Slide]

The results we saw for HIV are probably even more striking than for HCV. Again, it is the same sort of plot where, at the zero time point is the first PCR positive donation. The blue color is PCR positive only. The yellow color is PCR positive and HCV antibody reactive. We have 1 donation, here, where we had a sample that was PCR negative and HCV antibody reactive. I will come back to that in a minute.

On this side of the graph we have plotted the negatives. PCR negatives are in green, where there are PCR negative as well as antibody negative. We did not have PCR, or have not yet received PCR results on any of these, in grey, but these do have the last antibody negative donation shown.

This particular donation may reflect the 5-15% of HCV viremic individuals that clear the virus particles but remain antibody positive but, of course, we are confirming our sample handling to assure that we maintain the sample properly.

The seroconversion period ranged in this study from 22-120 days, with a mean of 67 days and a median of 56 days. What is significant is the number of potential window period donations that can be interdicted with PCR testing of pooled samples.

For those of you who are wondering about ALT

elevations, ALT elevations would have been insufficient to defer the unit or the donor. The ALT was not as effective as PCR in identifying the HCV RNA positive. Twelve donors had no ALT elevation above our cut-off limit or were only above that limit at the date of the antibody seroconversion; 6 donors showed elevations above the limit for ALT, however, each of these donors was positive for PCR at least 28 days prior to the ALT elevation, and there are 2 donors for which we don't have ALT data for all of those samples.

[Slide]

Now I would like to switch and talk about the post-clinical trial testing. Alpha Therapeutic Corporation has continued to test samples of donations in a 512 matrix for HCV RNA after we completed the number necessary for the clinical trial. We gradually increased the number of plasmapheresis centers to include all licensed centers that supply source plasma to us for fractionation or sale.

As of the end of February of 1998, all centers were sending samples for PCR testing. Over 1 million donation samples have been tested between mid-September, at the end of the clinical trial, and the end of February. Of these donations, 0.015%, or 157 units, were positive for HCV RNA and nonreactive for other viral markers. An additional 32 units were HCV RNA positive and antibody reactive.

We do not have information on the number of donors

this represents, which I know is a question that will come up. We can state that the rate of positive donations found during our clinical trial is similar to the rate found in the post-clinical trial period. So, that is the number of positive donations over the total number of donations tested. Furthermore, this rate is comparable to rates reported by other laboratories. It is also worthy of mention that since we have implemented PCR testing the HCV antibody maker rate continues to decline significantly.

[Slide]

I am not very good at theoretical modeling of data. But we have a fairly large database we have been maintaining where we record the lookback units that we have from every donor that is repeat reactive. So, this is not positive confirmed. So, it is fairly significant database.

It is an analysis of the percent of units that would be interdicted, thinking about 3 different things: the recommended lookback duration that has come out from the FDA, and that is the lower set of bars. I have put on the right what that recommended duration is. The blue bar is HIV p24 antigen. The green bar is HIV antibody. The red bar is HBsAg. The yellow bar is anti-HCV, with respectively 3, 6, 12 and 12-month lookback recommendations.

Then, I know my window periods probably don't match what we said earlier, but to give you sort of the

maximum window period and what we would interdict for the 60-day hold, I also asked the same calculations to be done for the mean window period.

This database represents all of the repeat reactives, and there may be other things also in that database where we wanted to do lookback that occurred during the calendar year of 1997. They all had to go back at least 1 year if the donor had donated because that is required for all, even though the recommended donation lookback may be only 3 months, but within our system we record all of them within a year. Some go back even further than that if our data entry clerks are so inclined.

As a reminder, I can tell you we implemented the minimum 30-day inventory hold in July of '97 and increased the hold period to a minimum of 60 days as of January, 1998. As we look at this, the percentages that we can see in terms of the maximum window period for HIV is virtually 100% with the 60-day hold. It is about 70% or so for HBs, with a maximum window period of 87 days. Then, for HCV, about 46%. Using the mean window period as a calculation, we are at 100% for HIV, 99% for HBsAg and about 77% or 75% or HCV.

We believe that with PCR this window period, or the number of units that we can interdict will approach 100%. Part of the reason we believe that it will approach 100% is also because of the qualified donor program and the

reduced incidence that we will have with PCR.

[Slide]

In conclusion, our data demonstrate that PCR testing in small pools of plasma samples is an effective method to further close the window period for detection of HCV or HIV RNA. PCR testing, in conjunction with the 60-day inventory hold and the qualified donor program significantly reduces the potential for window period units to be added inadvertently to plasma pools for manufacture of therapeutic products.

Of course, this is not the end of the story since plasma products are subjected to validated viral removal and/or inactivation steps to assure higher margins of safety, as Dr. Tabor described earlier. And, as always, we continue to explore measures to further ensure increasing the levels of safety and confidence in the quality of our products.

Thank you for your attention to this presentation.

DR. HOLLINGER: Thank you, Ms. Preston. Yes, a question?

DR. MITCHELL: I didn't understand the second to the last slide, where it shows that the longer the hold, the smaller the proportion of captured --

MS. PRESTON: Yes, I know this is difficult, and we are doing some other theoretical modeling. In our

database, I know every donation where a donor subsequently had a repeat reactive or some other incident so that we wanted to do a lookback. Okay? I know what each of those [not at microphone; inaudible], at least a year, sometimes more than a year. Then I asked our statisticians to take a look and just calculate very simply, because I wanted what was real data, what would be captured with a 60-day hold because, obviously, not for all of 1997 do we have a 60-day hold in place. We implemented a 30-day hold in July, and so forth.

We calculated of those donations what percent would be captured. This is actually the percent of all of the donations that we had in our database. So, for some donors we actually have 2 years worth donations in that database because they had been a very long time donor. The FDA has a recommended lookback donation that they have published for us, and that greatly exceeds the maximum window period for a margin of safety. That is 3 months for HIV antigen, 6 months for antibody and 12 months HBV and HCV viral markers. So, based on the FDA recommendation, we don't capture as high a percent. When we look at the window period for each of those viruses, using either the maximum window period or the mean window period, that is where we see that we can capture a good percent, in fact up to 100% for HIV, with the 60-day inventory.

DR. MITCHELL: Are you saying that in 1997 you only captured that percentage of units, or are you saying that if you start today and go on into the future you will only capture that percentage?

MS. PRESTON: As of January 1, 1998 that would be the percentage that we would capture when we implement the 60-day hold.

DR. KOERPER: Does the 60-day hold assume that somebody comes back within the 60 days, seroconverts and you discard the unit?

MS. PRESTON: We would discard the unit when we do a lookback.

DR. KOERPER: Right, but if the person doesn't come back, then you are going to put it in?

MS. PRESTON: That is right. We wouldn't have a positive result to do a lookback on.

DR. VERTER: Is that saying that for HB, if there is a 60-day inventory hold and the mean window is 59 days you would, therefore, capture them all?

MS. PRESTON: Ninety-five percent.

DR. VERTER: All right, but if it is 87 days, because that exceeds the 60-day limit, it would be released.

MS. PRESTON: That is correct.

DR. MARTONE: If you go back to this figure that you had showing the PCR test, or the various tests on the

left-hand side, it looks like that last case there theoretically could have eluded the 60-day inventory hold. I realize the numbers are small but that is 1/4 rather than 1/100.

MS. PRESTON: Well, for HIV we would go back 60 days -- we would have an inventory hold at least for 60 days from the point that they were positive. Now, in today's world, without PCR, that would be where this yellow is. Now that we have PCR available to us under an investigational new drug application, that 60 days actually starts a lot earlier. So, without PCR that 60 days would go back to that point, that point, that point, and this one would never have been detected.

DR. MARTONE: So a unit may have slipped by.

MS. PRESTON: That is right. But with PCR in place, and we still have the 60-day inventory hold, so with PCR --

DR. MARTONE: Well, with PCR it is theoretically possible you would have missed that last one too.

MS. PRESTON: Why do you think that?

DR. MARTONE: Because you have had over 60 days worth of negative PCR tests.

MS. PRESTON: But as soon as that one is positive, as soon as someone is determined to be positive --

DR. MARTONE: I realize that, but that might have

occurred beyond the 60 days.

MS. PRESTON: Yes, I mean, that is still the issue we just talked about. If a donor does not return and has a positive test result and we aren't aware of a positive test result --

DR. MARTONE: Okay. With respect to these 4, do you go back and make an effort to find out why you have had 4 people giving so many donations, what the risk factors were and why they slipped through the preliminary screening test?

MS. PRESTON: That is probably not something that we are able to do as well as, say, CDC or the state authorities. These donors who have been found positive by PCR are counseled with respect to that, and we have to report them depending on which state it is, but we try to get them to counseling as quickly as possible. Obviously, we will ask the question, and our donor centers ask the question, "well, you know, you're PCR positive and we have a lot of negative donations." But that doesn't always elicit a response as to what happened.

DR. HOLLINGER: Thank you. Dr. Linden?

DR. LINDEN: It still looks to me like your figures are really the effect of a quarantine, not hold. You are assuming, aren't you, that people are being tested at the end of the 60-day period? I mean, if they dropout

before they ever convert, even with the PCR, you are not going to know about them. I mean, you didn't correct for that, did you? I mean, your gold standard is that they had a positive test. Right?

MS. PRESTON: Well, I don't think that there is any way for us to be able to know something that we don't know. So, if someone does seroconvert, we are not going to know that. We talked before that the quarantine is definitely a gold standard. For us, I think what is more important is what does that do to our product availability? I think during all of the time that we have thought about the voluntary initiatives, as each company has thought about it, it is in areas for how to improve the safety margin. Quarantine was certainly something that we could think about, but I think that with the logistics of that and the incredible concern with product availability, it seemed that we could achieve almost the same thing, plus the fact that we have viral inactivation and removal, and we have a very good clinical history with these agents in terms of safety.

DR. HOLLINGER: You have had viral inactivation and you have had some HAV transmission?

MS. PRESTON: HAV?

DR. HOLLINGER: Yes.

MS. PRESTON: Yes, we do, and we implemented another viral inactivation step to try to take care of that.

DR. HOLMBERG: I just want to add to what we were talking about this morning as far as more information coming the next time. With the discussion on quarantine and the hold, I think if we went back and looked at what the FDA was saying this morning, it would help the committee to see some sort of evidence of the efficiency of your lookback and your retrieval of the products.

DR. HOLLINGER: Thank you. I think we will go on then. Thank you very much, Susan. The next speaker is Dr. Thomas Weimer, from Centeon.

Presentation

DR. WEIMER: Thank you. My name is Thomas Weimer. I am with Centeon. I am responsible for PCR development. I was asked to give you an overview of our PCR system an share some data we have on detecting window period donations by PCR.

[Slide]

The system was developed to test plasma units for fractionation for hepatitis B virus, hepatitis C virus and HIV. It was entirely developed by Centeon. The system consists not only of the pooling strategy and the PCR assay, but also of the software which helps in tracking the samples through the system and takes over some of the data evaluation.

To be able to test only 3.5 million donations

which are fractionated per year by Centeon, we pooled and validated 2 laboratories, one in Knoxville, Tennessee in the United States, and one in Marburg, Germany. The system has been implemented in Germany for European plasma in July, last year. It is only 4 weeks ago that we got FDA authorization for PCR testing under an IND in the U.S., so, please, do not expect data from that study.

[Slide]

The objectives of the system are to screen all plasma, which is negative by standard serology, by additional PCR testing; remove PCR reactive units from fractionation; notify and counsel donors with PCR reactive donation and defer them from further donation; to use only PCR nonreactive units for fractionation; and, thereby, add an additional safety factor to the current inactivation and removal methods.

[Slide]

This slide highlights somewhat the assay and software controlled pooling process. We do pilot pools prior to fractionation at different steps, up to the maxipool of 1200 donations, which is subjected to initial screening which includes a high-volume virus concentration step for maximum analytical sensitivity. We have a robust, though manual, nucleic acid preparation method, and we do nested PCR for high sensitivity and specificity with

subsequent fluorescent detection of amplicons.

[Slide]

The system has been validated, and the laboratories are run on the currently Good Manufacturing Practices. This slide shows the essential parts of that validation. Of course, we validated the assay in terms of sensitivity and specificity robustly. Also, the computer system has been validated, as well as all the laboratory equipment. Personnel training is an important factor in setting up new laboratories with our very sensitive method. After having transferred the methodology to the quality control labs, they repeated part of the validation to demonstrate equal performance. The semifinal validation demonstrated that the laboratory and the software work properly. I will show you some data on the last validation which we call the overall performance qualification, which aims to demonstrate that all PCR-related functions in the system work together properly from plasma collection through pooling and PCR to identification of the unit and removal to a fractionation pool which should be PCR negative.

[Slide]

Now, this highlights some of the validation data. In terms of sensitivity, you see the analytical sensitivity of the primary screening assay of the maxipool. Once we are talking about numbers, we must make reference to the

standards used to be able to compare this data.

For HBV we use the Eurohep standard, which will be the upcoming WHO standard. The sensitivity is about 1 genome equivalent.

For HCV, where we use the Pelispy, we have sensitivity of 5-7 genome equivalents. With respect to the WHO standard, we are about 1 international unit/mL.

For HIV, we use NIBSC and have sensitivity of 15-41 genome equivalents/mL.

In terms of specificity, we demonstrated that we pick up the major genotypes and subtypes, including subtypes of HIV. There is no cross-reactivity with other viruses.

In terms of robustness, we have seen that the 3 laboratories have comparable validation results, and they have comparable excellent performance in collaborative studies.

[Slide]

Now, this is now the data from the final stage of validation of the PCR lab in Marburg. We have sent through the system about 350,000 donations which were negative for current serology. We tested those specimens at the end of the 60-day hold period, and those samples consisted of about 80% of recovered plasma from a European source and about 20% of plasmapheresis samples.

The positives we screened out were 2 HBV, 21 HCV

and no HIV. The virus load, as we heard several times today, for the HCV positives was very high and such a unit would have had 10^{11} genome equivalents. The virus load for the HBV positives as low, as expected because there is good sensitivity of the HBsAg immune assay. So, that means that even eliminating a single one of those positives significantly decreases the viral load of fractionation.

The last bullet point is an important one, which says that all fractionation pools made from PCR pres-screened plasma were, indeed, PCR nonreactive for all the 3 viruses, and this has now been a total of 66 pools.

[Slide]

In conclusion, we feel that we have established a PCR screening system for routine, high-throughput testing which consists of a feasible pooling strategy of highly a sensitive and specific PCR assay, and an information technology which supports collection, testing and logistics.

The system has identified window periods of hepatitis B virus and hepatitis C virus which have not been identified with current antigen antibody assays. So, this system further reduces the virus load of fractionation pools and complements the viral inactivation technologies applied to plasma derivatives. The implementation of PCR testing may well eliminate real or perceived differences between viral marker rates of remunerated and non-remunerated

donors.

Thanks for your attention.

DR. HOLLINGER: Any questions or Mr. Weimer?

[No response]

Thank you. The final presenter for the open discussion today is Theo Evers, representing the European Plasma Fractionation Association.

MR. EVERS: Thank you very much. My name is Theo Evers. I am the Executive Director of the European Plasma Fractionation Association. I appreciate the opportunity to present some data from Europe.

[Slide]

The EPFA, the European Plasma Fractionation Association, is a trade organization for the not-for-profit manufacturers of plasma products in Europe. All manufactured products are on the basis of blood and plasma from voluntary and paid donations.

[Slide]

This just lists here the countries where our organization has member organizations. The data set I am going to present to you today is from the European countries, with the exception of Greece. In some countries we have 2 member organizations, just to warn you in case you are checking numbers.

[Slide]

I guess a general consideration of why you collect data sets is similar to what you have heard. It is necessary to determine the level or degree of reduction of risk you have achieved, to confirm that you collect from low-risk populations, to confirm the exclusion of donors at risk, and to ensure that low risk will be achieved in case of newly emerging and unknown viruses.

[Slide]

The data we have collected are HIV, HBV and HCV. They are collected retrospectively from routine data for years 1990-1996 from first-time and repeat donors, voluntary, unpaid donors of whole blood in up to 8 European countries.

[Slide]

Just as a way of guidance to the numbers, first-time donations in terms of prevalence, and first-time donations include all potential donors tested for the first time; repeat donations, and you will see in the data that there are still ranges of rates, difference in rates between the different organizations. The marker rates, as presented, are pooled and weighted by the reciprocal weight of the exact 95% confidence intervals.

[Slide]

I will now go through a couple of sheets which present the data on first-time and then repeat donors.

Starting with HCV, I will just alert you to the fact that we have presented the data in per 10,000 donations. If you look at the total number of donations, the numbers in parentheses are the number of participating organizations, member organizations of EPFA, and you see that the database has increased over time and is not constant. If you look at the 1996 data, you will see that the ranges are indicated as well between the different member organizations.

[Slide]

Here are the marker rates indicated for HCV for the repeat donors. An analysis done on the data, in particular looking at the contributions from the individual organizations, shows that the decrease over years is significant for all member organizations.

[Slide]

The rate for first-time donors for HIV-1 and 2 -- again, I allude to the fact that we are talking about per 10,000 donations, and for all organizations there was a significant decrease.

[Slide]

Repeat donors, HIV, again the same for all organizations contributing to the data set, and over the years there was a significant decrease in marker rates.

[Slide]

First-time donors for HBV, and the same can be

said for the repeat donors for HBV, here the decrease, if you look at the pooled data, is primarily caused by a number of organizations with large donor populations. The other contributing organizations, their marker rates are steady over years.

[Slide]

This is the last data set on the repeat donors.

[Slide]

We will, obviously, continue the collection of these data, and it is clear that some of the collection of data needs to be adapted to ensure better assessment of the data. Future studies should include the rate of confirmed seropositivity among first-time donors to monitor the donor population, the rate of seroconversion among repeat donors and our inter-donation interval to estimate risk resulting from one or more window donations, and the total rate of confirmed positive donations to estimate total error risk.

[Slide]

As an additional requirement, we have identified that it is needed to develop and adapt standardized systems to ensure that you will have an evidence-based comparative analysis of residual risks. Comparison so far has been quite difficult because most studies have different bases that they calculate their numbers on, and it is urgently required that these standardized systems will be developed.

[Slide]

In final conclusion, we can say that the risk of infectious donations among voluntary, unpaid donations in Europe is low and decreasing, and further improvements are necessary for increased transparency of residual risk. Thank you.

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

DR. BOYLE: Could you tell us what proportion of your domestic needs for blood products for your 8 member nations are met by your volunteer pools, and what proportion are met by paid donations in the United States?

MR. EVERS: We are talking about the cellular components that are in general self-sufficient, as we call it in Europe. For the plasma products self-sufficient has not been achieved. The latest data set which has been prepared by the European Commission stems from 1993 data and there were still substantial additional needs for increased collection or other measures to achieve self-sufficient. The 1995 data are due to be presented any moment. So I have no firm recent data on that.

DR. BOYLE: Thank you.

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

DR. MCCURDY: At one time, I understand, Europe was getting virtually all of their plasma as a byproduct of whole blood donations, or maybe red cells were a byproduct

of whole blood donations. Are you now doing plasmapheresis or is it still coming as recovered plasma from whole blood?

MR. EVERS: When we talk about the member organizations of EPFA, most of them use recovered plasma.

DR. MCCURDY: Recovered plasma?

MR. EVERS: Yes. In a few countries there is no plasmapheresis going on. In other countries, like in Germany, there are plans to increase the total number of plasmapheresis activities.

DR. MCCURDY: This is plasmapheresis from volunteer donors?

MR. EVERS: Not necessarily.

DR. HOLLINGER: Thank you. Any other responses from the public hearing? If not, I am going to close the public hearing and I would like Dr. Ruta -- Dr. Ruta, could you read the questions?

Let me tell the committee that FDA is not asking us at this time for a yes, no, abstain or otherwise on this. It is primarily a discussion only. They would like to hear any thoughts of the committee regarding the presentations today as they relate to the questions that will be presented for you.

Open Committee Discussion

DR. RUTA: Thank you very much, Dr. Hollinger. There are two questions which we have for discussion

purposes for today. The first question is, given the safety record of virally inactivated plasma derivatives, should any demonstrated differences in marker rates between paid versus unpaid donations raise new safety concerns?

Shall I go ahead and read them both?

DR. HOLLINGER: Yes, go ahead.

DR. RUTA: Okay. Do committee members have any comments on the scope and soundness of FDA's approach to assess risk or paid versus unpaid donations regarding either data collections or our plan for analysis?

DR. HOLLINGER: Thank you. I would like to open this up for discussion by the committee. They have the questions before them to read. Who would like to begin?

We can start on the first question, given the safety record of virally inactivated plasma derivatives, should any demonstrated differences in marker rates between paid versus unpaid donations raise new safety concerns? Considering all factors here, the potential for other technology being used, issues -- anybody? Yes?

DR. KHABBAZ: I think we heard this morning and this afternoon some of the concern with new and emerging agents and ones that may not be inactivated. That may be one reason for concern.

DR. HOLLINGER: Yes, Dr. Martone?

DR. MARTONE: On the other side of that coin, I

think we have heard a lot of data regarding agents that we know about, and some evidence to suggest that the safety record will improve when these new tests are being used.

DR. HOLLINGER: And you are not concerned about paid or unpaid? I think Dr. Strauss dealt with that adequately in some respects.

DR. KOERPER: I think we have to keep in mind that Dr. Strauss' paper defines a very unique, well defined, highly educated population living in the middle of the United States, and I don't think that it is entirely comparable to paid donors in other parts of the country. So, I applaud him for his marvelous job in getting these people to come back and for having such a low infection rate in those paid donors, but I think that I don't find them to be equivalent.

My concern about a difference in viral marker rates between the paid and unpaid donors, excluding Dr. Strauss' group, is that if the paid donors have a significantly higher marker rate for these defined viruses that we are testing it might suggest a slight tendency towards some kind of behavior that might expose them to other viruses that we are not yet testing for. So, that would be my concern when there is a difference in viral marker rates between the paid and unpaid donor groups. I would applaud any means for lowering the marker rates in the

paid donors to that of the unpaid or voluntary donors.

DR. HOLLINGER: Do you think that some of the programs designed, or the program that he has at that center with the small number of people could be utilized by large organizations, like the American Red Cross or other organizations, in terms of scheduling more people in, coming at different times and so on? Do you think that is not probably possible?

DR. KOERPER: I think those are goals that other organizations should aim towards. Clearly, it is going to take more time to have the people come in for the various presentations, signed informed consent etc. It is going to involve more time on the part of the staff at those donor centers, but if that will achieve retention of high quality donors it would be worth it in the long run, I would think, because fewer donations would have to be discarded.

DR. HOLLINGER: Yes, Mr. Dubin?

MR. DUBIN: First of all, I would agree. I don't think Ma and Pa with a pitchfork are necessarily representative of the United States. Although, clearly, the program there, as you say, is very good, and commendable, and interesting, and a unique job is being done, it doesn't apply to Los Angeles, San Francisco and New York City, or Miami --

DR. HOLLINGER: Only the pitchfork, eh?

[Laughter]

MR. DUBIN: Only the pitchfork! And, what I am struck by over the last 10, 15 years, reading study after study citing from 5-10 times more dangerous paid donors, and the difference is that technology seems to be closing that open space between paid and unpaid. But if technology is what is closing that space then, again, we are back to ensuring that the technology is correctly applied in ways that continue to close that space, because I think that there are still concerns that we certainly have about paid donors and some of the figures. And, the only thing I think making a change in the past is the application of PCR testing, of new kinds of screening. So, I think we need to be clear on, again, operational standards, Good Manufacturing standards. Operating procedures are again, as they have been, an achy issue.

But, in closing, I would say even with the application of technology there are still differences that we should be concerned about in a paid system, and I will leave it at that.

DR. STRONCEK: I guess it is hard for me to compare the numbers from the organizations, but I was quite impressed by the safety of both the paid and unpaid donors, and I agree with the presenters today that even if you don't pay a donor directly, oftentimes they do get other gain and

I don't think we should look at whether or not we pay them in terms of dollars or other ways, but I think you need to look at what kind of results you get as far as safety of the products.

I think, yes, there is a potential if you pay donors and go into the wrong populations -- there will be problems. But I think what we have seen here is that these groups have been very responsible and they have taken a number of steps to ensure that their products are safe. I think the FDA could continue to allow groups to pay donors as long as it is done in the way they are doing it at this time.

DR. HOLLINGER: Yes, Dr. Callero?

DR. CALLERO: Speaking as I think the only sociologist on this panel, much of what I heard today I didn't comprehend, but this is one area where I do have some expertise and I think we have to be careful here because when you begin to expand the pool of paid donors it is going to have implications, sociologically and culturally, in terms of what that means to the pool of volunteer donors. So, the cultural meaning of what it means to donate blood, and the oxymoron of paid donors notwithstanding, I think we have the possibility of creating a situation where you may decrease volunteerism as you increase the proportion of paid donors. Those kinds of implications need to be considered

also.

DR. VERTER: I need clarification on something. Is it fair to say that when we are comparing things that the whole blood or the volunteer and the apheresis with the source or the paid?

DR. HOLLINGER: What is the question, again?

DR. VERTER: In some of the tables --

PANEL MEMBER: Yes.

DR. VERTER: Okay. Given that statement, if you look at the data that has been presented, it seems to me there is a very mixed statement going on. If you look at the REDS study stuff that was presented this morning, there were some prevalence rates in the so-called paid that are less than in the whole blood. If you look at some of the data that I believe Dr. Ruta presented, the first time there is a clear difference but the repeats are similar. So, it is not an obvious conclusion from the numbers that I have seen today, whatever that is worth.

DR. MCCURDY: It seems to me that the issues really involve the agents, as I mentioned earlier, that re not inactivated, and the new agents that we don't know about that may emerge. I am not sure how to work with those. I think the inactivating procedures, as I understand them, are robust enough so that they will take care of anything but a gross error in manufacturing that allows too many or too

heavily contaminated units in.

So, I think that is the issue, and the only way I know of approaching that issue is to get some prevalence rates or seroconversion rates of some of the viruses that re not inactivated. I think there are some data, not presented today, on parvovirus B19 present in donor pools, and also perhaps hepatitis A virus. They would give you an idea of the differences that might occur in the different source of donors.

DR. MARTONE: Let me take up on something Joel brought up. I think part of my lingering concern about this is the confounding effect of the data that was presented. Here you have the whole blood donors, who are largely or almost 100% volunteer, with less frequent donations and you are trying to compare that to the paid apheresis donors, which give donations more frequently. I guess the ideal situation is to stratify the analysis and compare apples to apples and oranges to oranges. I don't think we have had that even for volunteer apheresis patients versus paid apheresis patients. Maybe we have had that analysis and I missed it.

DR. HARTIGAN: There aren't any.

DR. MARTONE: Well, that is the point. I mean, you have two different groups with different variables and you are trying to look at those two things and you can't do

that. You have to stratify that analysis.

DR. HARTIGAN: You can still look at the prevalence rates in the first-time donors in both donor pools. Even in the paid donors, the guys who only contribute one donation get thrown away. But in the whole blood donations those one-time people don't get thrown away. But if you look at the first donation and the prevalence rates of infections in those groups -- that is what we were looking at, those guys, the people who come in for paid donations, tend to have higher rates. But then if you look at the ones that come back for repeat donations, those rates have gone down. Now, some of those go down because they are discovered to be positive on their first donation so they are thrown away, but it is not clear that there is a real difference in the paid guys versus the unpaid guys among those who repeat or are qualified donors.

DR. MARTONE: I am still concerned, however. I think the appropriate analysis would be -- if the question is, is there a difference between paid and unpaid and you are looking at apheresis centers, then you compare paid and unpaid but you don't have any unpaid to look at. The same with the whole blood donation situation, if the comparison is paid versus unpaid then you need to stratify by that, but you can't do it because there are no paid whole blood donors. So, in essence, you are trying to use some

surrogates here which are confounded by number of donations, and I don't see how the question can be answered in that situation.

DR. KHABBAZ: The question is not whether there is a difference in paid and unpaid. The question as stated is, if there are differences in marker rates between paid and unpaid, is this important? I think the points that you and Dr. Hartigan made are that we have not heard comparable rates really. I mean, we have heard about the qualified donors and that is fine; that looks good. But we have not heard of the first-time donor. There are also the other markers. We have not heard comparable data to be able to answer. My own sense is that, yes, it is important, and I started by saying that one of the important reasons is the agents that we cannot inactivate and the ones that we don't know about, primarily.

DR. HOLLINGER: Yes, the other issue too which we haven't quite dealt with is that most of the things we have been discussing today have been with fractionated plasma or plasma that can be stored. Of course, the issue with platelets is even a little bit more. They have to be used quickly and they represent a little bit different facet. That goes along then with perhaps the very highly qualified individuals who are going to be chosen for that because, right now, the issue of whether those can be tested in time

for their usefulness. So, that is another issue.

The other thing I have heard from the committee, just listening here, is that there is confusion still about this inventory hold, and there seems to be some discomfort about qualified donors whose samples are drawn and then they don't show up for six months and the samples are used. That seems to be issue that needs to be dealt with somewhat, at least to find out how many of those turn out, by more sensitive techniques, to be positive.

Any other questions? Yes, please, Miss Knowles?

MS. KNOWLES: I still think we need to revisit the whole issue of looking at the donor deferral interview.

DR. HOLLINGER: About what?

MS. KNOWLES: The donor deferral interview and the questions. I think that is something that will help clarify some of these issues.

DR. HOLLINGER: Thank you.

DR. MITCHELL: I think that the steps that have been taken regarding the qualified donors -- I think that there are two ways that you can look at it. One is the donors and then you can look at the technology. I think that both of them have gone very far and are very good in protecting the blood supply.

However, I have some concerns about using technology and relying on technology for a number of

reasons. One of them is that when you add something to a product, then you may come up -- if you try to preserve or improve the blood supply by adding things that kill bacterial viruses, and so on, I think that there tend to be some side effects. First of all, it is not always foolproof and, second, there may be unintended side effects of adding things to the blood supply.

So, I think that even though we have gone very far in technology, we need to look at alternatives, other things that can be done rather than adding to the blood, such as the microfiltration and so on.

The other portion of protecting the blood supply is the donors. I think that the qualified donor system looks like it is very good, and I hope that it pans out to continue to be like that.

The issue of whether the donor is paid or unpaid I think is not as important as how the donors are selected and who the donors are who continue to give blood. I think it sounds to me like there might be ways of encouraging people who are qualified donors to continue to donate more often, and to help[protect the blood supply not only for things we know but things that we don't know about.

Something that I would like to see though at the next meeting is a head-to-head comparison between inventory hold and quarantine as far as effectiveness. The inventory

hold, from the data that was presented today, looks like it is relatively effective in protecting against a number of markers. But I would like to see a head-to-head comparison to the quarantine as proposed by the FDA.

DR. HOLLINGER: We have been dealing pretty much with question 1. Does anybody have any responses for the FDA regarding question 2, which has to do with comments on the scope and soundness of FDA's approach to assessing risk of paid versus unpaid donations regarding data collection and planned for analysis. Does anybody want to make any statements on that particular issue?

DR. HARTIGAN: Well, I am not sure what their plan for data collection or analysis is. It is hard to comment on it if it wasn't identified.

DR. RUTA: I think our plan for analysis right now is that -- well, first in terms of data collection. We have made a request of industry to present data, and you have seen a partial presentation today. There is still additional information that we are waiting for. Of course, some of the information we have only seen today also so we have to go back and look at it and see if we agree with the way it was analyzed.

I said that the FDA will try and work with the IND holders to see if we can look at the same questions in terms of what is happening with PCR in terms of the incidence and

in terms of lookback retrieval efficiency. I was struck by a comment that as the PCR positives are going up the antibodies are going down.

The plans for analysis are to some extent equations that we have shown you. As you have seen, there is some discussion within the community who normally looks at this in terms of how do you analyze the data. We are still going to have to try and figure out between what Dr. Satten presented and what the FDA statistician presented as to what we think is the proper approach in terms of modeling the data. Beyond that, we will also use the simpler equations to answer the simpler type of analyses.

DR. HOLLINGER: Thank you. Dr. Boyle?

DR. BOYLE: One specific issue on data collection, one of the biggest questions that is raised is about donors who don't come back. What is their risk factor? What is going on?

Is anybody currently or is anybody planning to go back to a sample of donors who don't come back and retest them to see what kind of risk is out there at some fixed interval, whether it is a month, 2 months or something else?

DR. RUTA: That is something we can consider. We haven't considered that right now and we will have to take that under advisement.

DR. HOLLINGER: Not seeing any further comments,

first of all, I want to thank everybody for their patience in staying here late tonight. We are going to reconvene at 8:00 in the morning. I would like to ask those who are going to present tomorrow afternoon -- we have a very full schedule -- please look at your slides and make your presentation succinct but keep the information that is important.

[Whereupon, at 6:00 p.m., the proceedings were recessed, to be resumed at 8:00 a.m., Friday, March 20, 1998.]

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