DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

61st MEETING

Thursday, December 10, 1998

8:05 a.m.

Double Tree Hotel
Ballrooms I and II
1750 Rockville Pike
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
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P A R T I C I P A N T S

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Linda A. Smallwood, Ph.D., Executive Secretary

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Paul R. McCurdy, M.D.

CONSULTANT

Mary E. Chamberland, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. SMALLWOOD: Good morning and welcome to the 61st meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. I apologize for the little lateness we are starting. There was an emergency here in the hotel, so we were a little late getting started but I hope that we can remain on target.

At this time, I would like to read the conflict of interest statement. This announcement is made a part of the record at this meeting of the Blood Products Advisory Committee on December 10 and 11, 1998.

Pursuant to the authority granted under the committee charter, the Director of the FDA Center for Biologics Evaluation and Research has appointed Dr. Paul McCurdy as a temporary voting member for all committee discussions. Based on the agenda made available and on relevant data reported by participating members and consultants, it has been determined that all financial interest in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the committee's discussions have been considered. No waivers under Section 208 were necessary.

In regards to FDA's invited guests, the agency has determined that the services of these guests are essential. There are reported interests which are being made public to

allow meeting participants to objectively evaluate any presentation and/or comments made by participants.

The interests are as follows: Dr. William Hoots receives consulting fees from regulated firms, including the Genetics Institute, Bayer, and Baxter. In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in the committee discussions. A copy of the appearance determination addressed in this announcement is available by written request under the Freedom of Information Act.

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

Are there any declarations to be made at this time? If there are none, I would like at this time to introduce to you the members of the Blood Products Advisory Committee. As I call your name, would you please raise your hand. Dr. Blaine Hollinger, Chairman. Dr. Marion Koerper. Dr. Norig Ellison. Dr. David Stroncek. Dr. Paul McCurdy.

Ms. Katherine Knowles. Dr. Donald Buchholz. Dr. Kwaku Ohene-Frempong. Dr. Richard Kagan. Dr. Joel Verter. Dr. John Boyle. Dr. Jeanne Linden.

We have some members of our committee that are absent today: Dr. Rima Khabbaz. And Dr. Mary Chamberland is sitting as a representative from CDC. Dr. Chamberland, would you raise your hand, please? Dr. Chamberland is sitting as a special consultant to the committee. She will participate in the discussion, but she will not be voting.

We also have absent today Dr. Corey Dubin.

Tomorrow, we will have as guests of the committee Dr. William Hoots, Dr. Craig Kessler, and Dr. Margaret Rick.

I would also just like to announce that the committee members have been given a list of tentative dates for the Blood Product Advisory Committee meetings in 1999. Those dates are March 25 and 26, June 17 and 18, September 16 and 17, December 9 and 10. Again, these are tentative dates, and you may check through the usual manner to determine if these dates have been confirmed.

At this time, I would like to turn over the proceedings of the meeting to the Chairman, Dr. Blaine Hollinger. Thank you.

DR. HOLLINGER: Thank you, Dr. Smallwood. Welcome, everyone. This is probably the best time to have a meeting of this committee when all the media and everything

is down on the Hill. So we should bring up very controversial issues today.

[Laughter.]

DR. HOLLINGER: We do have several topics today. We're going to start out with some committee updates. This will be followed by some workshop summaries, two workshops particularly which have a great deal of interest to all of us, the Donor Suitability Workshop and the Blood Licensing Workshop. And then we're going to go back to something we've talked about before about a year ago and revisit the hepatitis B anti-core re-entry with perhaps an algorithm to look at, and finally, today there will be some discussion on end-user notification initiatives for plasma derivatives. So that will take place today. There will be a couple of issues for the committee in regards to the discussion and recommendations. Other parts of it are just for information only.

So we'll start out then with the committee updates, and Dr. Mied will give us an update on HCV Lookback Guidance from, I presume, the meeting they just had recently. Is that right, Paul?

DR. MIED: That's correct. Thank you, Dr. Hollinger.

[Slide.]

This morning I will provide the committee with an

update on HCV lookback. Specifically, I'll describe the FDA revised guidance for industry document and review the recommended time frames for implementation of HCV lookback by the industry. Then I'll summarize the actions of DHHS and the blood industry to implement HCV lookback and the current status of the lookback effort, and conclude by giving you an overview of the resolutions on HCV lookback approved by the Advisory Committee on Blood Safety and Availability just two weeks ago.

[Slide.]

On September 23, 1998, FDA issued a revised guidance for industry document on HCV lookback. The FDA recommendations contained in this revised guidance document are provided to enable quarantine and disposition of units from prior collections from donors with repeatedly reactive screening tests for anti-HCV. Additionally, FDA recommends that consignees of certain blood and blood component units collected since January 1, 1988, which were anti-HCV negative or untested be notified when donors subsequently test repeatedly reactive for anti-HCV in a licensed multi-antigen screening test and reactive in a licensed or investigational supplemental test. This notification would enable recipients to be informed that they had been transfused with units that may have contained HCV so that they may obtain further medical counseling.

This document was provided on the CBER home page for comment and for implementation on September 23rd and published in the Federal Register with a notice of availability on October 21st. Additionally, the guidance document was mailed to all blood establishments on November 20, 1998.

Now, since the comment period never really closes on guidance documents, comments on the revised guidance will be evaluated by FDA as they are received and changes made as warranted.

[Slide.]

The September 2erd revised guidance document replaced the March 20, 1998, guidance for industry which had undergone major revision by FDA in response to comments received from the industry and the public following its issuance in March. As a result of these significant changes in the guidance, FDA made known its intention to reissue comprehensive guidance on HCV lookback at a public meeting of the Blood Products Advisory Committee in June 1998. The March 20th guidance was withdrawn on September 8th by a notice on the CBER Website, and the revised guidance was issued on September 23rd.

FDA withdrew the March 20th guidance so that blood establishments would not be compelled to implement the previous outdated guidance which recommended that

notification of consignees start by September 20, 1998. The blood industry was aware that this action did not signal discontinuation of the lookback initiative.

[Slide.]

In accordance with good guidance practices, FDA incorporated into the revised guidance the previous recommendations on product retrieval from the July 1996 memo to blood establishments. Thus, the revised guidance document supersedes that memo. This major revision brought the agency's recommendations regarding the two parts of lookback--product retrieval and recipient notification--into one comprehensive guidance document.

[Slide.]

With respect to implementation of HCV lookback by industry, the time frames for the retrospective lookback in the revised guidance issued on September 23, 1998, are as follows:

Blood establishments should begin notification of consignees as soon as feasible and within six months of the date of issuance of the revised guidance--that is, by March 23, 1999.

Blood establishments should complete all notifications of consignees within 18 months of the date of issuance of the revised guidance--that is, by March 23, 2000.

[Slide.]

A transfusion service should begin notification of the recipient when notified by the blood establishment and should complete all notifications of recipients within one year following receipt of notification from the blood establishment--that is, by March 23, 2001, for the last of the notifications received.

[Slide.]

Now, FDA's role in the implementation of HCV lookback has encompassed the development of the initial guidance document in March, the revised guidance document in September, and also rulemaking on HCV lookback. And FDA's involvement in HCV lookback implementation will continue. Now that the revised guidance has been published, we will continue to establish policy through guidance by responding to comments on the revised guidance document and conducting inspectional surveillance of lookback activities. We will also assist other DHHS components in evaluating the effectiveness of the public outreach and targeted lookback programs. FDA is also committed to establishing requirements for HCV lookback through the rulemaking process. A draft proposed rule is awaiting DHHS and OMB clearance. FDA will publish the proposed rule, respond to public comments, issue a final rule, and conduct oversight of implementation of HCV lookback procedures by the

industry.

[Slide.]

CDC's role in implementing HCV lookback includes the publication of a morbidity and mortality weekly report, recommendations for prevention and control of HCV infection and HCV-related chronic disease, which contains guidelines on counseling and treatment. This MMWR was issued on October 16, 1998. CDC has developed and mailed educational materials to physicians as part of a general notification program directed at providers. Similarly, they have developed public education messages regarding the risks associated with transfusion prior to July 1992. And CDC is developing strategies to evaluate the success of the various public outreach and targeted lookback efforts.

Now, the current policy for identification transfusion recipients at risk for HCV infection includes direct notification of recipients of blood from donors who had subsequently tested repeatedly reactive on a multiantigen screening test, that is, the EIA 2.0 or 3.0, with a reactive supplemental test result, as I mentioned, and also general notification of all persons transfused before July 1992.

[Slide.]

I'm now going to summarize the current status of HCV lookback driven by EIA 2.0 and 3.0--that is, what people

are currently doing.

Blood establishments have implemented targeted HCV lookback programs prospectively, or based on current donor testing, and retrospectively, or based on review of records of historical donations tested using EIA 2.0 or 3.0. They have established written SOPs for lookback based on current and historical donations. They have been identifying prior collections from donors who were reactive on multiantigen screening and supplemental tests and have been performing additional tests on stored samples or, in some cases, on fresh donor samples. Now that the MMWR has been issued, some of the larger and independent blood banks are beginning to notify consignees.

The American Red Cross is also preparing to begin notifying consignees. I should point out that some smaller blood banks actually had started to notify consignees before the MMWR was issued. Some blood establishments are doing the lookback and the notifications in stages, first the RIBA 2 positives, then the RIBA 2 indeterminates, with additional testing as needed. There currently are evaluations underway to determine the utility of going back to first-generation EIA or EIA 1.0--that is, prior to the availability of the multiantigen screening test--in the targeted lookback effort.

The military and some private sector blood banks

have indicated they are considering doing lookback on EIA 1.0 repeatedly reactive donors. Some blood banks have initiated lookback based on EIA 1.0.

Now, while there are no outcome data available yet for many of these efforts, I'm going to summarize the limited information we've been able to obtain regarding the current status of lookback based on EIA 1.0. The military's experience is that many of their donors are first-time donors with no prior donations to go back and look for, so the number of lookbacks they have to do is considerably lower compared to the civilian population. They are doing lookback based on unconfirmed 1.0 repeat reactives. They have no supplemental test results and no frozen samples dating back to 1.0 screening, and it's difficult for them to call donors back in for additional testing. Most of their facilities have begun the retrospective review of records.

The American Red Cross presently intends to do lookback for EIA 1.0 repeat reactives, but only for those with reactive supplemental test results, which at that time was the investigational RIBA 2. Their projections are that because of extending the lookback to first-generation EIA, the number of repeat donors and components to look back on and the number of recipients to be traced and notified will increase by about one-third.

A major blood center in the Southwest is doing

lookback not only for all EIA 1.0 repeat reactives that are RIBA positive and indeterminate, but also for all unconfirmed EIA 1.0 repeat reactives, which actually make up the majority of their repeat reactives. Since they no longer have stored samples for additional testing, they are attempting to recall donors by letter for retesting. Overall, their lookback volume has increased 60 percent, from 12,000 repeat reactives to 19,000 repeat reactives, by extending the scope of their lookback to include EIA 1.0.

Another major blood center in the Midwest has stored samples for their EIA 1.0 repeat reactives, and they are preparing to do consignee notifications based on additional testing using EIA 2.0 and RIBA 2 on those stored samples. Extending the lookback to first-generation EIA has nearly doubled the volume of their lookback effort. So you can see that lookback based on EIA 1.0 is being approached in a variety of different ways.

The Advisory Committee on Blood Safety and Availability met in Washington, D.C., on November 24, 1998, in response to the Seventh Report of the House Committee on Government Reform and Oversight. The Advisory Committee discussed progress in the implementation of HCV lookback and the possibility of extending the targeted lookback program to include recipients of blood from donors subsequently identified as repeatedly reactive by the single-antigen-or

EIA 1.0--screening test for anti-HCV that was licensed in 1990.

[Slide.]

On November 24th, the Advisory Committee approved the following resolutions:

One, the Secretary of Health and Human Services should recommend legislation that would lower barriers to the use of federal databases for locating individuals at risk of hepatitis C infection.

[Slide.]

Two, the Department of Health and Human Services should allocate sufficient additional resources to permit the Centers for Disease Control and Prevention to work with state and local health departments to facilitate education, testing, and referral programs for individuals at risk of hepatitis C infection.

[Slide.]

Three, the Department of Health and Human Services should investigate supplemental sources of financial support to facilitate prompt completion of targeted lookback for individuals at risk of transfusion-transmitted hepatitis C infection.

[Slide.]

Four, the Health Care Financing Administration should remove financial barriers to testing of individuals

identified by current government standards as being at risk of hepatitis C infection.

[Slide.]

Five, the Secretary of Health and Human Services should take all necessary steps to ensure completion of current lookback programs within the currently recommended time frames.

[Slide.]

Six, the Advisory Committee on Blood Safety and Availability supports Recommendations 1A and 3 of the Seventh Report of the House Committee on Government Reform and Oversight. Recommendation 1A states that, "The Secretary of Health and Human Services should take the lead in coordinating the federal public health response to the hepatitis C epidemic, including implementation of a research plan." Recommendation 3 states that, "Federal educational campaigns on HCV infection should be launched immediately."

[Slide.]

Seven, the current targeted lookback program should be expanded to include recipients of blood from donors subsequently identified as repeat reactive by the single-antigen (EIA 1) screening test for hepatitis C infection that was licensed in 1990.

[Slide.]

Eight, implementation of the prior motion

regarding expanding the targeted lookback program to EIA 1.0 should be deferred until the Public Health Service has had an opportunity to review it and to present options for its implementation and evaluation to the Advisory Committee at its next meeting.

[Slide.]

Now, when the Advisory Committee on Blood Safety and Availability meets in January, they will examine options for extending the targeted lookback. Some of these options are to perform lookback based on EIA 1.0 repeat reactive RIBA 2 reactives--that is, positives only or positives and indeterminates, at the committee's discretion. As an alternative, to look back based on unconfirmed EIA 1.0 repeat reactives without a supplemental test result.

Should there be lookback for unconfirmed EIA 1.0 repeat reactives? If the answer is yes, it might be reasonable to consider limiting the lookback based on the signal-to-cutoff ratio in cases where supplemental testing has not been doing--in other words, perform lookback on a subset of the EIA 1.0 repeat reactives to capture the vast majority of the true positives and minimize the unnecessary false recipient notifications. And, of course, instead of donor-triggered notification, there is always the option of proceeding with direct notification of all identifiable recipients of blood transfusions prior to 1992.

So these are just a few of the options for extending the scope of the lookback for HCV to EIA 1.0, and the complete discussion of the pros and cons of these and other options will occur at the January meeting of the Advisory Committee on Blood Safety and Availability.

Thank you.

DR. HOLLINGER: Thank you, Paul, for that very complete update on the lookback issue.

Are there any specific questions? I know we can go through the whole thing, but I think maybe I'll just see if there are any specific questions. Yes, John?

DR. BOYLE: Just one question. Can you give us some sense of how many cases of transfusion-transmitted HCV we've had in the past year reported? In other words, what's the magnitude of the problem?

DR. MIED: No, I don't have a feel for the magnitude of the problem. I'm sorry. I don't have that as numbers.

DR. HOLLINGER: My understanding is that the CDC has had no cases of transfusion-transmitted HCV reported since 1995.

DR. BOYLE: In other words, no cases have presented since that time?

DR. HOLLINGER: Well, you're talking about since that period of time and looking at it, people who have

received transfusions since 1995.

DR. BOYLE: Right. But the question is, presumably it goes back, you could have a case presenting this year that had received the transfusion at a prior time. Is that correct?

DR. HOLLINGER: Oh, that's a different issue.

DR. BOYLE: Yes. I was just trying to see how many individuals are at risk showing, presenting now, next year, and the following year. Is there a reporting system in place that identifies cases, in this case, HCV, that are presumed to be transfusion-transmitted?

DR. MIED: Yes, there's a reporting system in place. As to what the numbers would be that come into that reporting system, I really--I don't have a feel for it.

DR. BOYLE: Okay. Thank you.

DR. HOLLINGER: Just anecdotally, from just seeing patients who are coming in to us to talk about their disease, you see a lot of patients who have had blood transfusions in the '60s, '70s, and sometimes in the '80s. But I must tell you, it's a rare person that I've been seeing who has received a transfusion from '88--I think this was said in '88, since--from '88 onward. For some reason or another, I just--I mean, I'm sure it occurs, but--it clearly has occurred. I've had some. But most of them have been much further back. It may just be because they're being

identified now as they're older, and the younger ones are other things that have just not been identified.

Yes, Ken?

DR. NELSON: There's a comment you made based on the Sentinel County surveillance because--I mean, not all cases are reported. Is that what that's based on?

DR. HOLLINGER: Just from what I understand from the CDC. Mary, maybe you can tell me. You should know.

DR. CHAMBERLAND: Sorry, I missed the beginning of the question. CDC has in place a couple systems of surveillance for cases of hepatitis; however, the rarity of transfusion-transmitted hepatitis C over the last several years has made it very difficult for CDC surveillance systems to have adequate sensitivity to detect these kinds of cases, and there have not been cases detected for the last several years, as best I know.

DR. HOLLINGER: Yes, Paul? Dr. McCurdy?

DR. McCURDY: I unfortunately missed one of the earlier comments, too, and it may be redundant. But our NHLBI REDS study came out with a figure based on seroconversions of around 1 in 100,000, and with 12 million transfusions a year of red-cell products, that's about 120 cases that one would expect. There are a few more from perhaps platelet transfusions or something in that neighborhood. But it's probably not much--I mean, it may be

more, may be less, depending on the window period cases. But that's a rough estimate.

DR. HOLLINGER: Yes, we hear that number all the time, but I got to tell you, Paul, where are the cases? You know, I hear that number, and 120, somebody ought to have a case out there to see that, and it's just not been reported. It's very confusing to me. It could be--

DR. McCURDY: That's accurate.

DR. HOLLINGER: Yeah, yeah. Yes, please, Dave?

DR. STRONCEK: I'd like to say for the transfusion services and the blood banks, the issue on the EIA 1.0 is a very difficult one. I'm very supportive of the efforts of the Blood Safety and Availability Committee to tackle that, and it sounds like they're head in the appropriate direction. Does this committee need to make a resolution to support them or anything in any way? There seems to be overlap between the responsibilities of the two committees.

DR. HOLLINGER: What would you suggest?

DR. STRONCEK: Well, I guess it would be prudent for us to wait to see what their outcome is, and then I imagine--I think they're headed in the right direction. I think I'm very supportive of the efforts to look back on people that have EIA positive assays and that have not been confirmed.

DR. HOLLINGER: I think I would be, too. I like

the idea of just on the 1's, anyway, of using the supplemental test if they have it, or if they have samples, go back. I would support also sticking with the cutoff ratios of 3.5 or so, to look at those. I'm not sure I'd support the unconfirmed ones at this point just because of the massiveness of it and the large number of false positives in that population.

Who's paying for all this, the lookback, by the way, Paul?

[Laughter.]

DR. HOLLINGER: Because it must be very expensive. Do we know, do we have any idea what kind of records are available for finding these patients? What was required, what were the regulations that were required of blood banks or transfusion services for having records of who received blood transfusions and so on? And are these records on computers, or are they just in paper files somewhere, archived off in storage centers or what?

DR. MIED: From what I hear, Dr. Hollinger, the answer is yes. They're in all forms, and it's just very difficult to search through. You're talking about records from the blood transfusion--

DR. HOLLINGER: Yes. I mean, that's a very mammoth--and right now the blood banks are primarily paying for this; is that correct? The blood services?

DR. MIED: No, I'm not really sure who's paying for it at that level. I am getting a feel for the massiveness of the job that the blood establishments have before them. We're talking, for a large blood center, thousands of letters going out and thousands of records for repeat reactives being searched. It's an enormous undertaking.

DR. HOLLINGER: It must be, yes.

Dave, yes, please?

DR. STRONCEK: Well, I'm a little concerned, though, about the non-uniformity right now of the response of the blood industry to the EIA 1. It seems like many blood centers are doing--taking a different course, and I don't think that looks good for anybody. And I don't think the public would understand it. I would prefer that the blood industry take the correct path and not necessarily the cheap path. And if it's appropriate to go back--it might be expensive, but if it's appropriate for them to go back and look at all EIA 1 positives, even if they're not tested in a confirmation assay, then I think that's what should be done.

DR. HOLLINGER: Thank you, Dave. Okay. I think we'll go on. Thank you.

The next committee update is on malaria deferral. Dr. Heintzelman?

Dr. HEINTZELMAN: Good morning.

[Slide.]

I'm going to review our current draft document for updating the malaria guidance that we have. Guidance for industry, recommendations for donor questioning regarding possible exposure to malaria.

[Slide.]

Specific recommendations. FDA's current thinking regarding recommendations for deferring blood donors at increased risk for malaria are as follows:

[Slide.]

Many of you will recognize this as a compilation of prior guidance rolled into a modernization. One, permanent residents of nonendemic countries who travel to an area considered endemic for malaria by the Malaria Epidemiology Section, CDC, U.S. Department of Health and Human Services, should not be accepted as donors of whole blood and blood components prior to one year after departure from the endemic area. After one year has passed since departure from the malarious area, such otherwise suitable prospective donors may be accepted provided that they have been free of unexplained symptoms suggestive of malaria and regardless of whether or not they have received antimalarial chemoprophylaxis.

[Slide.]

Two, prospective donors who have had malaria

should be deferred for three years after becoming asymptomatic.

Three, immigrants, refugees, citizens, or residents of endemic countries should not be accepted as donors of whole blood or blood components prior to three years after departure from the area. After the three-year period, otherwise suitable prospective donors may be accepted if they have remained free of unexplained symptoms suggestive of malaria.

[Slide.]

Four, persons who may possess partial acquired immunity to malaria, such as those that have resided in a malarious region--immigrants, refugees, citizens, or residents of endemic countries--should not be accepted as donors of whole blood or blood components for a period of three years since their last visit to a malarious area.

[Slide.]

Five, we are considering an additional question: In the past three years, have you been outside the United States or Canada? Many blood banks already ask this.

If the answer is affirmative, follow-up questions such as this second-tier level: In the past year, have you visited any rural areas in Mexico, including resorts located in rural areas?

If a prospective donor gives an affirmative answer

to this question and if the rural area is located in a Mexican state considered at risk for malaria by the CDC, then the donor should be deferred for one year from the date of departure from the area.

[Slide.]

Finally, these recommendations, if accepted, would apply to donations of whole blood and blood components.

We have a couple of additional topics or areas that we're considering under discussion. I should advise you that we have been in discussions with representatives from the Centers for Disease Control to develop this proposal, and they have had some valuable input into this. One of the items, the additional items, is to define the use of the term "resident" to mean a person that has resided in an area for longer than one year. And, secondly, to review concerns about dusk-to-dawn activities and the risk of acquiring malaria in malarious areas during those times.

That's a summarization of where we are currently with this document.

DR. HOLLINGER: Thank you.

Any questions from the committee? Yes?

DR. ELLISON: I didn't understand your last comment about dusk-to-dawn activities.

DR. HEINTZELMAN: There's concern that the Anopheles mosquito activity is peak in low-light hours. I

think that's pretty well recognized. And there are certain times when people may have gone into a malarious area when they're at--say during peak sunlight hours such that there would be little, if any, risk of a mosquito biting them and transmitting the disease. And, currently, there is guidance out there that's been discussed that suggests if you were even to enter a malarious area at a time other than from dusk to dawn, that such was at very low risk for acquiring malaria.

That's the rationale for it. The difficulty is, as you undoubtedly have recognized, quantifying when dusk and when dawn occur. It's intriguing to even ask when was sunrise today here in our own area and to hear a variety of answers that come out because it is clearly on the basis of the person that's involved in these activities would be rather opinionated. And so that is a difficult area.

Mary Chamberland has been a part of our discussions and may be able to further that.

DR. CHAMBERLAND: Essentially what we're trying to strive for here is to have the guidance to blood collection agencies be in line with the guidance that CDC gives out to travelers vis-a-vis the need for malaria prophylaxis. When travelers are going to malarious areas or questionable areas and contact CDC or consult the Yellow Book about whether or not they need to take prophylaxis, some of this hinges on

whether or not they will be engaged in being outdoors in daytime versus evening or nighttime because, as was stated, mosquito activity really does not occur until evening hours.

So what we'd like to do, there should be some consistency between deferral and prophylactic recommendations, and we're going to have to work on trying to bring those in line. I agree it can be a little complicated.

DR. MITCHELL: Yes, I agree that that is very complicated, and I think that, again, we're at the point where we're not going to be getting a large number of people who are going to say, well, you know, I was there during the daytime but I left at 7 o'clock at night and it started getting dark. I don't expect we're going to get a lot of people like that. From my perspective, we should err on the side of caution and take that out altogether, and consider that anybody who has been in a malarious area is at risk.

The other question that I had was about the residents who had been away from a malarious area from three years and then went back to visit, you know, one year later, then they're deferred for another three years. Is that the way that--

DR. HEINTZELMAN: I believe that's the way it's stated in number four.

DR. MITCHELL: Okay. And why would that be? That

seems to be--

DR. HEINTZELMAN: Well, the issue of concern is that they may have, as a result of their residence in an endemic area, may have developed a level of immunity to the organisms, and when they have left and then returned, they may be recently infected and have a level of parasitemia in their blood that hasn't yet suppressed, though they may possibly be asymptomatic. That's the rationale for it.

DR. MITCHELL: So you're considering that a resident would be assumed to have some level immunity. Is that--

DR. HEINTZELMAN: Well, we do identify that now as someone in our--in number three, a person that is at risk, yes.

DR. MITCHELL: Thank you.

DR. HOLLINGER: Ken?

DR. NELSON: As one who for the last 25 years has not been able to donate blood because I've gone to Thailand several times and yet have never taken malaria prophylaxis because the area in Thailand that I visit in the Central Valley there's no malaria. And I notice that you break it down fairly completely for Mexico, but not for--because Mexico is commonly visited, et cetera, but not for other countries. And I'd like to get a sense of as the guidelines for blood donation are in place now, how is it working both

in terms of the blood supply and the transfusion-transmitted malaria? Because I can see that one could make the guidelines much more accurate, precise, realistic, and increase the number of donors, and I guess with international travel increasing at a very dramatic rate over the next decade, we may find that nobody in this room could be a blood donor by having, you know, visited a country where there was endemic malaria. But in many countries, particularly in Asia, malaria endemicity is focal. It's not in the big cities; it's not year-round, et cetera. And there are many, many visitors who are essentially at no risk of malaria.

I just don't have a real feel for how the current guidelines are working in terms of the blood supply and the risk to recipients.

DR. HEINTZELMAN: Well, I think one of your questions was what's the rate of malaria associated with blood transfusion, and the last number that I saw was that that was about 1 in 4 million donations, approximately.

DR. NELSON: So about three per year, is what you're saying?

DR. HEINTZELMAN: Roughly.

DR. CHAMBERLAND: Yes, folks at the malaria branch have been reviewing reported cases of transfusion-induced malaria for the last 30 years or so, and on average, there

are one to two cases of transfusion-induced malaria reported each year. There have been ten in the period 1990 to 1998.

DR. NELSON: And were those cases people who met these guidelines or people who the guidelines should have but didn't prevent from donation? Is that known?

DR. HEINTZELMAN: Both. I believe that the investigations were conducted in those cases, and in some of the situations, the guidelines, if they had been--if the individual that donated blood had abided by the guidelines as presented to them, they would have been prevented from donating. So that's true, and that's a problem that we face in all of our areas.

DR. NELSON: What about the other side of the equation? How many donors who walk in the door--you may not have those figures, but maybe somebody who is running a blood bank in the audience could give us that. I could see, you know, that depending on the population you looked at, that could be a real problem.

DR. HEINTZELMAN: We recognize that. We've heard that from many of the representatives from blood banks. And part of--it may not have been obvious as I went through it, but part of the fifth question, the second tier, addresses rural areas in Mexico. And what we begin to identify is that--you know, as you said, there is a tremendous focal nature to malaria and a variety of areas that we might

consider to be endemic, and that being the case, we were trying to begin to tease out the separation from urbanized and rural areas where there was such risk. Some of these resorts are clearly very urbanized that are in Mexico. There's a large number of travelers in the United States that go to Mexico for a variety of reasons, and by separating rural resorts from urbanized ones in these areas, we are beginning to identify the focal nature of malarial transmission.

DR. NELSON: In Thailand, there are areas of mountainous areas rather than--I mean--

DR. HEINTZELMAN: There will be easy areas to start and much more difficult areas to go to, I'm sure.

DR. OHENE-FREMPONG: There were several references to symptoms suggestive of malaria, and if I remember correctly, some of them would be going back over like a three-year period. Would you give some examples of how somebody will be questioned as to whether they've had symptoms suggestive of malaria? It seems to me that it's so vague that most people would have had some febrileness within a three-year period?

DR. HEINTZELMAN: Yes, that's true, and if that febrile illness was associated with travel to an area where malaria was endemic, then it may be a step on the conservative side to defer them. But that is the intent of

it.

The symptoms themselves are generally fairly well recognized by people that live in these areas because it's such a common disease.

DR. HOLLINGER: What's the incubation period for malaria?

DR. HEINTZELMAN: Generally, less than three years. One year--

DR. HOLLINGER: But I mean--

DR. HEINTZELMAN: From time of bite?

DR. HOLLINGER: Somebody who's, yes, infected and then developing of symptoms, what's the range?

DR. HEINTZELMAN: Earliest is within a couple of weeks that I'm aware of. I'm not aware of the outside.

DR. HOLLINGER: Okay.

DR. NELSON: You can get recrudescent malaria for years.

DR. HEINTZELMAN: Right.

DR. NELSON: The incubation period is a bit irrelevant.

DR. HEINTZELMAN: We've reviewed the time periods suggested in the document and believe that three years will cover the vast majority of cases with the exception of malariae, which we don't believe we can develop guidances. We would defer everyone forever if we tried to do that.

DR. HOLLINGER: Jeanne, last question.

DR. LINDEN: Two fairly quick questions. One, I'm not sure that the number of people who would be present only during the daytime hours is that small. It's my understanding there's a fair number of cruise ships that drop people at a port during the day and then they're back on the ship by afternoon. Are there any data available on the numbers of people that we're talking about that might fit into that category?

And my second question is: Is there a timetable under which those last couple of questions are going to be considered in some sort of definitive recommendation arrived at?

DR. HEINTZELMAN: We don't--well, let me answer your second question first. We don't have a definitive timetable. We're working on this currently. Part of the problem is, just as you suggested, it's very difficult to develop numbers for whether your cruise ship dropped you off, you went on an excursion and came back. If that port was in a malarial endemic area, it may or may not have been well urbanized, and that can further confound the issue.

There are other examples of daytime activities that are at high risk such as boat cruises, river cruises down a rich area for malarial breeding, Anopheles breeding, and, therefore, prevents--you know, a very worst-case

scenario. And so even if you're out during the brightest parts of the day, the sheer nature of the area that's being visited may increase the risk significantly for any marginal activity on the part of the mosquito.

Does that answer your question?

DR. LINDEN: Yes. Thank you.

DR. HOLLINGER: We'll go on then. Thank you very much.

We have next an update on the analyte specific reagents, a final rule, and if you could summarize this, you get a great deal of gold stars.

DR. WILSON: I hope I live up to that. Can I have the first overhead? And maybe you could keep the lights up.

[Slide.]

Actually, what I'm going to be presenting is an update, and, of course, I will not be able to distill all the elements of the rule, so this is not going to be all-encompassing. I'm going to try to target it to issues that have recently emerged relative to HIV, HCV, and reimbursement.

An ASR--an analyte specific reagent--is kind of the active ingredient of an assay, for example, an antibody, an antigen, or a nucleic acid probe. The ASR would be purchased by a clinical lab to develop an in-house, or commonly referred to as "home brew," assay.

A CDRH Advisory Committee was conducted in January of 1996 where this rule was openly discussed. The rule was proposed formally, published in March of 1996, and then a final rule was published in November of 1997, and there was an implementation time one year from the date of that final rule. So several weeks ago, the rule became effective.

[Slide.]

To follow Dr. Hollinger's lead here, this is the final rule. It's available on the CDRH Website. The actual regulation is approximately one page of text, but there's 33 pages, including the summary details and questions and answers, preamble-type information. That's why I'm not going to try to capture all the nuances of it in this update.

[Slide.]

Now, here's the condensed version. An ASR is a medical device. It's classified under 21 CFR 864, and as a medical device, the ASR needs to be registered--the facility needs to register, it needs to list. In other words, the manufacturer of the ASR needs to register, list, and follow quality system regulations, formerly known as GMPs.

Now, some ASRs require PMAs prior to being able to put them in commercial distribution, so that the ASR manufacturer would file the PMA. That means the manufacturer of the antibody or the nucleic acid, et cetera.

And the PMA would contain not only the characterization, the physiochemical characterization of the particular ASR, but also it would include its use in an assay. So the manufacturer of the ASR would need to show by integrating it into an assay and providing performance characteristics, sensitivity and specificity, that this ASR is capable of, in fact, producing an answer that is reliable for medical diagnosis, et cetera.

The clinical laboratories would then purchase this ASR for "home brew" assays. They would develop their own assay, and they, the clinical labs, would not be filing the PMA.

[Slide.]

Now, the ASR regulation, as stated under 864.4020(b), Class III, or PMAs, are required when the analyte is intended as a component in a test intended for use in the diagnosis of a contagious condition that is highly likely to result in a fatal outcome and prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition. And the rule specifically uses as an example human immunodeficiency virus or tuberculosis.

[Slide.]

How are these tests regulated or how are these ASRs regulated within FDA? All tests used for donor blood

screening are regulated by the Center for Biologics, and the center employs the Public Health Service Act as well as the Food, Drug and Cosmetic Act, as appropriate.

Tests used for diagnosis and monitoring of retroviral infections are regulated by CBER under the Food, Drug and Cosmetic Act, and the reason why CBER regulates these products is that in the inter-center agreement of 1991, it was determined that CBER would have jurisdiction over these products. The important point is that the ASR rule applies to medical devices, and it's just which center exercises the regulatory authority over them. But the ASR rule applies to the medical devices, regardless of which center.

Finally, tests used for diagnosis and monitoring of hepatitis infections--that is, not for blood donor qualification--are regulated by CDRH under the Food, Drug and Cosmetic Act.

[Slide.]

Now, HIV ASRs that are diagnostic in commercial distribution require a premarket approval based on the ASR regulation. And this intended use would also include detection and monitoring for genomic variants or quantitative viral loads for therapeutic management purposes.

[Slide.]

Now, as with all sponsors of all the tests that the Center for Biologics--and I'm sure our sister agency, CDRH, also does--we meet with sponsors, and we would propose to meet with ASR manufacturers if they elect to request a meeting, and we would give them detailed advice on filing of the PMA as well as what it would take in terms of the approval process.

[Slide.]

Now, HCV ASRs are regulated jurisdiction-wise through the Center for Devices and Radiologic Health, and currently, CDRH is not calling for PMAs on the HCV ASRs. It's important to note that as public health considerations and concerns are never constant--they're always changing--PMAs may be required in the future if public health considerations warrant.

Again, despite the fact that the PMA is not filed, manufacturers of ASRs are medical device manufacturers. They must register, list, and follow the quality system regulations. In-house tests which are manufactured from such ASRs must meet the CLIA standards, and disclaimers must accompany the test results. The disclaimer is basically the following: In the regulation on that last page of the Web page site, it describes how when a test result is generated in a clinical laboratory from an ASR-derived "home brew," the results need to have accompany--the report needs to

state that this test in so many words has not been approved or cleared by the Food and Drug Administration. So there's notification to the ordering physician that this test has not been cleared by the FDA.

I'd like to make some just very quick closing remarks. We do have written permission from one test kit manufacturer that enables us to state that this manufacturer is in the process of filing a PMA for a complete kit, HCV PCR viral load. So that is in the process of being filed.

In regard to HCFA reimbursement, FDA provides the regulatory status and other relevant information to HCFA upon their request and when we have information that the firm will allow us to disclose. HCFA then evaluates the usefulness of that test as it would normally evaluate the use of any test, and in closing, HCFA makes the decision as to whether reimbursement is to be granted, not FDA.

Thank you.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: Thank you. For the purpose of completeness, Len, if I could mention that there is a second condition in the regulation that establishes a PMA requirement for the ASR, and that is the condition where the analyte is intended as a component in a test intended for use in donor screening for conditions for which FDA has recommended or required testing in order to safeguard the

blood supply or establish the safe use of blood and blood products, for example, tests for hepatitis or tests for identifying blood groups. I state that simply for completeness.

DR. HOLLINGER: And that would take a stronger regulation?

DR. EPSTEIN: Yes. The PMA is a premarket approval application.

DR. HOLLINGER: Dr. Stroncek?

DR. STRONCEK: So that would mean tests for genomic amplification testing for HIV and HCV, they're regulated the same way? The presentation suggested that hepatitis tests are regulated slightly differently than HIV tests. But for the purposes of testing blood products, they're regulated in the same way?

DR. EPSTEIN: Yes. If the analyte specific reagent were a component in a donor screening test or a test otherwise related to blood safety, then it would be captured under the PMA provision the same as for HIV.

DR. HOLLINGER: First of all, I think just as a good rule, as you know, I feel there are a lot of good in-house "home brews" out there that are probably equally or better than some of the kits which are present. And many of them are laboratory--many of them are based on the laboratory more than the kit, particularly for PCR testing.

So I think this is a good opportunity for these tests to still be used.

I would have preferred that probably, instead of the disclaimer--I think the disclaimer is appropriate, but it would have been nice if it would have also said something to the effect that--the disclaimer that is supposed to be used by in-house testing was that this test was developed and its performance characteristics determined by--and then the laboratory name used, and then it says, It has not been cleared or approved by the U.S. Food and Drug Administration. It would have been nice if it also said, Nor has it been disapproved, as well, and something else to the effect that, however, the test must meet CLIA standards.

That would have been an additional factor that I think would be useful because it always gives the connotation that if it's not approved, it may not be very good.

The other thing, too, is I notice in this CFR, this 21 CFR that you put up here, Leonard, it just says that for a Class III, a premarket approval, it says when the analyte is intended as a component in a test intended for use in the diagnosis of a contagious condition; it says nothing about management or therapeutic management. Yet a couple slides later, it says that the premarket approval must be done for quantitating viral load for therapeutic

management purposes. There's some difficulties there, I think, with the CFR and what you intend perhaps to use it for. That may need to be changed some way or other, possibly.

Yes?

DR. BUCHHOLZ: I wonder if you could amplify a little on the rationale behind the original manufacturer of the reagent, the analyte specific reagent, being required to file a PMA, and yet the users of that agent in a test not have to file a PMA. And my question really is: Why would you put a burden on the manufacturer of the reagent that is different than what, in essence, is the real utilization of the test in terms of it being a very critical test that would put it into Class III device category?

DR. WILSON: I think I can give you a short answer. The ASR is what travels interstate. It's in interstate commerce, so the FDA has jurisdiction the way the regulations are written relative to interstate commerce.

One of the concerns that was raised that prompted this was the quality of "home brew" tests, notwithstanding what Dr. Hollinger stated, that there are--FDA clearly recognizes there are good-quality "home brew" tests. I think it's fair to say that not all "home brew" tests are of the best quality. And this was an effort to take the active ingredient and essentially independently verify that at

least the physiochemical characteristics and its capability of producing an accurate answer have been established. There's flexibility in that where a laboratory could do even a better job by developing their own version of it. So that was the best cut that we could make.

DR. HOLLINGER: Dr. Gutman?

DR. GUTMAN: I have two comments in response to the issues you raise. The first is about the disclaimer. The disclaimer represents a minimum language, a minimum data set for explaining what's going on. The agency has communicated that if labs wish to communicate either in the report itself or in educational materials the fact that this product is in compliance with CLIA and meets the requirements of ASR and, therefore, obviously doesn't need to go to FDA, we don't preclude a clever lab from communicating to folks what's going on in either the report itself or some other context for explaining this rule. And I think that from our perspective--and we may be parochial and inbred--we're using diagnosis in a more catholic sense in that when we think of diagnosis, we're thinking of management therapy, screening, and diagnosis. And we may be playing a little loose with words, but diagnosis is for us a broad term in which lots of things comfortably fit.

DR. WILSON: And might I add that whether it's diagnosis or monitoring, the accuracy and the quality of the

result is what we're trying to drive at. We don't think that there should be any distinction between a test that monitors versus a test that detects a particular marker. The quality should be there regardless.

DR. HOLLINGER: Sort of like the definition for sex, I guess.

[Laughter.]

DR. HOLLINGER: Okay. Thank you.

Our next committee update is on supply updates on plasma derivatives, Dr. Mark Weinstein.

[Slide.]

DR. WEINSTEIN: I will give the committee a brief update about product shortages. I will summarize some of the causes for the shortages, the current status of some products, and actions that FDA and other groups are taking to alleviate the shortages.

[Slide.]

With regard to the reasons and causes for plasma derivative shortages, I've outlined three items here: industry-wide compliance issues, increased demand, and insufficient manufacturing capacity.

With regard to the first, we have two companies that are under consent decree, and others have received warning letters and have significant compliance issues. All of these companies are working to varying degrees and at

varying rates to improve their quality assurance programs and physical facilities. However, coming into compliance has slowed the output of product delivery. The industry-wide nature of this compliance problem, rather than occurring in one or two companies, makes this problem particularly acute.

Another issue is this increased demand. Demand for a number of products, particularly IGIV, has increased significantly. For IGIV, the increase in demand is thought to be about 10 percent per year, primarily in off-label use. For Factor VIII, the increase has averaged about 6 to 7 percent per year for the last four years.

Thirdly, insufficient manufacturing capacity. Industry underestimated the demand for plasma derivatives and analogous recombinant products, particularly in the case of recombinant Factor VIII.

[Slide.]

I'll turn to the current status of some of the products. I will concentrate on IGIV, which is currently in the most severe shortage.

This graph shows the aggregated monthly distribution of IGIV in the United States for 1998. The monthly distribution is indicated by the dark bars in this graph. The first of the month inventory is indicated by the light bars. That is the product that manufacturers have

under their control the first day of every month.

The projected level is the estimated level of product needed to meet demand based on extrapolating the distribution data from 1996 by 10 percent per year. 1996 was the last year where we did not have reports of chronic shortage.

The graph indicates that for the year so far, distribution of IGIV is down about 30 percent below what we estimate it should be. The low first of the month inventory suggests that reserves are being used up quickly.

Now, a number of other plasma derivative products are also in limited supply. These include some clotting factor--alpha-1 PI and 5 percent albumin. We have heard from consumers about the difficulty of getting clotting factors, particularly plasma-derived Factor IX. Estimating what the true demands are for these products and how they will be met in the near future is very difficult because of a rapidly changing market situation.

Now, in the case of Factor VIII, a new recombinant Factor VIII plant has recently been licensed, and we anticipate that some of the demand for recombinant Factor VIII will be alleviated by the output from this plant. In the case of Factor IX, the manufacturer of recombinant Factor IX has reported that they have enough Factor IX to meet national demand. We recognize, however, that more of

this product has to be used compared to plasma-derived Factor IX and that not all patients respond as they do to plasma-derived Factor IX when using this product.

In the case of 5 percent albumin, distributors have reported to us that there is a lack of 5 percent albumin. Overall, the total albumin distribution in the United States has decreased about 20 percent compared to 1996 figures. We do not have separate figures for the 5 percent albumin compared to the total albumin output, but information supplied to us by industry makes it appear that the distribution of 5 percent albumin is down approximately 30 percent during the period from August to October compared to six months previously. However, estimating the true demand for albumin is difficult because of the changing usage pattern, particularly in light of the British Medical Journal article reported to this committee by Dr. Finlayson in September about the disadvantages of using albumin.

[Slide.]

I will now turn to some of the actions that the FDA and other PHS agencies have taken, as well as consumer groups and industry, to help relieve the shortage, particularly with reference to IGIV. Among these are to inform physicians about approved uses of products, for example, through an MMWR document. Our intention is to inform physicians about approved uses of the products and

uses for which there is reasonable clinical support. The CDC is preparing an MMWR report in conjunction with FDA and the Immune Deficiency Foundation that will give information on the impact of declining IGIV availability on patients and will outline the clinically supported uses of the product.

Another action that we are taking is to collect and evaluate data about distribution and demand. Manufacturers are now required to submit distribution data and are working through the International Plasma Products Industry Association, IPPIA, and Georgetown Economic Services to supply this information to us. The FDA receives aggregate as well as individual company data.

Although distribution figures are a month behind the present situation, these figures are helpful in indicating general trends about product distribution. The data also helps us to estimate what the impact of new sources of material will have on distribution and how the lack of output from one or more firms will affect supplies.

The FDA is interested in, of course, expediting lot release and encouraging electronic submissions by industry. The FDA continues to improve our lot release program to get submissions out of FDA as quickly as we can without compromising our review process. We have also encouraged industry to submit lot release protocols electronically, which will save on FDA review time.

We're interested in expediting review of industry compliance submissions. FDA is working to review compliance submissions as expeditiously as we can, and at the same time assure the quality of our review. This includes focusing our reviews on key compliance issues, reviewing the work of third parties hired by industry to help them come into compliance, and forming teams within the agency to review submissions quickly.

The FDA is encouraging importation of products that meet FDA criteria. The FDA currently is reviewing half a dozen IND submissions that will permit importation of IGIV. We, of course, will not permit the importation of products that do not meet FDA safety criteria.

We're interested in streamlining clinical trials where possible. The FDA is open to new ideas about how clinical trials might be conducted to reduce the number of patients that have to be involved in these studies. We have met with the Immune Deficiency Foundation about this issue and look forward to further dialogue regarding clinical trials.

Lastly, the FDA has actively encouraged the development of an approved emergency distribution network for IGIV. The Immune Deficiency Foundation has proposed a plan for emergency distribution, and the IPPIA has supported this activity. These organizations will present information

about this plan in the open public hearing.

DR. HOLLINGER: Questions of Dr. Weinstein? Yes?

DR. STRONCEK: I had a question and a comment concerning both the supply of plasma and analytic specific reagents. The question--these are all reactive issues. Are you doing anything proactive? What I'm getting at is, in six months from now, we'll be required to test plasma by genomic amplification testing. We just heard the rules about analytic specific reagents, and I think those rules are very nice for mature tests, but they're going to be difficult to deal with with evolving tests, such as genomic amplification testing. My understanding is we're going to have to use an IND mechanism to approve, at least initially, the test we're going to use to provide the genomic amplification testing.

Do you have plans to expedite the review of these INDs or somehow relax the mechanism so we don't have a situation where blood establishments are having difficulty establishing this genomic amplification testing or having it evolve to meet--as technology changes to do a better job so we don't jeopardize further the supply of plasma?

DR. WEINSTEIN: Actually, for the plasma derivative industry, the supply of plasma is not the critical issue in alleviating the shortage situation. It is more to do with the compliance issues within the

manufacturing facilities rather than directly the supply of plasma coming into the plants here. And I've outlined some of the things that we are doing to try to accelerate the output of these plants regarding the plasma derivative issue.

DR. STRONCEK: Well, that might be true, but I think we cut off discussion a little on the analytic specific reagents. I still would encourage the FDA to make sure their mechanisms of approving assays, for new assays, are flexible enough to allow rapid changes in technology. And I think this is going to be an issue for the genomic amplification testing.

DR. HOLLINGER: Dr. Koerper?

DR. KOERPER: Dr. Weinstein, I think that we are all encouraged that your now getting these monthly reports from industry on inventory versus distribution levels. But I'm curious as to what the next step is, what you are going to be doing with this information. Has any consideration been given to setting critical levels below which an alert might be issued to treating physicians saying, you know, we're now down to one-third so limit your use of these products? An example would be to notify hemophilia treatment center directors about a critical level so that elective surgery could be postponed, which uses huge quantities of Factor VIII and Factor IX, sort of analogous

to an alert on a drought day where you don't water your lawns because the water level is critically low. I'm wondering if any thought has been given to sort of setting these levels and beginning to notify treaters when these levels are approached or reached.

DR. WEINSTEIN: I wish our model, our system was refined enough at this point to really give us that sort of critical information here. Right now, as I mentioned here, we are sort of a month behind in this kind of firm quantitative data. We are very attuned to reports that we get from clinicians about the difficulty of getting material. Information is also given to us by distributors, and so we are looking for maybe that early warning, very rapid, you know, on-the-spot information to help us with that sort of analysis here.

But we also do have a committee within the PHS agencies to help us develop a model system whereby we can determine what the actual level is at a particular time, and this might include calling pharmacies at hospitals to find out what their material is on the shelf at a particular time. Right now we're not quite there yet, and this is a difficulty.

DR. KOERPER: But you see your agency moving in that direction?

DR. WEINSTEIN: Yes, yes.

DR. HOLLINGER: Dr. Tabor?

DR. TABOR: I'd like to respond to Dr. Stroncek's comment. You need have no fear that the review of nucleic acid tests will delay or contribute to any shortages. We're very aware that nucleic acid testing is really one of the hot regulatory topics of this part of this decade, and these INDs are being given as great attention as we can, and I would say even our rapidly diminishing resources in CBER are having no effect on that. So at the present time, essentially all of the plasma being collected in the United States is being tested under IND using nucleic acid tests-- I'm sorry, all of the source plasma, and a very large proportion of the recovered plasma also.

DR. HOLLINGER: Before we go on, we have an open public hearing. There are three people who want to speak on this issue here. It may answer some of the questions. If I may, I'd like to have them go ahead and make their presentations on the committee updates. This is on the supply issue, and the first one is Mr. Jackman representing the International Plasma Products Industry Association, or the IPPIA.

MR. JACKMAN: Good morning.

[Slide.]

I'm Dennis Jackman, Vice President of IPPIA for North America. We represent the four largest commercial

fractionators of plasma-derived products, alpha therapeutics: Baxter Health Care, Bayer Corporation, and Centeon. We are acutely aware of the IGIV supply shortage in the United States and what that presents in terms of difficulties for patients.

I'm here today to announce that our member companies will be partnering with the IDF on their developing an emergency supply program, and we think that that program is going to be very helpful in helping to meet the critical needs of patients in an emergency supply situation.

I think the IDF would be best qualified to discuss exactly what's going to be in that program, but the short of it is that they have a physician panel where qualified physicians will identify emergency needs and be able to call in, and our companies will be providing supply or allocating supply that would be available for that emergency need. So it's a very targeted way of meeting critical-need patients.

Of course, this is in addition to other actions the companies have taken. Companies have implemented emergency supply programs. All of our member companies and a number of the non-member companies as well also have implemented emergency supply and have had a significant impact on that supply. And we know there's increasing demand for the needs for those emergency products.

We also are investing in plant upgrades and process improvements. We have figures that indicate that over the years here, we've invested over $380 million in plant improvements, process improvements, and some of that is having an effect. The plant was just approved for an upgrade, a process upgrade in this year. It's increased production significantly. That is having an impact on the supply in the U.S. market. They're also investing in new techniques that would increase yield from plasma and a number of other factors as well.

We are attempting to license and import additional products. Some companies have applications and are working with FDA on getting additional products in here that would meet U.S. requirements to help alleviate the shortage in supply. Then, of course, Dr. Weinstein referred to the data program. Our companies and also Novartis and American Red Cross are participating in a program to provide data now on a monthly basis which shows consumption in the U.S. versus inventory and provides a ratio on inventory to consumption. It's helpful in trending what's going on in the marketplace.

I'm addressing IGIV today because this is in reference to the IDF program. We are aware of products in other areas, and we're taking steps in those regards as well. Many of these things would apply in terms of investment in plant upgrades and process improvements. As

was referred to, we just had a facility open for recombinant Factor VIII where a major investment--that's kind of a major increase in output for the U.S. supply as well.

So that's what we're doing. We're happy to do this, and hopefully all these actions will help us to ameliorate the effect of the shortage of supply until supply can catch up.

DR. HOLLINGER: Thank you, Mr. Jackman.

The second group that has asked to speak today is someone from the Immune Deficiency Foundation. I apologize. I don't have a name for this, so if you would, could you state your name?

MS. O'DAY: I'm Miriam O'Day. I'm Vice President of the Immune Deficiency Foundation. We are pleased to hear the plans that the FDA has to streamline the licensure process and assist with imports. We're also pleased to be here today to talk about partnering with industry on the IGIV safety net program.

The program features are basically that we'll be setting up a physician registry. We'll be enrolling physicians. And IGIV from the IDF program, we ask them to access that only as a last resort. Physicians enrolled in the program will agree to restrict the use of IGIV obtained from the program to high-priority, medical-necessity uses, principally, but not exclusively, primary immunodeficient

patients, and physicians in the program will permit the retrieval of unused product at periodic intervals according to established protocols. We'll ask the physicians enrolled in the program not to re-sell or redistribute the IGIV from the program and that we'll engage a third party to handle the logistics of the program.

Thank you very much.

DR. HOLLINGER: Thank you.

The third one is Mr. David Cavanaugh from the Committee of Ten Thousand.

MR. CAVANAUGH: Thank you, Dr. Hollinger. I have two comments, on the HCV lookback update and also on the supply issue.

COTT, the Committee of Ten Thousand, is disturbed that efforts to press for notification of those exposed to HCV in the blood supply is proceeding so slowly. While this country has had several years of congressional and federal advisory committee oversight hearings on the subject, no patient notification has yet begun. Canada, on the other hand, announced six months ago a $3 billion government payout to exposed persons. BPAC should join other voices calling for rapid progress and pressing for efforts to contact those exposed in the 1980s, not just those testing repeatedly positive on later, more sensitive tests.

We continue to call for the fullest and most far-

reaching lookback possible regarding the exposure of nearly 1 million Americans to transfusion-associated hep C between the early 1980s and 1997. We are concerned that, as currently structured, the lookback will potentially exclude from notification up to two-thirds of those exposed to hep C contaminated transfusions. From our perspective, this should be an issue of the right of individual blood recipients to know that they were exposed to hep C and should be tested. Rather than setting the cutoff point of the adoption of the HCV PCR test, 1992, it should be set in 1990 when the HCV antibody test became available. For those who fall outside this period, we would propose a "Dear Resident" letter being sent to every home in America stating that if you received blood or blood products or blood components during the 1980s, then you should be tested for hepatitis C. This issue, simply put, is about the right to know and speaks directly to the public's trust in the safety of this nation's blood supply.

We must indicate what the priority is in this situation. We must not repeat the mistakes of the past as it impacts public perceptions about the blood supply and those that are tasked to manage it.

Regarding plasma supply, the IPPIA promised last spring to provide monthly updates to FDA and Blood Advisory Committees on current and projected production, inventory,

and demand. To date, after the initial release of the company of this announcement, only one such update has been issued publicly. BPAC should demand IPPIA deliver on its promise to assist both staff and advisors, much less consumers, in monitoring production, especially given the need for attention to amelioration of current and foreseen shortages and beyond regarding the need to assure an adequate and safe supply.

Thank you.

DR. HOLLINGER: Thank you.

Mr. Jackman, or someone, would you like to respond from IPPIA about the latter part? No? Okay. Go ahead, please.

MR. WALSH: Mr. Chairman, I'd like to ask for a point of clarification with respect to Dr. Weinstein's comment. John Walsh, Alpha-1 Foundation, Alpha-1 National Association.

With respect to the A1PI product availability, there's one product and one manufacturer currently available for our community. At maximum production, Bayer cannot produce enough product to meet current demand. We're identifying more than one person each day with alpha-1 antitrypsin deficiency that is eligible for therapy.

Two, we're very concerned about the potential impact of the alpha therapeutics recall and its potential

impact on delaying the delivery and production and approval for their BLA for an A1PI product from alpha therapeutics.

Third, we support and certainly endorse the initiative of the FDA, CBER, to increase or improve upon the clinical trial design activity. Since the last BPAC meeting, industry has experienced additional difficulties in getting an IND design approved or clarified from a third manufacturer, and we would also encourage FDA and would certainly like to work with them and industry to design a clinical trial design for an aerosol product which would significantly alleviate some of the issues that we are experiencing with the blood supply by IV.

Thank you.

DR. HOLLINGER: Thank you.

Yes, please? And state your name, please, and organization.

MR. BABLAK: My name is Jason Bablak. I'm with IPPIA. I just wanted to respond to Mr. Cavanaugh's remark.

Since the congressional hearing where we promised to provide the data on a monthly basis, that data has been available on a monthly basis, running one month behind, to FDA, the HHS Advisory Committee where we promised to do that, also to the congressional oversight committee and to other individuals who are interested. Certainly if someone is not receiving that data, if they would like to contact

us, we'd be happy to make that available to them.

DR. HOLLINGER: Thank you very much.

Now, Dr. Boyle, do you have a--John?

DR. BOYLE: Yes. First I'd like to thank the FDA and Dr. Weinstein for giving up that update, but I'd certainly like to take advantage of it and ask two questions.

One is that we saw from the 1998 estimates that IGIV is running about 30 percent below--or was running 30 percent below the projected demand for that year, and the question is: What about next year? Based upon what you know about licensed product, imports, expected shutdowns, are we talking about 30 percent, 50 percent or 10 percent?

DR. WEINSTEIN: We hope, of course, that there will be continuous improvement, but there is no predicting. Generally, this is a long process. We know that. This is not going to be solved overnight. The information that we have from companies suggests that it will be more on the order of years before they come into full compliance.

There is a ramping-up process here. As conditions improve, more product can get out here, but we can't be very optimistic that this problem will be solved soon.

DR. BOYLE: Then the second question is: In terms of where new product can come from, one of the issues, obviously, is the licensing of new products. You indicated

up there that the flexibility of the FDA in trying to work out clinical trials and so on to bring that along, but would you characterize FDA requirements now for clinical trials compared to the clinical trials that put the current products on the market as more demanding or less demanding?

DR. WEINSTEIN: Probably more demanding. We ask for statistical rigor in our approach here. We have to be very careful, of course, about allowing licensing new products here and reducing our standards because of the shortage situation and then later on coming back and reviewing the situation and perhaps having allowed the product to go forward without the sort of rigor that we feel is necessary. In other words, we can't be pushed by the shortage situation alone to relax our licensing requirements. We have to make certain that they are being met.

But we are, as you know, flexible and willing to hear new ideas that you may have for helping us streamline the process of approval.

DR. BOYLE: Thank you.

DR. HOLLINGER: Two things. There is a letter for the committee's information, there is a letter in your packet about a statement from the American Liver Foundation on HCV, HCV lookback primarily, so I just want you to know about that. There's no one here that's going to be speaking

on that, but it is in your packet and it's quite complete.

Are there any other public comments on any other topics under the committee updates? I know you.

DR. HOLMBERG: Jerry Holmberg, Navy Blood Program. I wanted to go back and readdress the issue of malaria, and I do appreciate Dr. Linden's comment about the cruise ship industry. Since I do represent an organization that has cruise ships--

[Laughter.]

DR. HOLMBERG: --I want to address an issue and hope that the agency will include this in their definition on cruise ships, dusk-to-dawn activity.

As you know, we very often pull into port and then maybe pull out and just cruise along the shores for a while. And I think that what we also have to consider--and I wish the agency would consider--is the fact of the distance that the cruise ship travels offshore.

DR. HOLLINGER: Thank you, Jerry.

Any other comments?

MR. NAGLER: My name is Rick Nagler from the Hemophilia Federation of America. In regards to the cruise ship industry, on any given day there are 68,000 people at sea on cruise lines. But it's just not limited--the problem's just not limited to cruise lines. You also have freighters coming in from the Far East, and I think that

would be a far greater problem.

In regards to the hepatitis C, what I see developing is the same thing that happened back when HIV was first being talked about. I happened upon it by stance, and had it not been for me going to a specific doctor, I would not have learned about hepatitis C. I learned about it I guess within the last two years. But for all those people that are out there that don't have regular access to a doctor, they are not being informed about hepatitis C, and the same thing is happening, again, as happened in regards to public notification with HIV.

DR. HOLLINGER: Thank you.

Any other comments from the committee about any of this? If not, then we will formally close the open public hearing--what Dr. Smallwood said I had to say, and I do everything she tells me. There is another open committee discussion on the workshop summaries, and I think we'll have some presentations--two presentations, the first one on donor suitability workshop, and Andy Dayton I think will provide that to us now.

DR. DAYTON: Last year at this BPAC, we examined the question of deferring men who have sex with me from giving blood. It was felt at that time by all of us that we wanted to examine the issue further, and we also felt that in doing that it was a good opportunity to examine the

general question of lifetime deferrals for high-risk behavior.

As part of that re-examination, on November 21st, a couple of weeks ago, the FDA sponsored a workshop on donor suitability. This workshop was intended to gather scientific information to assist the FDA in efforts to update and revise the blood regulations on donor suitability. The FDA has relied on guidance documents and recommendations to quickly communicate important information to the regulated industry while protecting the public health. Several of the exclusionary criteria discussed had been issued as guidance documents in the past.

The theme of this workshop was to examine data relevant to the maintenance of lifetime deferrals for individuals who have engaged in certain high-risk behaviors. We heard scientific information on the risk of transmission of HIV, HBV, HCV, HTLV, and also generally emerging infectious diseases in the following high-risk categories: men who have had sex with another man, even one time, since 1977; men or women who've exchanged sex for money or drugs since 1977; and men or women who have abused intravenous drugs.

A secondary theme of the workshop, which wasn't as extensively covered as the primary theme, was concerned with partners of people in these high-risk groups. There were

epidemiologic presentations on the introduction of retroviruses into human populations, the prevalence and incidence of HIV, HBV, HCV, and HTLV in individuals who engage in activities thought to be high risk for infection, the prevalence and incidence of these agents in blood and plasma donors, the impact of these donor deferral criteria on blood safety, and other presentations were on donors who do not provide correct answers to deferral questions, advances in donor testing and narrowing of the window period by introduction of investigational genetic tests for HCV and HIV, and a policy model that assesses the impact of any changes to these donor criteria, which was basically the model that I discussed last year.

It's very difficult to summarize the diversity of data that we received. Certainly every speaker had a lot of caveats about almost any number. But let me give you some of the highlights and the major points from our perspective, if I could have the first overhead, please?

[Slide.]

Even closely related viruses with similar transmission routes can have very different risk factors, and this relates to the variable biology of different viruses. This is even more true for unrelated or distantly related viruses, and these considerations impact our choices of model viruses for formulating policy.

Finally, transmission of viruses, even retroviruses, from animals to humans is not unusual. It happened periodically throughout history. It happens occasionally currently.

[Slide.]

One of the important criteria in making a policy change is to try to understand the magnitude of the changes that may result from changes in your policy, and we have had Linda Dawe come up with some estimates of the potential new blood donors that would be allowed to go to the testing stage of giving blood with various changes in deferral criteria. Now, on this slide I'm listing the number of new donors in various categories that would now appear and get through the questionnaire stage and be allowed to be tested for giving blood under a one-year deferral policy.

For men who have sex with men, there would be approximately 130,000 new donors a year. For intravenous drug abusers, there would be somewhere between 110,000 and 440,000 new donors per year in that category. We asked for the general numbers on people, men or women, who exchange sex for money or drugs; it's a little bit hard to pin down those numbers, but Linda gave us an estimate for female sex workers, and it's possible that in the neighborhood of 83,000 new donors in this category could present with a one-year deferral policy.

It should be understood that there are large error limits on these numbers. Nobody really know what the rates of donation are going to be in these groups. These estimates were based on assuming that you'd have a donation rate in these groups similar to the overall population donation rate of 5 percent, and that may or may not be a correct assumption and it may or may not vary from one group to another.

[Slide.]

I'm only going to highlight a couple of the interesting data points, but one of the things that was fairly clear was that the incidence data for most of these diseases is much harder to acquire than the prevalence data, in general. Consequently, we have much poorer estimation of incidence risk than prevalence risk for most of these disease categories.

[Slide.]

This is just some of the selected data on incidence. For instance, HIV in the MSM population has an incidence rate in the neighborhood of one to three per 100 person-years. Be careful because some of these numbers are in person-years and some of these are in 100,000 person-years, or KPY. But this is one to three per hundred person-years. Intravenous drug abusers, for instance, in New York City have an incidence rate of about 1.5 per 100 person-

years. For HCV, for instance, in the intravenous drug abuser population, it has an amazingly, stunningly high incidence rate, roughly in the 10 to 20 range per 100 person-years.

If we take these incidence rates and just multiply them by the number of new donors appearing and how frequently--or what's the outer time limit of when someone seroconverts, we can come up with rough estimates for how many infectious units might enter the blood supply with the projected changes in policy--not projected, I should say discussed change in policy, for instance, a possible one-year deferral policy. And when we do this for HIV, these numbers turn out to be somewhere in the neighborhood of 0.2 to 0.7 new infectious units appearing into the blood supply by window period donations per year. Those are very rough numbers. We certainly aren't in a position to be held to them.

But with HCV, for instance, with a very high incidence rate, and particularly in intravenous drug abusers, which are a very large--comparatively large segment of the population, it's possible we could see as many as 40 to 160 units slipping through. Again, that's a very rough number, and we certainly don't want to be held to it yet. But it's indicative of the kinds of policy considerations that we're hearing.

[Slide.]

Now, just to highlight some of the more striking prevalence data, for HIV in men who have sex with men, numbers in the 6 percent to 36 percent range are not uncommon. It varies tremendously according to city and region. For example, again, HCV in the MSM population, we're looking at a prevalence rate in the neighborhood of 4 percent. For HTLV, in a New York City study, the prevalence in intravenous drug abusers is in the neighborhood of 4.5 percent.

Again, if you calculate the prevalence rate times the number of new donors that might appear, you might have as many as 2,600 or, as we estimated last year, maybe 1,500 new infectious--infected people, new donors appearing who are infected, who get to the questionnaire stage, get through the questionnaire stage, and get to the testing stage, and that's about a doubling of the burden on the testing stage.

For HCV in the MSM group, we could conceivably have numbers in the 1,000 to 5,000 range of new units which would be burdening the testing stage.

[Slide.]

We have talks on risk factors in blood donors who turn out to be positive for these diseases, and the findings are in accordance with what you'd expect from the prevalence

data. There's a hierarchy of risk factors in HIV-positive blood donors. The hierarchy is MSMs and then IVDUs and then heterosexual contact with the above, in that order.

[Slide.]

Similarly, for instance, the hierarchy of risk factors in HCV-positive blood donors, by far and away the largest contributor were IVDUs, and then lower down were history of transfusion and sex with an IVDU.

[Slide.]

We did not go into lengthy discussions of questionnaire design, but it is a somewhat--although somewhat peripheral to the main themes, it was brought up in discussion, and it certainly is important in terms of policy considerations. And there was a very strong feeling by the members of the workshop who participated in this discussion that we should be paying very strong attention to the design and validation of every question that goes into the questionnaire. Questionnaires are effective but there's room for improvement.

[Slide.]

So we are now analyzing the data to formulate a full policy review. Any proposed changes in regulations will be made in a careful and deliberative manner by the FDA in consultation with the NIH and CDC prior to publication for public comment. The challenge before us is to maintain

safety and availability of blood and plasma products. The FDA must balance enthusiasm based on the improvements gained by advances in test technologies with due caution based on the past tragedies of disease transmission.

Thank you.

DR. HOLLINGER: Thank you, Andy.

Any comments? Yes, Dr. Boyle?

DR. BOYLE: Just a quick question, something I'm not clear on. As I understand it now, the questionnaires that are being filled out by donors to determine whether they're deferred or not are basically all paper copy. If somebody had a computer-assisted, self-administered program where somebody actually filled it out at a computer terminal, shortened the interview length and so on, would that require a license because it's software related to medical products as opposed to the hard-copy questionnaire?

DR. DAYTON: We do regulate it. Somebody perhaps from--

MS. GUSTAFSON: A study was done in the early 1990s on computer-based donor interviews, and it was presented to BPAC--I don't remember exactly which year. But we did tell the industry that we would be amenable to reviewing applications for computer-assisted donor interviews, and we have just recently approved one computer--an interactive video. So, yes, they come under the license

supplements or the license applications for the licensed blood banks.

DR. HOLLINGER: Dr. Linden?

DR. LINDEN: Dr. Dayton, has there been any consideration by the agency to the possibility of eliminating even the one-year deferral for products that can be frozen for at least the duration of a window period and the donors retested, such products as donor retested plasma and semen, particularly?

DR. DAYTON: We're open-minded about that, but we don't have a decision on it, unless I'm mistaken.

DR. HOLLINGER: Dr. Chamberland, do you have a comment on the workshop?

DR. CHAMBERLAND: I guess I wanted to use this as a segue to apprise the committee members as well as those of you who are here today about another workshop that will be held in January of 1999. I believe the committee members actually have an announcement about this, but sort of related to the issues of donor suitability, CDC in partnership with FDA and NIH and the Department of Defense is sponsoring a public workshop on the potential for transfusion transmission of tick-borne agents. So we're moving into a different realm here.

The workshop will be held January 14th and 15th of next year in Atlanta, and the objective of the workshop is

to review current information on tick-borne pathogens and their potential for transmission by blood transfusion. We'll also look to identify what gaps in research priorities are out there and identify approaches to reducing the risk of transfusion-related infections from tick-borne agents.

Information about the workshop is available on CDC's Web site, cdc.gov, and we have also with the help of some of the umbrella professional organizations, such as AABB and ABC, American Red Cross, announcements are going out through their weekly newsletters and the like. If people do wish additional information that are here at this meeting, please come and see me and I can apprise you of that.

DR. HOLLINGER: Thank you, Mary. Thank you, Dr. Dayton.

The next information or workshop summary is going to be by Mary Gustafson on the blood licensing workshop.

MS. GUSTAFSON: Thank you.

Just yesterday, the Office of Blood Research and Review hosted a workshop for the blood and blood components industry. The workshop was held to introduce the concept of licensing using a self-certification to a set of licensing criteria in lieu of the submission of detailed supporting information with a license application. The initiative is being undertaken under our Blood Action Plan to further

streamline the licensing process for blood and blood component products. It is part of FDA's continuing effort to achieve the objectives of the President's Reinventing Government initiatives and is intended to reduce unnecessary burdens for industry without diminishing public health protection.

We presented information to indicate that we have made strides in simplifying the application process and in reducing application approval times. However, we also presented information that showed the budgetary constraints that affect staffing and the likelihood that further streamlining or even maintenance of the current performance will not happen without our instituting more drastic streamlining measures.

With that background, we presented the concept of self-certification licensing. We advised that our proposed approach is to pilot the concept in two specific areas: blood component gamma irradiation and red blood cell immunization to produce immune source plasma. In preparation for conducting the pilot, we will publish draft guidance documents with our proposed licensing criteria. The notice of availability for the draft guidances will announce our intention to conduct the pilots, request comment on the concept of self-certification licensing, request comments regarding desire to participate in the

pilot, and request comments on the draft specific licensing criteria.

Following the comment period, we will assess whether the pilot is viable in terms of interest in the overall license concept, interest in the proposed pilot areas, and the comments on the draft guidance documents themselves. If there is adequate interest, we will publish a notice of availability of the final guidance document and announce the commencement of the pilot.

Applicants in the pilot licensing program will submit a license application, and FDA will try to conduct a pre-licensing inspection within 90 days to assess the applicant's ability to self-certify compliance with the specific licensing criteria, after which the licensed supplement would be approved.

We were able to release the draft guidance for the pilot licensing program for gamma irradiation of blood and blood components. The document was posted on the CBER Web page on Tuesday. A notice of its availability for comment and announcement of the agency's desire to initiate the pilot licensing program will soon publish in the Federal Register.

We did not have a large crowd at the workshop, but were very pleased with the audience's willingness to participate freely in a question-and-answer session and

group discussion. We received positive and enthusiastic support for the concept of a self-certification licensing program. There were concerns raised about the selection of pilot areas: whether the universe of potential applicants for gamma irradiation of blood and blood components is great enough to support a pilot, and whether the proposed pilot for red blood cell immunization offers any economy over our current review method, and if it presents an increased risk to recipients; the method of evaluation, specifically, our use of a pre-licensing inspection as an evaluation tool, and whether the pre-licensing inspection would need to be a component of self-certification licensing in future pilots and licensing rollout; suggestions for other product areas to either substitute for the initial pilot or for rollout to other product areas; ideas concerning industry participation in the development of licensing criteria guidance documents; and comments concerning our proposed licensing criteria.

We FDA staff left the workshop encouraged that the participants heartily endorsed the concept of self-certification licensing. We are looking forward to more comments and suggestions when the document is published and recognize that we have quite a bit more work to do to ensure that the pilots chosen are ones that will encourage participation, that guidance documents are appropriate, and that our evaluation methods for the pilots are reasonable

and fair.

Thank you.

DR. HOLLINGER: Thank you.

We're going to move on, then, to another issue that will require some response and recommendations from the committee, so we're going to start out with an introduction and overview on the hepatitis B anti-core re-entry issue, and we'll go on to the serology of hepatitis B, and then we'll take a break at that point and then come back for a presentation of the AABB proposal.

Dr. Biswas?

DR. BISWAS: Thank you very much, Dr. Hollinger.

If I could have the first slide, please?

[Slide.]

For the remainder of this morning, we will be discussing proposals for the re-entry of donors who are indefinitely deferred from donating blood and blood components for transfusion because they have tested repeatedly reactive for anti-HBc on more than one occasion. I will give you some background information, and I'll skip a few slides in the interest of time, and I will describe to you the FDA's proposal for re-entry. Dr. Cathy Cantilena will then talk about the serology of hepatitis B, and Dr. Roger Dodd will talk about the re-entry proposal of the AABB.

[Slide.]

This slide shows the various markers for which blood for transfusion is tested for these days, and the one that we will be concentrating on is this one, anti-HBc, antibody to hepatitis B core antigen, but I will have to start off by mentioning this one, hepatitis B surface antigen, HBsAg.

[Slide.]

Now, HBsAg testing was introduced in the early 1970s for the prevention of post-transfusion hepatitis. However, after it had been introduced and after the so-called third-generation tests--those were RIAs--after they had been introduced in 1975 for donor screening, post-transfusion hepatitis still occurred.

Now, most of this was the so-called non-A, non-B hepatitis, which we know today is mostly made up--almost all of it is hepatitis C, but at that time there were some cases still of post-transfusion hepatitis B. Now, at about the same time, talking about the mid-1970s, anti-HBc detection tests were being developed and became available to hepatitis researchers about that time.

[Slide.]

Now, in the last 1970s and early 1980s, studies showed that anti-HBc is a surrogate marker for non-A, Non-B hepatitis. As I said, it's mostly HCV infections, and, of

course, at that time there were no specific tests available for HCV. In particular, two studies--one done at the Clinical Center at the NIH and the other a multi-center transfusion-transmitted virus study--indicated that about 30 to 40 percent of post-transfusion hepatitis, most of it being non-A, non-B hepatitis, would be prevented if anti-HBc donor testing was not done. At that point, as a result of these two studies, anti-HBc testing of blood for transfusion was implemented voluntarily by blood collection centers in the mid-1980s.

[Slide.]

Now, in May 1990, donor testing for anti-HCV was implemented. It was a specific test, reasonably specific test for HCV. And at that point the utility of anti-HBc donor testing was questioned because, as I said earlier, anti-HBc testing had been implemented as a surrogate test for non-A, non-B hepatitis, which is most hepatitis C, and there was now a specific test available.

[Slide.]

At a Blood Products Advisory Committee meeting in January 1991, the Advisory Committee formally recommended anti-HBc testing of blood for transfusion because it would contribute to blood safety by reducing the incidence of post-transfusion hepatitis B.

[Slide.]

They did this because studies presented at that meeting indicated that prior to anti-HBc testing, post-transfusion hepatitis B was not fully eliminated by HBsAg testing. Also, studies indicated that transfusion of HBsAg negative, anti-HBc positive units are in rare cases associated with post-transfusion hepatitis B.

[Slide.]

Now, in September 1991, the FDA issued a memorandum to blood establishments. This memorandum recommended the testing of blood for transfusion for anti-HBc and for using only anti-HBc negative blood for transfusion.

[Slide.]

This memorandum also recommended that donors should be indefinitely deferred from donating transfusable components if they were repeatedly reactive for anti-HBc on more than one occasion, and this is the focus of today's discussion.

At that time, as there was no supplemental or confirmatory tests--and there still isn't. As there were no supplemental/confirmatory tests available, no re-entry protocol was recommended at that time.

[Slide.]

Now, I think it's important to point out, when one goes back to the time of the voluntary implementation of

anti-HBc testing in the mid-1980s, it's important to point out that indeed anti-HBc testing was followed by some additional reduction in post-transfusion hepatitis of both hepatitis B and non-A, non-B. However, it is unclear whether this reduction was due to anti-HBc testing or how much of it was due to anti-HBc testing because of the introduction of testing and searching donor questions for the evaluation of HIV infections and, hence, HBV infections. This occurred at about the same time that the anti-core testing was implemented.

[Slide.]

I should also like to point out that at an NIH Consensus Development Conference, January 1995, the panel recommended continuation of testing donors of transfusible blood for anti-HBc because, as they put it, it may prevent some cases of post-transfusion hepatitis B and because it may act as a surrogate marker for HIV.

[Slide.]

So under discussion today are those situations where the donor has two repeatedly reactive anti-HBc test results and is indefinitely deferred.

[Slide.]

Now, I just want to make one quick digression, talk about plasma for further manufacture into plasma derivatives and point out that source plasma donors are not

screened for anti-HBc, and in regard to recovered plasma, those anti-HBc units that are untested, that are non-reactive or repeatedly reactive are acceptable for use. And the reason for this is that if anti-HBc units were excluded from pools, anti-HBs titers will be diminished. Most anti-core units also have anti-HBs. And we believe that anti-HBs contributes to the safety of plasma products from HBV infection.

[Slide.]

Skip over this, and I'll just go through this. This is FDA's proposed re-entry algorithm. The donor is re-entered if after a minimum of eight weeks subsequent to the last repeatedly reactive anti-HBc test a new sample is collected, and this sample is negative for HBsAg, anti-HBc, and anti-HBs, and also if any time subsequent to the negative tests in one above the donor presents at a blood center and is found to be suitable.

I'll stop at this point.

DR. HOLLINGER: We're going to have Cathy Cantilena talk to us about serology of hepatitis B.

[Slide.]

DR. CANTILENA: I'll begin by just stating what the current AABB standard is for hepatitis B virus testing, and Dr. Biswas has nicely reviewed what the FDA has recommended that blood centers do. The AABB standard states

that prospective donors shall be indefinitely deferred from donating blood or components for transfusion who: have a history of viral hepatitis after their 11th birthday or who have had a confirmed positive test for HBsAg or who have had a repeatedly reactive test for anti-hepatitis B core on more than one occasion.

[Slide.]

What I'd first like to go through then is the background, a little bit about the epidemiology of hepatitis B infection, and then the basics in regard to serology, and Dr. Hollinger can correct me if I'm wrong on any of it, I'm sure. Then I'll finish up by telling you in a little bit more detail about three of the studies that might be pertinent to hepatitis B serology.

First of all, what we see is that approximately 45 percent of the global population live in areas with a high prevalence of chronic HBV infection. That is where more than 8 percent of the population is HBsAg positive. Forty-three percent live in areas where a moderate prevalence or 2 to 7 percent of the population is HBsAg positive, and 12 percent live in areas where there is a low prevalence, less than 2 percent of the population being HBsAg positive.

In high-prevalence areas, the lifetime risk of acquiring hepatitis B virus infection is more than 60 percent, and most infections are acquired at birth or during

early childhood when the risk of developing chronic infection is the greatest. In these areas, because most infections in children are asymptomatic, very little acute disease related to HBV occurs, but rates of chronic liver disease and liver cancer in adults are very high.

In low-prevalence areas, such as in the U.S., the lifetime risk of infection is less than 20 percent. Most HBV infections in the low-prevalence areas occur in adults and in relatively well defined risk groups.

[Slide.]

Pictorially, this represents the hepatitis B virus Dane particle and the components. It's a 42-nanometer, partially double-stranded DNA virus in the family Hepadnavirideae. The hepatitis B surface antigen comprises the outer envelope. The hepatitis B core antigen is an inner component. It's a nucleocapsid that encloses the viral DNA. Inside the core particle is a molecule of circular DNA and an endogenous DNA polymerase.

HBe antigen is the third viral antigen, and it's a soluble protein that's associated with the hepatitis B core antigen. It's found in hepatitis B surface antigen positive serum. Its presence indicates hepatitis B core antigen particles and high levels of circulating hepatitis B virus.

[Slide.]

What I'll just proceed through now are the

serologic definitions of each of these antigens. Hepatitis B surface antigen, as I have mentioned, is a viral envelope glycoprotein, and it's the basis of the hepatitis B virus vaccine. The antibody that's produced in response to hepatitis B surface antigen is anti-HBs. It is a protective and neutralizing antibody. Anti-HBs can become, however, undetectable in persons who have fully recovered from the disease, and I will get back to this when I talk about acute hepatitis b serology.

Hepatitis B core antigen is a nucleocapsid, as I mentioned, that encloses viral DNA. Its associated antibody, anti-HB core, is in all patients who have ever been exposed to the hepatitis B virus, and it's not protective. Its presence alone cannot be used to distinguish acute from chronic infection. The IgM portion of the anti-HB core response is associated with acute infection or flares of chronic disease. The IgG anti-HB core antibody, when it's generated, generally persists for life.

[Slide.]

Hepatitis Be antigen is the circulating peptide, as I mentioned, from the core region. It marks active viral replication, and it's present only in persons with serums HBV DNA. HBV DNA is the best indicator of active viral replication. The antibody produced in response to hepatitis

B antigen is anti-HBe, and it appears when the e antigen is cleared and the virus is no longer replicating.

[Slide.]

This slide is shown by way of introduction to orient you to the types of consequences that can occur after an acute hepatitis B virus infection. First, either you can get recovery from infection or chronic infection following acute disease. Most frequently what is seen is the transient subclinical infection that's associated with production of antibody and permanent immunity. About 25 percent acute symptomatic hepatitis B virus infections recover--most of these recover, and I'll show the serology of that in a moment.

On the other hand, 5 to 10 percent of adults with acute hepatitis B virus infection do not recover and remain HBsAG positive for life. Unfortunately, the proportion of infections that become chronic is higher in infants and children, as I mentioned, who have immature immune responses. They become asymptomatic chronic carriers of hepatitis B surface antigen.

Typically, acute illness accompanying onset of the carrier state is mild and asymptomatic, and the diagnosis is made months to years after the initial infection.

A smaller proportion of chronic hepatitis B virus infections go on to have active liver disease, and 10 to 30

percent of these are at risk for developing cirrhosis, and both of these outcomes of chronic hepatitis B surface antigen carriers have been associated with the development of hepatocellular carcinoma.

[Slide.]

This slide shows the typical serologic course of acute hepatitis B virus infection. The incubation period, as you'll note, is approximately--or averages 60 to 90 days, and you can look at this slide from a perspective of development of antigens in serum, as well as the later development of antibodies. It's a little bit complex, but I'll try and walk you through it here.

During the incubation period, hepatitis B surface antigen appears. This appears in association with hepatitis Be antigen, DNA polymerase, and HBV DNA. These signify active viral replication and appear, as I say, along with the hepatitis B surface antigen.

As the serum transaminase peaks, the levels of HBV are at their peak or even beginning to decrease at this point. Hepatitis B surface antigen, in contrast to HBe antigen here, remains detectable in serum through the clinical illness and disappears in convalescence, and it may require up to six months to reach the undetectable stage.

The antibody responses, as I mentioned, are complex, and in order to remember it easier, what I usually

do is I know that they come up in alphabetical order--first c, then e, and then s. Anti-hepatitis B core rises shortly before the onset of illness. Initially, it's both an IgM and IgG response. With recovery, the IgG antibody increases while the IgM antibody decreases and eventually disappears. All patients with acute HBV infection produce anti-HBe, which probably persists for life.

Anti-HBe rises next and usually appears when HBe antigen becomes negative. It disappears, as I mentioned, in a few months to years.

Finally, anti-HBs rises during recovery. Then after, HBs antigen is cleared. The window period between the disappearance of HBs antigen and the appearance of anti-HBs antibody characterizes what's known as the window period marked by anti-hepatitis B core antibodies, that is, from here to here [indicating].

The presence of anti-HBe at this time indicates that the e antigen has been cleared and the virus during the window period may no longer be replicating.

It's worthy to note that in 5 to 15 percent of acutely infected patients, the anti-HBs may, in fact, fail to develop and wane, in fact, with time in individuals who actually serologically recover from infection. The only remaining serum marker in these individuals would be the anti-hepatitis B core antibody.

[Slide.]

To move on to looking at this point at the chronic course serologically of hepatitis B infection, initially the antigen patterns of chronic infection are similar to acute infection. However, they do not decrease with time or with ALT elevations, as do the acutely infected and patients who recover. The antibody responses during chronic HBV are marked by high sustained titers of anti-hepatitis B core without specific anti-HBs. Initial IgM response decreases with time, but this is in contrast to acute infection, and it can persist for years. Patients who remain HBsAg positive do not produce specific anti-HBs but remain positive for anti-hepatitis B core.

Once chronic HBV is established, the activity of chronic liver disease and the presence of serologic markers can also change with time. In at least half of the patients, HBe antigen, which has persisted, disappears and anti-HBe rises. The loss of HBe antigen is also associated with a loss of HBV DNA and DNA polymerase.

Unlike acute disease, however, the HBsAg would persist in the liver--in the serum, I'm sorry. The persistence of HBsAg in the serum without evidence of active viral replication is--and not associated with hepatitis, is usually what we refer to as the healthy carrier state. Some patients who lose e antigen develop anti-e and may

ultimately even lose HBsAg and go on to develop anti-HBs. These patients who clear antigen and no longer have active liver disease may be left with portal fibrosis and even post-necrotic cirrhosis.

[Slide.]

What I'll show in this slide is a simpler version of what was just shown on the slide in black and white, and that HBe antigen can persist over time, and about half of the individuals who have chronic hepatitis B virus infection, the other half may go on, in fact, to develop an anti-HBe antibody response perhaps years after they have had chronic infection.

[Slide.]

What I'll do now is move on to discuss three of the studies that are relevant to HBV serology, and specifically in more detail, I'll talk about Dr. Seeff's study and Dr. Silva's study and one of the studies I picked up yesterday that I think might be important to talk about this morning. I'll just mention here a study by Dr. Reherman that was in Nature Medicine in which he looked at HBV specific cytotoxic T lymphocytes which persisted in subjects who had recovered clinically and serologically from acute hepatitis B virus infection decades earlier. His subjects, who were considered serologically recovered from acute infection, who had anti-hepatitis B core and several

of whom had anti-hepatitis B surface antigen, 11 of 17 of his subjects displayed HBV DNA in their serum and/or peripheral mononuclear cells. The presence of DNA happened to be directly related to the strength of the CTL response. His results reinforced the belief, his belief that hepatitis B may persist for years after recovery and that infection may be held in check by the cytotoxic T lymphocyte response.

I just wanted, before I move on from this slide, to mention a very nice review by Dr. Lee in last year's New England Journal of Medicine this month an overview of hepatitis B virus infection and serology.

[Slide.]

First I'd like to just summarize the results of the article that appeared in the New England Journal of Medicine by Dr. Seeff back in 1987. It represents the largest point source outbreak of hepatitis B virus infection that affected about 50,000 U.S. Army personnel. It was specifically linked to lots of yellow fever vaccine that were stabilized with human serum.

In 1985, a group of 597 veterans were interviewed and divided into groups, what I've noted here as Groups 1, II, and III. The first group received the vaccine and was symptomatic for hepatitis with jaundice or other symptoms. Group II was a group of soldiers who had been vaccinated with the contaminated vaccine but were asymptomatic for

disease. And Group III were a group of soldiers who had received the vaccine that was free of serum at a later date after 1942.

You'll note that 98 percent of the Group I veterans had serologic markers of past hepatitis B infection, the majority of whom, 90 percent of whom had both antibodies to core and surface antigens. Seven percent of these veterans also just had hepatitis B core antibody alone. Notably, only one individual in the entire study had persistent hepatitis B surface antigen.

In Group II, 77 percent of the vaccinated veterans had hepatitis B virus serologic markers. Seventy percent of these individuals, again, had both anti-core and anti-surface antibodies, and the remainder either had core alone or surface antibody alone. None of them had hepatitis B surface antigen, and these results are both significantly different from the control subjects of whom only 6 percent had serologic evidence of prior disease and 7 percent HBsAg alone--HBs antibody alone.

What is also notable from this study is that only 1 percent in the Group I, as I mentioned, has surface antigen, representing really an unexpectedly very small number, less than a quarter of a percent of people in the study who were healthy young males at the time that they acquired infection that went on to have chronic disease.

[Slide.]

In conclusion, Dr. Seeff was able to draw the conclusion that hepatitis B virus immunity is lifelong in those acquiring acute and natural infection, and that there was a low hepatitis B surface antigen carrier rate, 1 in 348 among healthy young adult males who acquired infection, and I stand corrected in that there was, in fact, molecular testing done. The individual who was infected was HBV DNA positive. As a control for that, he tested by molecular hybridization 108 unselected subjects in this study who were HBV DNA negative.

[Slide.]

To briefly mention Dr. Silva's study, he examined subjects, 133 patients, via the Indian Health Service, who were also hepatitis B core antibody positive prior to hepatitis B virus vaccination. Only 9 of these individuals were hepatitis B surface antibody positive. What he found was that only 3.8 percent of the 133 persons positive only for anti-core were also positive for HBV DNA by PCR. Repeat PCR on these individuals proved that there was HBV DNA in their serum in four of the five. However, follow-up samples 1 to 5 years apart after the initial serum draw were negative for HBV DNA.

In conclusion, what was found was that HBV DNA, in fact, was not found in 96 percent of serum samples from

individuals with only anti-core when tested by EIA in an area where the prevalence of HBV was moderate.

[Slide.]

I'd just like to show you some overhead slides I prepared in the wee hours of the night last night. This is a study that you may be familiar with, one by Dr. Dickson that appeared in Gastroenterology in December of last year-- I'm sorry, in November of last year, that looked at the transmission of hepatitis B virus by transplantation of livers from donors who were positive for anti-core. It was a retrospective analysis done on liver transplants between 1989 and 1993 at four different centers throughout the U.S.

The results of this study are impressive and a little bit scary in that they found that, first of all, 3.8 percent of liver donors were anti-core positive, and this is looking at over a 1,000 liver donors in transplantation. Hepatitis B core antibody testing is not required by the United Network for Organ Sharing or the Public Health Service, so it's done on most people who donate their livers.

Hepatitis B virus infection developed post-transplant in 18 of 23, or 78 percent of recipients who had anti-hepatitis B core positive donors versus in only 30 to 651 control patients who received HB core negative, livers from HB core negative donors.

[Slide.]

This is a more detailed analysis of the data presented in that paper post-transplant hepatitis B virus infection among recipients from the core positive donors who had core detected in their serum. Notably, I'll just point out that none were HBsAg positive among the donors.

In terms of recipient status, it didn't seem to matter what their vaccination status was prior to transplant, and three of four recipients developed hepatitis B post-transplant after they received the core positive liver. The control numbers are very much the same in terms of proportions.

If the recipient of the liver was anti-HBs positive, as was the case in three, one of these patients developed post-transplant hepatitis B virus infection compared to 85 percent of those who were anti-HB negative. In terms of the recipient status, when you look at anti-hepatitis B core antibody, surprisingly, none or zero--small numbers here, but neither of the patients who were core positive prior to transplant developed new or post-transplant de novo hepatitis B virus infection as opposed to 83 percent of those who developed infections post-transplant, after getting a core positive liver.

In terms of donor status, if the donor was also anti-HBs positive, as was the case in 18 of the transplants,

15 of the recipients, or 83 percent of those who received their lives, developed de novo post-transplant hepatitis B virus infection.

To follow up here in regard to molecular testing, one of seven serum tested--and the study didn't state which sera were tested, but were positive for HBV DNA by PCR.

[Slide.]

In conclusion, it appeared that the de novo post-transplant HBV infection occurs at a high rate with recipients of donors who had anti-hepatitis B core regardless of the recipient immune status or the donor's apparent serologic recovery, and that transmission of hepatitis B virus suggests that virus may persist in the liver despite serologic resolution of hepatitis B virus infection.

[Slide.]

To summarize, the last slide shows that anti-hepatitis B core as a sole marker of HBV infection could signify four different things: first, a false positive EIA after testing; secondly, the loss of anti-HBs with time or failure of anti-HBs to develop after infection; third, the window phase of acute hepatitis B virus infection, that is, as I mentioned, after HBsAg disappears and before anti-HBs appears; and, last, the HBV carrier state with undetectable HBsAg and low levels of HBV replication.

In sum, blood collection centers at present are left in a quandary regarding how to best assess the meaning of hepatitis B core antibody alone when it's detected in donor serum. Hepatitis B surface antibody may be helpful in many cases to determine the immune status of the patient who has had an acute infection. However, there is evidence via molecular testing as well as evidence via liver transplant data that I've shown here that what was thought to be recovered HBV infection serologically may, in fact, represent in a few cases HBV infection that persists. And it's possible that the presence of anti-HBs and anti-HB core may represent immune control of viral replication at a level that's below conventional means of detection and that it's not apparently injurious to the serologically marked individual.

Thank you.

DR. HOLLINGER: Thank you, Dr. Cantilena.

We're going to take a break now for half an hour. We'll reconvene again at 11:15.

[Recess.]

DR. HOLLINGER: We're going to start this session off today next with a presentation of the AABB proposal, and Roger Dodd from the American Red Cross will discuss this.

[Slide.]

DR. DODD: Thank you very much, Dr. Hollinger.

Dr. Hollinger has kindly given me two minutes with a 25 percent bonus for the holiday season. I fear I may go over a little bit. I'm Roger Dodd. I do indeed work for the Red Cross, but today I am speaking on behalf of the American Association of Blood Banks, and I appreciate the support provided by Steve Kleinman, by Gary Tegtmeier, and by Susan Stramer in putting this proposal or this talk together.

[Slide.]

What I want to try and do today is to give you a little background, and this in a sense is both the information I wanted to bring you, some points that are of importance, and the outline to my talk. I think that the committee should know by now that anti-HBc is, in fact, currently the highest prevalence marker among tests for voluntary blood donors. In general, the prevalence will be about 1 percent, plus or minus about 0.3 percent--that is, if you take routine blood donors and you test them by the standard algorithm anti-HBc and you end up with repeatedly reactive results.

However, these test results can in some cases be non-reproducible, that is, a reactive test on the same sample may not be reactive at some time in the future on the same sample, or may be non-reproducible across time, that is, the same donor may be reactive on one time and not on

another.

It's clear that some of the tests currently in use for donor screening have false positive results, and at least one manufacturer, Abbott Laboratories, has tracked down a cause of these false positive results to an IgM-like interfering substance which can, in fact, be eliminated by appropriate pre-treatment of samples or inclusion of a reductant in the test methodology, and I'll talk to that in a moment, too.

There are data, some of which I'll show you, that indicate that of the currently available licensed tests for anti-HBc the same sample will give different results on two different tests, in part due to some of these false positive outcomes. I'll also comment on the fact that a number of studies have been performed that try to associate either infectivity for hepatitis B virus or the presence of HBV DNA among blood donor samples. The general outcome is that there's an infrequent relationship between infectivity or DNA and anti-core, but it's certainly not--there certainly is some appearance of these two markers together.

As has been pointed out by Dr. Biswas, there is currently no confirmatory or supplementary algorithm for anti-core testing. There's a very strong feeling that re-entry may be desirable, and before finishing, I do want to illustrate some data which may cause some concern in the

committee in discussing these issues.

[Slide.]

So, currently, we really are interested in talking about three anti-HBc tests which are designed to detect both IgM and IgG anti-HBc. There's a bead format test which relies on inhibition of adherence of labeled marker to bead by the donor sample, Corzyme by Abbott. There's also a microplate-based test, which is a more familiar antiglobulin direct enzyme immunoassay currently marketed by Ortho. And we will spend a little time talking about the Prism test which is under development by Abbott Laboratories. This is a microparticle-based test. It's an inhibition chemiluminescent assay which includes a reductant which does deal to some extent with this false positive interfering factor.

[Slide.]

The reductant incorporated is a mild reducing agent. It does, as one would expect, produce IgM reactivity, but most of the IgM-related reactivity in the current inhibition assay turns out to be false reactivity, and the FDA and former committees have dealt with this issue at some depth, so I'm not going to say much more about it.

Studies do show that true IgM for anti-core are also HBsAg reactive, and the reductant is incorporated in the current diagnostic tests for anti-HBc and in proposed

donor screening tests, in particular the automatic Prism test.

[Slide.]

I want to show two data sets that relate to the current specificity of anti-HBc. The first represents all data derived from blood donor screening in 1996 in the Community Blood Center of Greater Kansas City, represents some 83,005 donors, all of which were screened by the Corzyme, the bead inhibition assay.

The initial reactive rate--number of initially reactive samples was 795, or almost 1 percent of the total number of donations. On repeat, the rate dropped to 0.67 percent, just slightly outside the margin on my first slide. But with this 0.67 percent, only 34 percent, or 189 samples, were judged to be truly positive for exposure to hepatitis B virus, and this true positivity was assigned on the basis of the sample also being found reactive in the antiglobulin direct test and/or reactive for antibodies to hepatitis B surface antigen. And you heard Cathy Cantilena talk about the significance of anti-HBs in this context.

Individuals who were anti-HBs reactive but had a record of hepatitis B vaccination were excluded from this particular definition of a true positive. These were data generated by Gary Tegtmeier. So this is an illustration of why there's interest in re-entry because of the relatively

large number of samples that are not confirmed, for example, by a second anti-core test.

[Slide.]

In another data set from the REDS study provided to me by Steve Kleinman, approximately 3 million repeat donations--this is donations from donors who had previously given--from five blood centers were analyzed, and within this 3 million repeat donations, there were 4,274 donors who newly presented with an anti-HBc reactive or repeat reactive result. So this doesn't represent the mass of blood donors. It represents blood donors who were previously non-reactive becoming reactive. These individuals were non-reactive for all other routine markers tested for blood donors.

Of those 4,274, 1,233 made donations subsequent to their anti-HBc reactive donation. Within those, 748, or 61 percent, of these donors were anti-HBc negative on all future donations, using the same test; 104, or 8 percent, showed fluctuating patterns, that is, one donation might be reactive, a subsequent donation might be non-reactive. And only 31 percent of this total continued to be anti-HBc reactive on all future donations.

[Slide.]

Also within this study population, samples were available of 742 of the 4,274 donations. These were the actual samples. Of these, 51 continued to be positive in

the test of record and were--or reactive, I'm sorry, and were anti-HBs reactive; 33 were negative in the test of record but were anti-HBs positive. So these are the subject donations. These are not subsequent donations. And of these two groups, 84 percent of this group--that is, the repeat reactive anti-core anti-HBs reactive, 84 percent were reactive in a second licensed test for anti-core.

Of the ones that had failed to continue to show an anti-core positivity in Corzyme but were anti-HBs reactive, 21 percent were reactive in a second enzyme immunoassay for anti-core.

Then there was the subgroup which would probably represent those that we would consider on the basis of Dr. Biswas' presentation as potentially available for re-entry. They either continued to be reactive in this sample by anti-HBc Corzyme or were non-reactive by anti-HBc and were anti-HBs non-reactive. And these had only about 14 or 7 percent positivity by a second anti-core test. These data represent values obtained from testing a subset of all of the samples. So that of these 657 potentially serologically re-enterable samples, 587 would be likely to have come through the sort of algorithm that Dr. Biswas presented us.

[Slide.]

Let me now speak briefly to the issue of anti-HBc and hepatitis B virus DNA or infectivity. My point here is

to indicate that whatever other data you've seen, among blood donors unselected anti-core positives are rarely associated with strong evidence of HBV infectivity, but this is not excluded.

In studied performed in Canada by Mo Blajchman in which a blinded study was performed on donors that had been screened by surrogate tests--that's ALT and anti-core--this is donors who had not been screened by ALT and anti-core, there was some 138 patients each of whom received at least one anti-core reactive blood unit. There were in the entire study, including these 138 patients, no HBV infections.

Recently, Dr. Sue Stramer had looked at anti-core reactives collected from the American Red Cross. These were reactive only by anti-core using our current test of record. They were tested by PCR for HBV DNA at a reputable reference lab. None of them was positive for HBV DNA.

In the previous data that I showed you from Dr. Tegtmeier, 78 of the true anti-HBc positives in his study--and these were selected as either having a high signal for anti-HBc and low levels of anti-HBs, or a relatively low anti-HBc and a high anti-HBs, within this group 5 of 78 of these true anti-HBc positives were actually HBV DNA reactive. One of these actually turned out to be reactive in a more sensitive test for HBsAg. So there are some data here that suggest HBV DNA may be present in donor samples

that are core positive or core reactive.

[Slide.]

In terms of the blood collectors, the desired outcome of a re-entry protocol is to be able to re-qualify blood donors who have a false positive anti-HBc result, and as Dr. Biswas pointed out, a donor can give after an initial reactive, but more than one reactive result on subsequent occasions results in a permanent deferral. And the re-entry is particularly desirable when a new test of record is to be implemented. For example, if a blood establishment were working with the current bead assay without reductant and were to move to the direct antiglobulin test or, when licensed, a reductant-based test for anti-HBc, because with the many individuals who were being deferred on the basis of the past test which has now been superseded by one with different characteristics and performance characteristics. So this really pretty much follows what Dr. Biswas said, and this is the AABB version, if you will. In order to qualify for re-entry eligibility, an individual would have to be anti-core positive on more than one--or repeat reactive on more than one occasion, would have to be negative for anti-HBs or for anti-core by a second licensed test, and this is perhaps a difference from what Dr. Biswas said--sorry. Non-reactive or not tested by these additional tests to be eligible for the re-entry sampling and further evaluation.

If reactive for anti-HBs or anti-core by a second licensed test, the individual would not be eligible for re-entry.

[Slide.]

We would suggest that a reinstatement sample be drawn subsequent to this determination of eligibility. We chose greater than or equal to 90 days. Let me assure you that this was a figure drawn entirely out of thin air. The concept is to at least permit evolution of any serologic response, as has been outlined by Cathy Cantilena, and would certainly not challenge a 56-day figure here.

The reinstatement sample would have to be tested for HBsAg, for anti-surface antibody, and we suggest for anti-core using a second or different licensed test. And any reactivity in any of these samples would render the donor not eligible for further donation. If non-reactive on all of these tests, the donor would be eligible for re-entry.

At this point, my colleagues would urge me to sit down and shut up because we've arrived at the same point as Dr. Biswas.

[Slide.]

However, I do believe that there are some data that generate some concern, and the committee may need to think about these in considering whether it's appropriate to go above and beyond this outline algorithm.

Dr. Cantilena discussed in very nice detail the fact that in the presence of anti-core there was definitive evidence of viral survival, at least in the liver. There are some studies--she mentioned one, not necessarily in the donor population--that show a higher frequency of HBV DNA with the presence of anti-core, and I'm going to draw your attention, although perhaps I shouldn't, to some recent data from a clinical trial. I believe that these data have some deficiencies and should be subject to review before policy decisions are made on the basis of these data. But the question that I'm really asking you to think about is what is the significance of a discordant result in two anti-HBc tests.

[Slide.]

This represents some data from an American Red Cross component of a formal clinical trial in which the reductant-based anti-HBc automated from Abbott, the Prism test, was compared against our test of record, the Ortho antiglobulin direct test. There were 4,152 samples that were evaluated. These were routine donor samples. And both Ortho and Prism found 19 of these to be repeat reactive for anti-core. Of these, one was DNA positive.

There were also seven samples that were reactive by Prism and non-reactive by Ortho. Of these, 3 were reactive or positive for HBV DNA. Conversely, there were

seven samples that were reactive by Ortho, non-reactive by Prism; one of these was DNA positive; 4,119 samples were concordantly negative on both tests, were not tested for DNA.

These two samples were negative for all HBV serologic markers, but two of these three had a weak anti-HBs finding. Interestingly, in the same clinical trial, there were a number of other blood centers that did not generate any DNA positives, and we believe that these data need to be looked at very carefully before they are taken to be the truth.

[Slide.]

The consequence of this kind of finding is that maybe at least for the development of data or potentially for the development of a bulletproof re-entry algorithm, one might want to recognize the need for two anti-core tests to be non-reactive. I've put test of record here. I think not necessarily test of record, but definitely a test which is licensed and which is different from this licensed test. And this would allow you to eliminate, for example, Corzyme reactives whilst following through on two other licensed tests once another test is licensed.

Alternatively, one might want to consider, although one would have to use an investigational test, whether to permit re-entry for individuals who were non-

reactive on HBV DNA. So this would be a choice of additional steps if there were nervousness about stopping the re-entry protocol at this point.

That constitutes our presentation. Thank you very much for your time and patience.

DR. HOLLINGER: Thank you, Dr. Dodd.

Robin, I think you had some questions that you wanted to put up at this time, the FDA proposal and questions for the committee. Then we'll have--if there are any--comments from the public. Then we'll discuss it further by the committee.

DR. BISWAS: These are the questions for the committee:

Does the committee agree that a donor who has been indefinitely deferred because of having tested repeatedly reactive for antibody to hepatitis B core antigen (anti-HBc) on more than one occasion may re-enter the donor populations,

(a) if, after a minimum of eight weeks subsequent to the last repeatedly reactive anti-HBc test, a new sample is collected from the donor and this sample tests negative for hepatitis B surface antigen (HBsAg), anti-HBc and antibody to hepatitis B surface antigen (anti-HBs) in FDA-licensed assays; and

(b) if, at any time subsequent to the negative

tests for HBsAg, anti-HBc, and anti-HBs, the donor presents at a blood center and fulfills all suitability criteria for donors of whole blood and components?

Question 2: If the committee does not agree with question 1 above:

(a) should donors who test repeatedly reactive for anti-HBc on more than one occasion remain indefinitely deferred; or

(b) does the committee wish to suggest an alternative re-entry algorithm?

DR. HOLLINGER: Thank you.

I want to open this up then to anyone who might want to speak to this issue from the public. At this time it would be time to do so. Yes, please, Jacqui?

MS. MELPOLDER: I have a problem with the--

DR. HOLLINGER: State your name, please.

MS. MELPOLDER: I'm Jacqui Melpolder, NIH Clinical Center Blood Bank. I have a problem with people who are vaccinated who would never be allowed to re-enter, and I've had a number of people that I've had to put on deferral who give a very low level reactive on two different manufacturers' assays.

The other problem we're going to run into is every baby that's born--in the United States, anyway--the parents are told to vaccinate. So you're going to be running into a

problem now ten years down the road of running out of donors that anti-core pos.

DR. HOLLINGER: Anyone else like to speak? Yes, please?

MR. McPHERSON: Jim McPherson from America's Blood Centers. Obviously we're supportive of what Dr. Dodd brought before the committee. I think it's important to say that we've been struggling with this issue for ten years. We've deferred, permanently deferred over a million perfectly safe donors over the last ten years who are core positive, most of them very angry that they can't be donors anymore. And if you don't think donors get angry about that, well, I'll take your name and phone number and have some of them call you.

As Dr. Dodd noted, it is still the highest marker, and yet we also know even those donors who are true positives, the vast majority, in fact, in our experience, probably virtually all of them, represent no danger to the recipient. But we err on the side of caution by continuing to defer them. What we're talking about here is taking the next step of trying to re-enter those donors who we believe are truly false positive, and it's long past time we've done this.

Thanks.

MS. HOPPE: Ann Hoppe from Serologicals. Although

the source plasma industry in general does not test each donation for core, there are situations where we do with in vitro diagnostic source material donors, et cetera. It becomes a particular problem because oftentimes you have two donations in a single week, and you don't have the results of the first one back before the second sample is in testing. So you can end up with a valuable donor who is permanently deferred because he happened to be tested twice, either with an erratic lot of reagent or happened to have two very borderline results. So there ought to be a special exception, I believe, for in vitro diagnostic source material or some interval between the two tests which count before you permanently defer a donor based on those tests.

MR. NAGLER: Rick Nagler from the Hemophilia Federation and Chairman of the Hemophilia Association Capital Area. If you're going to consider doing this, as someone who puts this stuff into my own veins, may I suggest that perhaps one way to phase it in and get some knowledge about it is in your donor profile ask a person if they have been vaccinated for HBV, and ask the same other questions, same other risk questions. Perhaps what you could do then is if they are okay with the other questions and are suitable for donor, you could include those and then see what the results turn out to be.

DR. HOLLINGER: Are you speaking for the clotting

factor concentrates now primarily or something else?

MR. NAGLER: I'm speaking for blood in whole as the recipient of cryoprecipitate and having had been contaminated once with it. I mean, I've got A, B, and C. You know, do we have D, E, F, and G and all this? But, you know, I've had it once, and it's not a fun thing to go through. But perhaps if you seriously are considering it, at least start out small and start out in the safest way possible, and start out by letting those that have been vaccinated and are safe in all other manners and go from there.

DR. HOLLINGER: The only reason I was asking that question, as you know, the source plasma, recovered plasma, does not eliminate anti-core plus in the instance of blood now at this time. So that was the only reason for mentioning that.

MR. NAGLER: Okay. Thank you.

DR. HOLLINGER: Anyone else from the public?

DR. HOLMBERG: Jerry Holmberg, Navy Blood Program. I agree with Dr. McPherson's comment about re-entry and the number of donors that we've deferred in the past. I also can related to the anti-HBs that would be present in the immunized people, but I think that the algorithm that Dr. Dodd presented is a viable alternative to that. And I think that that should be considered.

DR. HOLLINGER: Thank you.

All right. If there are no other comments from the public, I'm going to close that portion of the session, and we'll open it up now for committee discussion of the questions that have been raised. Any comments? Yes, Dr. Linden?

DR. LINDEN: I'm fully supportive of this concept. I think we have been deferring a large number of people unnecessarily and upsetting and causing concerns among a large number of people unnecessarily, and that is of concern to me.

I have two questions for FDA, Dr. Biswas or--oh, there he is. One, why is DNA testing for HBV not part of your algorithm? And, secondly, what is the agency's position on this question about people who have anti-surface because they've been vaccinated?

DR. BISWAS: In regard to HBV DNA testing, that might become a part of a re-entry algorithm at a later date when the HBV--if and when the HBV DNA tests are approved and regulated by us, because at the moment the tests are done all over the place, we don't really know too much about them. You know, there are variations in sensitivity and specificity. So I think at the moment it's not really a--you can't really put it in an algorithm simply because of the inconsistency of the current tests.

In regard to vaccination, that's a very good point, and indeed that is something that we take on advisement, and when we--if and when we come up with an algorithm, we'll take that into account.

DR. LINDEN: Thank you.

DR. HOLLINGER: Yes, Mark?

DR. MITCHELL: I guess the question, again, to the FDA is about vaccination and whether it does product anti-c.

DR. BISWAS: No, it does not.

DR. MITCHELL: Okay.

DR. BISWAS: No, it does not.

DR. MITCHELL: So it--

DR. BISWAS: If a person develops--I'm not a vaccine expert, but the situation is that when somebody is vaccinated and responds, they develop just anti-HBs. It's only when you have--when somebody has gone through the disease, has been actively infected by HBV, that they do then later develop anti-core.

DR. MITCHELL: Okay. So, then, people who were vaccinated should not be deferred at the present time?

DR. BISWAS: That's a sensible conclusion, yes.

DR. HOLLINGER: Yes, Dr. Verter?

DR. VERTER: I just want to clarify something, and I'm going to address it to Dr. Dodd, I think, because you're the only one with numbers. But, believe me, if you've been

here before, you know--

DR. HOLLINGER: Even though they're incorrect, Roger.

[Laughter.]

DR. VERTER: Well, I'm not going to address that issue, but you know that I always say where are the numbers when I'm around here, so thanks for the numbers.

But in the two studies you presented--and I did the math rather quickly--I seem to get very varied incidence cases, or at least estimates of how many cases or the incidence of HBC. In the Kansas City data, it appeared--assuming the IR and RR are indistinguishable, a little less than 1 percent. In the REDS, it looked to me like it was maybe one-seventh of that. So--

DR. DODD: Yes, I'm sorry if I didn't explain the difference adequately.

In the Kansas City data, those data represented all donors who presented over a period of one year. So that would include first-time donors and donors who had been previously tested.

The data from the REDS study was selected to represent, first of all, only donors who had a record of previous donation, and the data that I showed you were those individuals whose previous donation had been negative for anti-HBc but on the current donation were reactive or repeat

reactive for anti-HBc. So this would represent, first of all, a screened population; secondly, either incident appearance of true anti-HBc or new appearance of non-specific anti-HBc. I think that one would anticipate that the positive predictive value within that group would be much lower than that which you would see for a total donor population.

Does that help to explain the differences?

DR. VERTER: Yes, and I appreciate that. What I was trying to get at was trying to--I'm looking at it in a kind of naive way of seeing what the risk-benefit is. The risk is to the people who obviously are going to get this, and I don't know what the consequences of getting hep B are, by the way. Maybe Blaine or someone can tell me that. But the benefit is additional donors who are entered into the pool--well, one benefit, at least to the blood banking community and to the people who need the blood and the components. But when I was looking through those numbers, it didn't seem to me like there was a humongous number, although someone said a million. So that's what I was trying to get at.

From your numbers, is there any way of saying how many donations or donors per year potentially are being excluded?

DR. DODD: I would look probably at the Kansas

City data as giving best guidance in this environment, and it would suggest that somewhere perhaps as many as 60 percent of those donors who were repeatedly reactive in a core test could be re-enterable. And that would--actually, in this particular case that would boil down to about a half--0.4 to 0.5 percent of all donations in the U.S., and you well know that that reflects about 8 million individuals who donate each year. So it is a meaningful number in aggregate.

Am I still note--

DR. VERTER: I agree with the 0.4 percent.

DR. DODD: Okay.

DR. HOLLINGER: Roger, stay up there.

I think the question that Ms. Melpolder brought up about anti-HBs becomes a real critical issue if you're going to use that as an eligibility criteria as more and more of the population become immunized. If I'm reading this correctly and you go back after repeat reactive anti-HBc and then you do HBs antigen, anti-HBs and anti-HBc, and if any of reactivity of those would make you ineligible, then that would be a real problem for you again.

DR. DODD: I think, Blaine, I was remiss in bringing up that point. It was a point that the AABB group had discussed in some detail, and, in fact, in one version of the proposal, it was specified that anti-HBs should not

be a basis for rejection if it was clearly associated with a history of vaccination. And I think it's reasonable to state, in extension to Robin's answer to an earlier question, that there had been some cases in the early trials of hepatitis B vaccine where vaccinees did, in fact, develop anti-HBc, but this was because they were judged to have been infected prior to receiving the vaccine. It was high-risk, high-incidence population. And I think that one could be confident that those individuals would likely continue to be kicked out by the anti-core requirements in the algorithm.

So it was indeed part of the AABB's original recommendation. We had confidence that the committee and the agency would pick up on that issue, but I'm glad it's being brought out.

DR. HOLLINGER: Do you know of any cases of hepatitis B that have occurred in a patient who is anti-HBs positive only, regardless of whether they had the vaccine or not?

DR. DODD: I don't know of any. That's not to say that it doesn't occur. I just don't know.

DR. HOLLINGER: You know, very early, when we looked at these issues--oh, yes, please?

DR. TABOR: The question is whether you can have a primary antibody response to a naturally acquired infection; correct, Blaine? You're asking whether in a naturally

acquired infection you can manifest it only by the presence of detectable anti-HBs?

DR. HOLLINGER: No. Because some patients will have anti-HBs and don't give a history of vaccination. It could be because they acquired it when--as you know, back prior--and I've said this before. Prior to 1970, about 0.8 percent of the immune globulin preparations had HBs antigen in it, and some patients actually were immunized probably because of that. So they may have an anti-HBs response without having an infection.

I can't recall of a patient I've seen where they've lost their anti-core and just retained their anti-HBs. And the reason I started to bring this up is because early studies back in '75, '78 or so, when radioimmunoassays first came out, and we looked at transmissibility to persons who received anti-HBs positive blood or anti-HBs and anti-HBc positive blood, we saw no cases of post-transfusion hepatitis in a fairly large proportion of studies. That was not only with our study, but I think that included also samples from the NIH as well. So I just ask that question because I don't know of any, and it would be important to know that.

The other thing, too, Roger, I always feel a little lost here with numbers because I don't have the numbers that are really important to me. For example, I

need to know when I look at this and try to make a decision from my own personal viewpoint about risk, I need to know something about the sample, the cutoff ratios. I am a firm believer that that has a great deal to do with false positivity, and so when someone tells me about 5 of 78 true anti-HBc positives were HBV DNA positive, I'd like to know more information about those 5. Were they--what was the anti-core ratio in those? I'll bet that they were relatively high, probably. I'd like to know whether there was anti-HBs in them. And they're probably negative, but I'd like to know that. I'd like to know what their anti-HBe status is also. That would be another validation point if it were positive. If it wasn't positive, it wouldn't bother me because a percentage of them are not positive.

And the same with the 200 anti-core positive only donations tested by PCR for HBV DNA. Again, I would like to know--I would have liked to have had that data because it's the only way I can come to grips with the significance of this large number of patients out there, many of whom I think are false positive.

DR. DODD: In the case of the Kansas City data, the DNA studies were done on 78 donations. I think 44 of those were defined as high ratio anti-HBc. I have the data back at my chair, and I'll tell you if I've got it wrong. Forty-four of them had a ratio of--a cutoff to sample ratio

of 5 or greater, plus or minus anti-HBs, I believe. And four of the DNAs came from within that group. The other 34 has values below 5.0 and the one came from that, but that might have been picked up by a different HBsAg test.

For the Red Cross data, I don't think I have those data. Dr. Stramer is in the audience. I don't know if she can dig the data up from her recollection. Apparently she can.

DR. STRAMER: Sue Stramer, Red Cross. Prior to answering that question, I'd like to also add that the Kansas City samples weren't tested for HBe, and Roger did state correctly regarding four of the five of the DNA positives having high S to CO ratios or cutoff to S ratios on the test of record, Corzyme test.

The 200 anti-cores were collected in sequence. They were not selected for S to CO ratio on the Ortho test. They were just sequentially collected anti-core repeat reactives that were non-reactive for other viral screening tests and were normal for ALT. So this would represent the entire gamut of anti-core reactivity.

DR. HOLLINGER: Thank you, Sue.

Yes, Dr. Nelson--oh, excuse me just a minute, Ken. Go ahead, Jay.

DR. EPSTEIN: Thank you.

Roger, can you answer for us the question how many

units potentially DNA positive would be allowed into the blood supply if we were to adopt in the one case the FDA-proposed algorithm and in the other case the AABB-proposed algorithm? And I ask this because I think the data of greatest concern that I heard this morning are that there are DNA positives among samples that have discordant assay results for anti-core. And you've showed us that there are sero-inconsistent donors over time, and you've showed us that if you do reflex testing of positives in one assay with the other assay, in either direction, that you can find positives in the discordants.

And just to make clear what I'm talking about to the committee, the FDA algorithm would permit you to retest the sample with either a new test or the test of record. The AABB proposal requires that you use a different test than the test of record, so that becomes material.

So I think the bottom-line question here is: How many units potentially infectious would potentially enter the blood supply if we do this at this point under these proposals?

DR. DODD: Jay, I would have to say that I haven't seen enough data to allow me to make that estimate, but it was just the data that you presented that led me to suggest that one should have two separate anti-core tests concordantly non-reactive for appropriate re-entry, or an

alternative would be to look for DNA. But I think that there are very little data that really speak in detail to that critical question, which is how often does a discordant sample--that is, reactive by one anti-core and non-reactive by another--actually contain detectable DNA.

I do have to repeat that the data that I showed you I presented as a caution, and I believe that there may be some other explanations for that. But it's data and it has to stand at the moment.

If we had the answer to your question, the whole thing would be a whole lot easier. I'm sorry.

DR. HOLLINGER: Dr. Nelson?

DR. NELSON: This has been an extremely difficult issue because I think we're--the risk is clearly low with either algorithm, but it still may not be zero. And I just wondered if there's any way, depending on what new testing algorithm is adopted, either--particularly if a new one is adopted, to set up a mechanism to do some screening to see whether or not we made the right decision by following the recipients of people who have received blood from donors that are transiently positive or that are--you know, whatever, that re-enter. And I realize that's maybe a difficult thing to do, but it would be certainly worthwhile doing because the consequences of hepatitis B can be serious. They can end up in cancer, liver cancer, or they

can end up a chronic carrier state, and it's not always a--it may be a self-limited disease, but it's not always trivial. And we should certainly try to prevent transfusion-transmitted.

It's interesting that the data in our study where we followed almost 15,000 donors who had received 150,000 units, we found evidence of hepatitis B transmission, but actually, one interesting thing was when hepatitis C testing was introduced, the rate of hepatitis B transmission was also reduced. So that although core testing was introduced as a surrogate for C, it's true that C testing is probably also a surrogate for B. So, you know, it may be not a large risk. It may be close to zero. I don't know whether it's zero. But it would be really nice in this selected--if the algorithm is changed, to set up a mechanism to do it by--to trace people who have received these units.

DR. HOLLINGER: Ken, in that early study, the one that you all did, you didn't have the donor samples, did you, to go back to?

DR. NELSON: No, we didn't, and that was a problem. And, you know, it's difficult because people get hepatitis B by being in the hospital from all the other things that happen to them in addition to blood transfusion and through the community. And so it's, you know, not an easy--to get the convincing data is not always easy.

DR. HOLLINGER: Mary?

DR. CHAMBERLAND: I wanted to ask if people thought before a new algorithm was instituted whether or not it would be possible to do further evaluation of--following up on the comment that you made, Blaine, about getting more information about signal to cutoff ratios, I mean, it seems what we've heard is that a very small proportion of these core positive people only are likely infected, you know, by evidence of HBV DNA. And so would there be a way to empirically study that by looking at signal to cutoff ratios to see if you could find the highest risk within those core only and whether that would be a way to approach this, you know, simply the collection of more data, and if it could be done in a fairly timely way, because the Red Cross data, as Sue indicated, was unselected data. But I'm wondering if we could look at that and try and get a better handle on signal to cutoff and try and cull out the highest risk.

DR. HOLLINGER: If we're not concerned about anti-core as a surrogate marker for something else at this point, first, from my standpoint, I perceive anti-HBc, anti-HBs positive blood as safe from getting hepatitis--from not getting hepatitis B. It would not--that would not be an issue for me. And if that were used as a cutoff level, that is, if the person has anti-core repeatedly reactive, and you do an anti-HBs on it and that one is positive, I could--I

mean, I can certainly feel very comfortable about allowing that blood to be transfused in an individual because I've seen no data to suggest that this is as at risk a product.

Now, what was talked about before about the risk of patients who--donors who have that and their livers are given to somebody else who are immunosuppressed, that's a whole different ballpark. This is like apples and oranges here, and we recognize that that is a potential risk. If you give the kidneys to another group of patients, they don't get hepatitis B. It's only in those individuals, the liver transplant patients that you see the hepatitis B occurring, and in some of this group of patients, which is why they've sort of withheld using donors who are anti-core positive.

But, anyway, from my standpoint, having an anti-HBs and anti-HBc would be a reasonable place for me to see that they could come back into the system. I'd be less comfortable about high anti-core positive only to be put in.

Yes, please?

DR. NELSON: Instead of excluding the false positive reactions, you want to exclude the true positives so they have protective antibody.

DR. HOLLINGER: Yes.

DR. NELSON: But in terms of the--what would that do to the numbers of donors that would re-enter? I think it

would probably be a smaller number, wouldn't it?

DR. HOLLINGER: Roger, do you have a question? Because that's an important issue.

DR. NELSON: I think that in this country--in China it would be the majority, but I think in this country it would be the smaller number.

DR. DODD: I think that that's difficult. Operationally, it's difficult because likely you would continue to have a reactive core result in the donors who you'd requalify by this algorithm. So you'd have to develop a mechanism which said that they could continue to donate with a reactive core result only if they sustained an anti-HBs or something like this. And I think it would be difficult. It would be difficult if one were to be inspected.

On the other hand, I wholeheartedly agree with you, and this is the actual algorithm for donor screening in Japan, as you well know, and they have a very low to vanishing levels of post-transfusion hep B. That is, they will transfuse a core positive if it's supported by a strong anti-HBs.

But I would like to make another comment in the context of the algorithm that the AABB proposed and somewhat in response to Dr. Epstein's question, which is that given that there are different blood collecting agencies using

different primary tests for anti-HBc, it should not be hard to look at some sort of cross-over experiment where you looked at concordant and discordant anti-HBc results perhaps for HBV DNA, and this probably wouldn't require quite as much funding as Dr. Nelson's suggestion. And I think it could be achieved appropriately, provided we were encouraged to do it.

DR. HOLLINGER: Yes, Dr. Boyle?

DR. BOYLE: I'd just like to make one observation. Whenever we're looking at a new product to be licensed, even one that is effectively a generic, though not viewed as such, we do require the prospective collection of data to basically assure ourselves of the safety and efficacy. Seeing a million donors that have been positive on a hepatitis B marker re-introduced into the marketplace or into the blood supply, I certainly would like to make sure that we do have the data to be sure that we are not creating a serious problem and that we treat that just as seriously as a new product, or at least seriously.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: Yes, Blaine, I just wanted to comment. You know, the FDA is aware that a positive anti-HBs indicates recovery from infection and that the blood is hepatitis B safe. The problem you get into if you consider re-entering those donors is that we do have the January 1995

NIH consensus workshop recommendation that we should not accept donations from people who actually do have a history of hepatitis B because of the issue of HIV surrogate risk. So we sort of get stuck on the horns of a dilemma. We know that's a useful tool to mitigate the hepatitis B concern, but now you've got an individual who falls epidemiologically in a cohort that may have risk for other transmissible disease. So we have not gone in that direction, or at least we won't until we can lay that question to rest.

DR. HOLLINGER: That's what I asked. You still look at anti-core not only for B but also as a surrogate marker for something else. Is that correct?

DR. EPSTEIN: Well, our policy, as it was established in 1991, based the recommendation for anti-core screening only on prevention of hepatitis B. However, there has been ongoing dialogue, and we remain mindful of the consensus committee opinion that such testing is still a useful surrogate for HIV risk in the window period. And I believe that current epidemiologic data still continue to support that. I believe the estimates that were brought forth at that time were that between 25 to 42 percent of all the HIV cases in the window period would have a hepatitis B marker. So if you're able to prove that it was hepatitis B, you really would have to put to rest the surrogate marker question for HIV to go forward with an algorithm on that

basis.

DR. NELSON: I was at that consensus meeting, and that's correct, and it was brought up that now that there was good testing for hepatitis C, did we need it as a surrogate? And it was--the strongest argument for keeping it was that it was a surrogate for HIV, even more than the risk of hepatitis B transmission. I don't know whether that--I don't know what the data are currently.

DR. HOLLINGER: Yes?

DR. MITCHELL: The data that was presented, although I missed part of it, but the data that was presented, I guess I feel that we should try to have the safest blood supply possible. I also look at the markers not only as an indication of hepatitis but also as an indication of high risk for other diseases. And so, you know, there's not an acute shortage of donors at this time, and so, you know, my approach theoretically would be to look at protecting the blood supply right now from things that we know about, but also things that we don't know about.

I mean, the liver transplant study does bother me because people who have received blood are more likely to be immune-suppressed. Yes, the chances of them getting a hepatitis C reactive antibody I think is very, very low. But, again, I think that it represents a higher risk, donors who are coming back into the pool, and so that's why I'm

concerned.

DR. STRAMER: Thank you. Sue Stramer again. I have two comments.

Firstly, to Dr. Epstein's comment regarding the January 1995 consensus conference, that was prior to the implementation of P24 antigen and prior to the implementation by many of the volunteer blood sector in 1999 of HIV GAT testing. So that's an issue that probably needs to be looked at again, because I don't know of 25 to 42 percent still holds up. It does not with our antigen positives that are also antibody positive. Only 10 to, at max, 20 percent of those still retain anti-core reactivity. So those data are probably worth reinvestigating for the surrogacy of HIV.

And then regarding the comment that was just made by the committee, blood safety and recipient safety was the number one concern that we looked at in the anti-core re-entry algorithm from the AABB, as Dr. Dodd presented. And, again, by adding that last tier, by adding the second test, that is, test of record, whether it's your original test or newly implemented test, must be negative as well as the second licensed core test or DNA investigational test not done willy-nilly by many laboratories around the country, but regulated by FDA through the IND process, all of--either of those two would have eliminated every DNA positive in the

study. So it would have assured safety if we're using DNA positivity or two anti-core tests to define safety.

DR. HOLLINGER: Yes, Dr. Kagan?

DR. KAGAN: Yes, as I understand it, we're still allowing donors who are core positive for the first testing to be donors. Do we have any data on transmission from that population of patients, and do we have any indication that maybe that group isn't any different than a proposed re-entry group in terms of their possibility for disease transmission?

DR. BISWAS: Yes, you're right that a donor--what you have to understand, though, is that although a donor who is repeatedly reactive the first time around--I mean, that unit is not transfused, so there is no data.

Blaine, I just wanted to make one or two other comments. Please understand that both of these--both the proposals--or the intent there is to show that the person did not have hepatitis B in the first place in regard to the question about safety of the blood supply. The other thing I'd like to say is that in regard to the 1995 NHLBI meeting, you have to understand that if somebody is anti-core, truly reactive, truly positive for anti-core, it means that that person had some time in the past a hepatitis B. And that works into what Jay was saying, that anti-core true positivity is a surrogate, seeing that HIV and HBV

epidemiologically are sort of somewhat similar.

DR. HOLLINGER: Roger, do you want to make your case for the greater than 90 days versus 8 weeks?

DR. DODD: No. It was pulled out of thin air.

DR. HOLLINGER: Oh, you just--

DR. DODD: Yes.

DR. HOLLINGER: Any other questions? Yes, Joel?

DR. VERTER: It's not a question. It's kind of--are you about ready to call for a vote?

DR. HOLLINGER: We're coming close, although I think Mary has a comment.

DR. VERTER: This may break protocol a little bit, but I have a kind of sense where people may be going, and I want to persuade them to do something else.

DR. HOLLINGER: Okay. Hold your thought just a minute.

Mary, do you have a comment?

DR. CHAMBERLAND: I just had a comment or a question. The concerns about anti-core serving as a surrogate for persons who may be infected with HIV but tested within the window period, wouldn't that concern be addressed by either the AABB or the FDA algorithm because there's an interval that's required between the two tests of eight weeks or 90 days? And so, clearly, anybody who would be in the window period for HIV on the subsequent testing

and then presentation at the blood bank for donation would have to test HIV negative, and I think we would all be reassured that they were known.

DR. HOLLINGER: Thank you.

Jay?

DR. EPSTEIN: I would disagree with that, Mary, because you're positing that they have a dual acute infection, whereas I think the way the epidemiologic data work is if you have this one marker, it means you're at risk for the other infection. The timing might not be that you just got infected at the same time.

DR. CHAMBERLAND: I agree. I thought I--perhaps I misunderstood, but I thought that people who had attended the consensus conference suggested that the reason for retaining the core testing was to cover issues related to window period for HIV.

DR. EPSTEIN: Yes, I agree, but--

DR. CHAMBERLAND: So that would be addressed, but general overall risk--

DR. EPSTEIN: --it doesn't mean that you were--right. But I think the idea is that you have a higher likelihood to be in the window period any time you're later tested.

DR. CHAMBERLAND: If you're at risk.

DR. EPSTEIN: Right.

DR. CHAMBERLAND: Right.

DR. EPSTEIN: It means that you're a member of a risk cohort. It doesn't mean that that particular collection was the high-risk collection. It could be your next one, your next one, your next one.

DR. CHAMBERLAND: Right. So the issue really is risk behavior, not window period.

DR. EPSTEIN: Right, right.

DR. CHAMBERLAND: From the consensus conference. Okay.

DR. HOLLINGER: Dr. Nelson?

DR. NELSON: One way to merger your two proposals, yours requiring surface antibody, would be if somebody is core positive as a donor that they get hepatitis B vaccine and then they can re-enter. Therefore, you know that they've got--you know, they're protected and--whether they were false positive or not. And as I recall, Paul Holland did a study of core positive donors and found that most of them had a primary response to vaccine--nearly all of them--suggesting that the core positives were false positive. But, you know, that would be the safest donor you could find, probably, with regard to hepatitis B.

DR. HOLLINGER: Unless they're a different sub-type than what the vaccine is, in which case they'd make an antibody to that other sub-type and still be affected. I'll

talk to you about that later.

Joel, you wanted to--

DR. VERTER: A couple of comments.

DR. HOLLINGER: Go ahead.

MS. MELPOLDER: Jacqui Melpolder again. I just have a question about--I can't quite figure out what (b) is saying.

DR. HOLLINGER: I got the impression they're saying if you consider them eligible, they still have to be a suitable blood donor. They can't come back in and be a donor unless they pass all the suitability criteria that they would--that any other donor would have. Is that correct?

MS. MELPOLDER: But they could come back and donate and then if they're--if everything's okay--I mean, you're sort of--

DR. BISWAS: Well, if the donor was deferred, the donor would be tested separately for anti-HBs, anti-HBc, and HBsAg, and that's not a donation. That's not a donation. And then any time subsequent to that they could then go to the blood collection center, be drawn, and then that collection would be tested for everything that it's usually tested for, and, of course, the donor go through the whole screening process.

There are two separate actions there.

MS. MELPOLDER: Okay. What happens if they come back after they've tested negative, they donate, and then they're positive again? Do you put them on a permanent deferral or do you allow them to go through the algorithm again?

DR. BISWAS: I don't know at this stage.

DR. HOLLINGER: Hopefully, it will be a small number, maybe.

DR. BISWAS: But thanks for asking the question.

[Laughter.]

DR. HOLLINGER: Yes, Joel, you wanted to clarify.

DR. VERTER: Actually, that last question is part of the reason for my statement.

This committee has a number of responsibilities, and they often run in conflict. And to me, this brings up three of them. One is the safety of the blood supply. One is the availability of an adequate blood supply for those needing it. And the other is the responsibility to the donor to be truthful and accurate in the statements we provide them. And that's the order I would just them in.

So having said that, I find I personally am in a position where industry is offering a more conservative approach than the government, which is unusual, and so that's why I'm a little nervous--well, I'm not going to vote for the question because of the second part.

But in addition to that, I wanted to make the following suggestion: We have a number of agencies and industry here with a lot of dollars at their disposal--the NHLBI, the CDC, AABB, and probably the Red Cross. I don't think it would take a tremendous amount of dollars to do a study, either a case-control or a small cohort prospectively, to answer almost all of the questions that have been posed by this committee, including the one that was just last raised, which is one of the things that was bothering me, that is, what is the probability that a donor comes in, is repeatedly reactive, then is tested, is negative through the AABB or the FDA proposal, donates, what's the probability that he is still or she is still positive but we don't know it yet or that he becomes positive later?

I think those are all reasonable questions, and I think they could be answered in a modestly funded study that's well designed.

DR. HOLLINGER: The other thing, too, is these tests do vary. If you have two tests out there and you have somebody who gets a false positive, let's say, by one test, that you're doing in the hospital setting or in the blood bank setting, and then you go and repeat it with the second test, which may be negative, for whatever reason, if that patient comes back in and gets retested now by the same

thing, it's probably going to be positive again on there, which would exclude them a second time around. So I can see these issues coming up, and until the test probably is cleaned up a little bit to eliminate that--and the reductant is, I think, a step in that direction, in my opinion--then that's going to be a real issue on this re-entry because I think they'll often come back as positive again.

But, anyway, let's--yes?

DR. OHENE-FREMPONG: I know we're getting close to decision time, but the issue of immunized donors I don't think has been addressed, as long as we have the anti-HBs in there.

DR. HOLLINGER: I agree. I think that's an issue which should be brought in, and I think we could add it. But, yes, go ahead?

DR. TABOR: I would like to differ with the opinion that industry is being more conservative than--

[Laughter.]

DR. TABOR: And I'm not often in the position of competing for who's the most conservative, but the entire issue of re-entry of anti-core positive donors is being addressed today because of an intense interest by the blood collection industry and the donors themselves to re-enter these individuals. If it were really left to FDA, we probably would keep these repeatedly anti-core positive

donors excluded. But there are scientific reasons to reconsider it.

DR. HOLLINGER: I think we ought to deal with the issues here and maybe vote on this. As I said, the issue I have is also about what you're bringing up, for example, the antibody, and I'd certainly--and we dealt with that at one point. You'd almost have to say something to the effect that in that first (a) part, "after a minimum of eight weeks subsequent to last repeatedly reactive anti-core test, a new sample is collected from the donor, and this sample tests negative for both HBsAg, anti-HBc, and antibody to HBsAg," and then one might want to put in there "unless a solitary anti-HBs test is associated with a history of HBs antigen vaccine." That is, if they were negative for HBs antigen, negative for anti-HBc, but positive only for anti-HBs, and t person says, you know, I received the hepatitis B vaccine, then that might not be one, as you mentioned, that would exclude them. Because if you don't put that in there, I will tell you that as time goes on here, you might as well just forget this algorithm because everyone's going to be--not everyone, but most patients are going to be anti-HBs positive.

So that would be the only thing that I would want to see in that first question, is to change that part, and the rest of it we could vote on it, but I'd like to hear

some comments on that. Yes, please?

DR. BUCHHOLZ: Do we have any information in terms of a donor that is anti-core positive and comes back, what the percentage of those people are that continue to test positive as opposed to test negative as opposed to test plus or minus at various subsequent testings? Because this issue of if I'm doing a certain test, I go and do something special to requalify this donor, the donor comes back in, he's going to go into my regular test again and very likely to be positive, I would assume, if this is a test specificity device. So is there information on how reproducibly positive these reactors are?

DR. DODD: A couple of points, Don. I think I showed some of that, at least for people who become positive after being non-reactive, something like 61 percent fail to maintain their positivity. I think at the inception of anti-HBc testing, it was something very similar, I think only about 40 percent of individuals maintained their positivity as a subsequent visit. It's certainly been published. But I would draw your attention to the main driver of this recommendation at this time, which is the situation where you change to a test that eliminates previous false positive causes.

DR. BUCHHOLZ: That was a single retest, those data that you just cited?

DR. DODD: I can't remember the data in any great detail. It all came out in the mid- to late '80s. It's out there in Transfusion. If the committee needs a reference, we can dig it up for them.

DR. HOLLINGER: As I view this, I think the real reason that they're asking is, if you really probably want to know about it, it's that you have all this group out there that they'd like to bring back in. And if you do now get a test that has more specificity, that has greater specificity, it allows you now to bring these patients in to be retested for the purpose of being blood donors. I don't think it's right now, you know, we'll change around and do this. Am I correct in that, Roger?

DR. DODD: Yes.

DR. HOLLINGER: So I think that's really the whole idea, that hopefully there will be tests with more specificity; then you could now bring these groups back in and test. So I think that's what they're looking for.

DR. BUCHHOLZ: If that's the case, is it premature to act on this until those tests are, in fact, in place? I mean, if that's the rationale, that new testing is going to make this go away, is this an appropriate action in the interim between now and whenever the test or tests become available?

DR. HOLLINGER: That's a valid question.

Paul, you had a question.

DR. McCURDY: I was going to follow up on Joel's comment about doing a study. It would seem to me that--not being very statistically inclined, but it would seem to me that the numbers are small enough that you'd have to have a rather large study to get any figures that you could believe, particularly when you're looking for a negative result rather than a positive one.

DR. VERTER: Right. The numbers would be large, but I think the cost might not be that much because all this testing is being done. So the issue would be the follow-up and the identification of a morbid event.

I may have talked too quickly, Paul, but that's my gut feeling.

DR. McCURDY: Well, if that's the case, I think that the institute would be happy to enter into some discussions as to how this might be done.

DR. VERTER: Blaine, do you want to submit an RO1?

[Laughter.]

DR. HOLLINGER: Along with the albumin one we're going to do?

DR. NELSON: Couldn't you just test the subset of recipients who received blood from the donors who were, you know, core positive and then not repeatedly positive and then negative on the next--so it would be a subset. It

wouldn't be all recipients. But you'd have to have a control group because you'd have to worry about non-transfusion-associated hepatitis B. It would be pretty complicated.

DR. McCURDY: I think you didn't have the donors in your study because getting donor-recipient-linked specimens is a fair tour de force, which turns into money.

DR. HOLLINGER: Any other things about the question up here? And then anybody--I mean, I brought up the issue that if I were going to change the question, I would change it to that addition. I'd add to that question the additional--in fact, I'll just bring that up as a motion here with the group, and then we can vote on that motion, and then we can vote on the question. But I'd like to see the (a) part changed to address the issue of the fact that if a solitary anti-HBs test is found in that group and it's associated with a history of HBsAg vaccine, that would not exclude that particular donor. At least that test is not going to be done when they come into donate blood, anyway, so it won't throw them out, which is the thing Roger was dealing with.

DR. BUCHHOLZ: Excuse me. I just have a procedural question. If we wish to do that, would it not be appropriate to, in fact, vote this question no and then entertain a proposal to consider an alternative?

DR. HOLLINGER: It would certainly be a reasonable thing to do. I agree with that.

Yes, Jay?

DR. EPSTEIN: I just wanted to comment that whereas I understand the logic, for the cases with history of vaccination, you would be substituting the fact of vaccination and anti-HBs as the safety precaution vis-a-vis a negative antibody. In other words, you really have two different algorithms operating at that point. It's really not the same algorithm, because you don't know whether the person pre-vaccination would or would not have had positive anti-HBs.

DR. HOLLINGER: Say that again, please?

DR. EPSTEIN: People can be vaccinated--most people who are vaccinated do not have their antecedent anti-HBs status determined. So there will be people with a vaccination history who have a positive anti-HBs who would have had a positive anti-HBs had they not been vaccinated, and you won't know that. The strength of the algorithm will be different.

DR. HOLLINGER: I guess I could come back to you and say do you know a patient who's had hepatitis B infection that has only anti-HBs circulating? Because I have not seen it. I mean, if you know of someone--

DR. EPSTEIN: I don't--I believe the literature--

DR. HOLLINGER: I'd like to know--

DR. EPSTEIN: I believe the literature reports about a 2 percent rate of assay discordance between anti-HBs and anti-HBc. I don't personally know whether that's due to assay variation or variations in the pattern of immune response.

Ed, you know that literature better than I do.

DR. TABOR: I can't remember the data in great detail, but it's my impression that in the volunteer studies conducted in the 1950s in which volunteers were inoculated with the same volume at the same concentration of infectious material, there were some individuals whose sole detected response was anti-HBs, and I don't know if that really answers your question. I'd certainly want to go back and look at the data before stating it with certainty. There was some small percentage that did, but I would have to check that.

DR. HOLLINGER: I know the study you're talking about quite well, and I don't recall that data, actually.

Okay. So let's--yes, Paul?

DR. McCURDY: I rather like the idea of not doing away with the test unless you have something to substitute for it, barring that the test is obviously a real bummer. And I think the suggestion that the two new core antibody tests that are coming down the pike appear to give better

specificity and essentially the same or maybe better sensitivity, that when those come in that would be a reasonable thing. It is also conceivable that soon after HIV and HCV RNA tests are available, there may become available by similar technology hepatitis B DNA testing. So substituting in one or the other of those areas might be a better approach than just going willy-nilly into it at this point.

DR. HOLLINGER: I'm going to call for the question, and, Robin, if you will read--well, you can all read that. Part 1, I think we'll vote on part, I guess (a) and (b) go together, basically.

DR. BISWAS: That's right.

DR. HOLLINGER: So I'd like to see a show of hands of all those in favor of the question that is put up there in 1(a) and 1(b), raise your hand, please. All those who are in favor of that question.

[No response.]

DR. HOLLINGER: Okay. All those opposed to the question?

[A show of hands.]

DR. HOLLINGER: Any abstaining?

[No response.]

DR. HOLLINGER: Okay. Would you read the...

DR. SMALLWOOD: The results of voting are: There

were no yes votes, there was unanimous no votes, 12 votes. I see that the industry representative agreed with the no vote and the consumer representative agreed with the no vote.

DR. HOLLINGER: Okay. Yes, Mark?

DR. MITCHELL: I think that we need to note, though, that the concept of bringing those people back in is not something that we're opposed to. As a group, we just don't think that currently with the level of knowledge that we have that that's an appropriate thing to do.

DR. HOLLINGER: Okay. The second part of the question on there is--basically we've probably answered some of that. It says: If the committee does not agree with question 1--I guess that's the sense of the committee here--it says: Should donors who test repeatedly reactive for anti-HBc on more than one occasion remain indefinitely deferred, or does the committee wish to suggest an alternative re-entry algorithm? Or an alternative suggestion, we could say just as well.

Yes, Paul?

DR. McCURDY: It seems to be that if there are two tests that are coming down the pike, perhaps when those tests get here, we should look at another algorithm that was proposed and submit it to us rather than have us try and develop an algorithm here. That would be very difficult to

do, I think, in a group this size.

DR. HOLLINGER: It might be the--if I may say, I have the sense of the committee, though, that it may be beneficial, at least, to address that 2(a) part there, should donors who test repeatedly reactive on more than one occasion remain indefinitely deferred. I mean, my own feeling is that they should not remain necessarily indefinitely deferred, and it would give the sense of the committee--may give, at least, the sense of the committee saying, look, from just what you say, we want to wait for more tests or do something else on that basis.

. I'd like to raise that as a motion, anyway, that we at least--that we vote on say 2(a). I'd like to throw that up to vote on 2(a), which basically is--yes, go ahead, John.

DR. BOYLE: I'm just a little confused. On previous occasions, something like indefinitely deferred just meant until the next time the issue is raised rather than, you know, we don't want to see them anymore, don't raise the issue again. And my concern here is that I agree with more information, with additional tests, I see no reason why these can't be resolved. But I'm not sure that's what I'm voting for if I vote yes to this. It's more like: Don't do this, but do something else and it's left open.

DR. HOLLINGER: Okay. I follow. Good point.

DR. MITCHELL: Could we maybe change the question to permanently deferred?

DR. HOLLINGER: To what?

DR. MITCHELL: Change the question to say that: Should donors who test repeatedly reactive for anti-HBc on more than one occasion be permanently deferred?

DR. HOLLINGER: I think actually they are indefinitely deferred and not permanently deferred, anyway. Is that correct?

DR. TABOR: Well, I wanted to say that we feel you don't have to vote on this question if you don't--

DR. HOLLINGER: Okay.

DR. TABOR: I mean, I think we would like to get the sense of the committee--

DR. HOLLINGER: But we want to.

[Laughter.]

DR. HOLLINGER: Don't take it away from us. We have so little to do today.

DR. TABOR: While I'm standing here, I also want to correct what I said before, Dr. Hollinger. I feel that you're correct that a true infection is always accompanied--anti-HBs is always accompanied by anti-HBc, and that those instances where there's only anti-HBs, it's usually felt to be a different situation.

DR. HOLLINGER: Okay. I think the FDA understands

and hears what we're saying here. Those in favor of not voting on the second question--

[Laughter.]

DR. HOLLINGER: --raise your hand.

[A show of hands.]

DR. HOLLINGER: Okay. So we're not going to vote on the second question. But I--go ahead, David.

DR. STRONCEK: I don't know where the Chair is heading, but I think that this is--

DR. HOLLINGER: Heading for lunch.

[Laughter.]

DR. STRONCEK: Yes, but this is an important issue for transfusion medicine, and I voted against this because I think donors should be tested on two tests. And I don't think we should just drop this and let it go several more months and not do anything. Maybe we can come up with an alternative over lunch, a proposal over lunch.

DR. HOLLINGER: Well, go ahead, David. I didn't really mean to cut it off because I agree with you. I think this is an important issue here. Would you like to make a suggestion, at least--

DR. STRONCEK: Well, I would suggest that maybe we could ignore the issue about the anti--I think we got hung up on the antibody to hepatitis surface antigen, and maybe we can deal with that at a different point, maybe when some

of these other tests are better, but I don't think that should dissuade the committee from looking at a proposal, and I'd prefer to have the proposal as recommended by the AABB and Roger Dodd, where donors are re-entered if they have two negative tests.

DR. HOLLINGER: Any other thoughts or discussion? Yes, Jeanne?

DR. LINDEN: Yes, I just wanted to echo that I'm supportive of this concept, and I would just encourage FDA to maybe think about things more and maybe tweak it a little. I don't know if the AABB proposal is specifically the one either, although I agree with Dr. Stroncek I like the idea of a second test being in the algorithm. But I would just suggest FDA give it further consideration. And I agree that when additional tests come down the pike, that's going to be extremely helpful.

DR. HOLLINGER: Okay. Don?

DR. BUCHHOLZ: Is it feasible, since we are meeting tomorrow as well, to basically suggest to FDA that they may want to reconsider the phrasing of the question and bring it up for a vote tomorrow?

DR. ELLISON: Yes, I know the answer to that, but...

DR. EPSTEIN: As a procedural matter, this issue is on today's agenda, not tomorrow's agenda. The committee

and individual committee members are free at any time to make suggestions to the agency. However, bringing it for discussion and/or voting tomorrow would be precluded by our administrative procedures. You know, concerned parties knew to come today.

DR. BUCHHOLZ: Later today?

DR. HOLLINGER: Well, I'm open--I think we ought to deal with this while we're here right now. If we have to go, we just go. We just take the time it takes. I think these are important issues. So go ahead, Joel.

DR. VERTER: When I made the initial statement, I was kind of leaning towards the AABB thing and being accepted, but I really feel now that we probably should table it until the real data that we need and perhaps the new tests are here. We've waited this long. I know there's always a concern about blood supply, but I don't hear any hue and cry that we're, you know, really seriously in trouble. I respect the issue of the donors and their sensibility, but I think given what I said before, I recommend that we just hang in there, one or two more meetings at least, until these tests are there, maybe until AABB, NHLBI, REDS, or whoever has other data can bring it to the committee.

DR. HOLLINGER: Is there a question before us then? Do anybody want to put it in the form of a motion of

anything here? The Chair will certainly entertain that.

Yes, Paul?

DR. McCURDY: I basically agree with what Joel just said, but most of us, I think, only saw the last algorithm that Roger put up when it was up there. I don't think it's in his group that was passed out. Maybe that could be passed out so that we could look at it over lunch and decide whether that's something we should consider or not. I think that probably the basic thing to do is what Joel said.

DR. SMALLWOOD: Again, procedurally, we have announced the time for the discussion of this topic, and to come back after lunch again would pose an administrative problem. It is understandable that some of the data you only received today because I just received it and it was handed out to you. I would piggyback on what Dr. Epstein said, that the committee can submit, you know, at any time to FDA, and that if upon reviewing you have comments relevant to this that you would submit to me and we can send that to the appropriate people for review.

DR. McCURDY: I'll second Joel's recommendation.

DR. EPSTEIN: Linda, I think it's the chairman's discretion whether to continue discussion today. I don't think that's precluded by our procedures. Tomorrow's a different matter because people didn't know to come.

DR. HOLLINGER: Well, if, Roger, you would please get that copied and make sure it's on the desk so we can look at it? Then we'll decide, you know, if we want to reopen that right when we come back from lunch, if not then we won't.

Yes, Ken?

DR. NELSON: I'm aware of some intensive research and studies that are going on right now with regard to nucleic acid amplification for HIV and hepatitis C in large numbers of donors and that there's a track, but is it correct--or is hepatitis B on the same track? Is there active research? Because the issue was brought up about the QC and reliability of the hepatitis B DNA assays. And I know, as I say, there's a lot of work on HIV and hepatitis C, but could you reassure me on that? Or what's going on with that?

DR. TABOR: Well, already at the present time, testing for hepatitis C is being done on the plasma in this country, and most of the people who are working on this are testing mainly for hepatitis C and HIV or only hepatitis C because those are the ones where the greatest improvement in the window period--eliminate window-period donations would occur. I think it's going to be a long time before we see a licensed assay for screening pools of plasma for hepatitis B because that's in the second tier, really, in terms of

payback.

DR. SMALLWOOD: I'd just like to take the opportunity to explain procedure here with regard to this particular matter. It is not permissible that the Advisory Committee would meet other than in this setting. They could not meet at lunch to discuss a topic, and that's why I had stated that it was prohibited. We have already started taking action at this point.

Now, if you wanted to continue to have discussion, you may do so, but that is the prohibition there. So that is the reason.

DR. HOLLINGER: So the issue is that no discussion on the topic, basically, at lunch. After we come back, we'll decide if it merits a reopening or whether we'll go on.

We're going to take a break now, and we'll reassemble--I'd like you back here at 10 until 2:00. Thank you.

[Whereupon, at 12:50 p.m., the committee recessed, to convene at 1:50 p.m., this same day.]

AFTERNOON SESSION

[2:00 p.m.]

DR. HOLLINGER: I thought I'd give a few minutes for anybody that might want to comment any further about the table that was passed out here regarding the figure that Roger Dodd--oh, you haven't gotten it yet? Sorry about that. Well, I saw it.

Well, if there are no further comments on the table which you haven't got--

[Laughter.]

DR. HOLLINGER: We're not going to call for a vote on anything with this, but I thought it would be--if somebody wanted to make some other statements for the FDA regarding the discussion we had earlier today, I'd like to give you an opportunity to do so in terms of what they might want to do with this.

If you look at this reinstatement sample, basically the difference is that once they have a non-reactive patient--or non-reactive individual, first is positive, a certain period of time later they're then retested, come in just for retesting for surface antigen anti-HBs, and a second licensed test, a different licensed test, and then those that are non-reactive, one of two things would happen: they could be tested again either with the test of origin, the original test, and/or a third test,

the possibility of a third test, and then again if they're reactive, they're not eligible. If they're non-reactive, they'd be eligible. The other alternative or part of the algorithm would be to test them for HBV DNA, and if they're reactive, they're not eligible; if they're non-reactive, they would be eligible.

Anybody have any comments that they want to make about that? The reason I don't want to bring it up for a vote is because I don't think we'll have a consensus, and so I really just want to let you have a chance to say anything. Yes, Marion?

DR. KOERPER: I just want to make one more comment about the testing for anti-HBs and this confounding factor, the fact that individuals may have been immunized and, therefore, be positive for anti-HBs. And I don't understand why anti-HBs is being included in this reinstatement sample testing because it's my understanding that anybody who is positive for HBC because they were infected with the virus would--they're either also positive for HBs or they have lost their HBs. So as I understand it, there is never a situation where someone who has been infected with HBC is only positive for HBs. So I don't understand why that's being thrown into the algorithm of one of the tests that they have to be negative for.

DR. HOLLINGER: Okay. Does anybody else have any

comments? Okay, yes, Dr. Ohene-Frempong?

DR. OHENE-FREMPONG: The question about the test of record, coming back again, if much of this anti-HBc may be due to false positive results, meaning that the test that was originally done may not be the best test, and if, you know, future-generation tests are better, why go back to try to validate the test that proved itself to be not so good?

DR. HOLLINGER: I guess the real issue with some of this is which test is right. I mean, that's always at issue. You know, you get a positive, and then you go do another test and it's negative. You like it because that means you can bring the person back in. But it could be in reality that that has a false negative.

It often is not that way, but it could be that way, and I think that's always an issue. But I think your point is well taken that--the thing I'm concerned about and I think the blood banking organizations all feel this way, too, is if they move forward with something like this now and start advertising, getting patients in and have them tested, and then they're found to be positive again, they're not going to come back a second time when you have a better, even a better test that is perhaps more specific for that. I think that's an issue that obviously they're concerned about, too.

Yes, Roger?

DR. DODD: Thank you, Blaine. Roger Dodd for AABB. I think Dr. Hollinger accurately expressed the intent of the algorithm, which was that this final level of testing for anti-HBc with another test which is labeled test of record doesn't necessarily imply--or at least on due consideration, would not necessarily imply that you had to go back to your original test of record, because you're exactly right, that could generate a problem.

But let's give a hypothetical. Suppose that you were testing, for example, with Corzyme and you then used a second test of Ortho, but wanted to move on to implement, assuming it would be licensed, the Prism test, that might be the test of record in this algorithm.

On the other hand, if you did want to go back and use your original test of record, Corzyme, it might make sense to redo that test so you don't inappropriately re-enter a donor who on presentation for donation would continue to be false positive by the test of record. So that would be an administrative convenience.

But I think Dr. Hollinger put it exactly right. Ultimately, and crazily enough, this might imply a potential for a three-test algorithm, although I don't think it's strictly necessary.

DR. HOLLINGER: We actually might be doing the blood bankers a favor by withholding this right now until

some better tests become available and the effort can be put forward, and we have a lot of other new data that's coming up, too, I think, with the GAT test and so on that might be very helpful to us.

I think we'll move on, then, to the rest of this afternoon, which has to do with end user notification. As you know, there has been a lot of interest from the consumers about the notification of plasma derivatives that there may be a problem with, and so this is to try to deal with this issue. There are not going to be any questions regarding it, but the FDA would like to have some discussion and perhaps even some recommendations made regarding this issue. So I think Dr. Weinstein is going to start off with an introduction and background. This will be followed by a review of the advanced notice proposed rule, the voluntary notification, and recent experience with previous notification.

[Slide.]

DR. WEINSTEIN: The FDA has long had an interest in improving public notification of recalls and withdrawals.

[Slide.]

In March of 1996, a task force of Public Health Service agency members was formed to examine issues of public notification. In November of 1996, the FDA, CDC, and NIH sponsored a meeting to discuss public notification of

withdrawals and recalls of plasma derivative products.

The goals of the meeting included informing the public about available notification resources, describing the roles and responsibilities of Public Health Service agencies, manufacturers, distributors, and private organizations in the notification process, and stimulating discussion about improving the notification system.

The FDA initiated procedures for informing the public about recalls and withdrawals of plasma-derived products. They included information delivery through a toll-free 800 number, Internet site, facsimile on demand, and an automated electronic mailing list service via the Internet.

[Slide.]

As part of efforts to improve blood safety, FDA initiated the Blood Action Plan in 1997. This effort includes improvements in FDA inspections, promulgation of ne regulations, an increased coordination within PHS to potential threats to blood safety. As part of this effort, FDA is considering proposing a regulation requiring that certain plasma-derived products be tracked from a U.S. licensed manufacturer through the distribution network to any patient having custody of the product. Additionally, FDA may require notification of consignees and patients having custody of a plasma-derived product in the event the

product is associated with a potential increased risk of transmitting a communicable disease.

The rule would also apply to any plasma-derived product which in the future may be routinely dispensed to the patient and held by the patient prior to administration. FDA is considering taking this action to help ensure notification of patients having custody of plasma-derived products when such products may be associated with a potential increased risk of transmitting a communicable disease.

This is being done so that patients may make informed, appropriate decisions. FDA intends to solicit comments and information from interested persons concerning the proposed regulation, and this meeting is part of that process.

FDA continued to meet with representatives of industry and consumer groups through 1998 to discuss ways to improve consumer notification of withdrawals and recalls. In August of 1998, the FDA met with representatives of the International Plasma Products Industry Association--that is, the IPPIA--to discuss FDA involvement with a voluntary consumer notification program that IPPIA and consumer groups were forming. This voluntary program was an outgrowth of the November 1996 meeting on notification and withdrawals which informed interested parties about the capacity of

certain businesses to directly and rapidly notify consumers and others about regulatory actions.

FDA has been invited to attend meetings of the IPPIA and consumer groups regarding this issue and will participate in any way it can to facilitate the development of this voluntary system.

In October of 1998, the patient notification system was implemented to inform recipients when a blood product is withdrawn or recalled. This system is being administered by the National Notification Center, with current participation by Alpha Therapeutics Corporation, American Red Cross, Baxter Health Care Corporation, Bayer Corporation, Cention, Genetics Institute, and Novartis Pharmaceuticals.

Individuals may register with the patient notification system and select whether they wish to be notified by telephone, express delivery letter, fax, or electronic mail. In addition, individuals can call the system through a 1-800 number or electronically to see if products they are using have been involved in a recall or withdrawal.

Individuals can register by telephone, electronically, or by completing a registration form, and information about the patient notification system has been made available to the public in a number of forms including

the home page of the National Hemophilia Foundation.

Since the start of this voluntary notification system, two recalls have occurred. Information from these recalls can be used to assess the effectiveness of this system to notify subscribers.

In this session of the meeting, Steve Falter, Director of Regulations and Policy Staff, CBER, will describe FDA's current thinking about rules that would require notification. Jason Bablak of the IPPIA will describe the voluntary notification system. And Dr. Bruce Ewenstein of the NIH, but here a representative of the Plasma Users Coalition, which is a coalition of plasma derivative consumer organizations, will tell about experiences subscribers to the voluntary notification system have had with the system during the recent recalls.

The committee is asked to discuss FDA's current thinking about requiring notification, the voluntary notification system, and to offer any further suggestions they may have about improving notification.

DR. HOLLINGER: We'll go on with review of advanced notice proposed rule, Steven Falter.

MR. FALTER: Good afternoon, everyone. Before I start, there's a minor flaw to the agenda in that apparently I've been transferred under the Office of Blood. It sometimes often seems that way with all the work they give

us, but I'm actually under the Office of the Center Director and work with policy development for all of the commodities regulated by CBER.

[Slide.]

Today my specific topic is to talk about an advanced noticed proposed rulemaking. The full title is r. You can read that for yourself. The purpose for the little question dude is both I like to play with graphics--I'm just learning--and because an advanced notice of proposed rulemaking, unlike a proposed rule, is in setting forth here's what FDA think they should do, please comment on it. It is rather a document that's intended to put forth a number of questions that we believe must be resolved before we can actually propose a given set of regulations. It is not even a commitment that will issue regulations. It is simply that we observe a problem, that we have some preliminary decisions about it and would like to put forward some questions, some requests for data or information about it. So that is what an advanced notice is, and that's what's being prepared in this case.

What actually happened in this case is that we convened a work group within FDA to actually develop a proposed rule, and I started causing trouble, both because I was in the mood and I was getting assigned to too many work groups, and so trying to limit the number of work groups I

work for, I started asking a lot of questions. And, finally, Jay asked, How can I get you out of my hair? And I said by issuing an advanced notice rather than a proposed rule.

So what I am going to present to you today is the background of some of those issues that caused us to prepare the advanced notice. The actual document itself is still under review. It's subject to departmental review, and I certainly cannot control how long they're going to take or what questions they have. We welcome your comments today, but I would ask that any comments that you want to be officially considered also be put onto the docket at the time of issuance of the advanced notice.

[Slide.]

First, let me give you just the primary premise that we're working under when trying to figure out what to do. It is that we believe, and consistent with recommendations offered by the House of Representatives' Committee on Government Reform and Oversight, and as has been extensively discussed, as Mark just iterated to you, we believe that consignees and patients who have custody of--you'll notice it says "blood-derived" product. Right now that realm is only plasma-derived products, but in the future there may be blood-derived products that are taken home--should be notified in the event the product is

associated with a potential--it doesn't have to be a documented one; it can be somewhat theoretical--risk of transmitting a communicable disease. Notice right now our concerns regarding notification are limited only to those problems related to the potential for transmitting a communicable disease. Heaven knows, there can be far more problems on any drug-type product.

[Slide.]

On the next slide here, it's not like nothing has been done, and Mark already covered that. We'll be hearing about the voluntary notification efforts. One reason why we're issuing advanced notice is that if we do decide to present forth a mandatory system, we have to be able to compare it to the voluntary system. We need data both on the voluntary system and some perspective or idea of how our mandatory system would work just to show that it is necessary to codify regulations and make it have force and effect of law. It also would be in the heart of information collection, and we have to very carefully document to the Office of Management and Budget, both in number of hours and in number of dollars, how this entire--what this entire exercise would entail. So this isn't totally a scientific concern, but it is also one dealing with dollars and time expenditure to get the job done for us to be able to issue a rulemaking on this. If something goes on with any of our

commodity recalls, we have procedures that are actually guidances, but they're in the Code of Federal Regulations as to how recalls should be done.

A very similar exercise are market withdrawals, the only difference being market withdrawals are done on a product which is not necessarily violative of the laws that we function under, but it is basically the same process.

Please keep this--for those who know what a recall is, keep the process in mind because notification and recall are very similar, and we want to avoid having duplication of effort and redundancy and having two very separate exercises, recall and notification, where basically you're repeating some of the same steps in both when they could be melded together. And I think we'll need your help on just how they can best become melded together.

[Slide.]

On the next slide, I'll present to you somewhat the scope of what we are considering, and once again, this is all open for comment and for additional advice. That's why we're issuing advanced notice.

Up there you see the several products that are currently licensed that we're aware of that are being taken home by the patient and being held by the patient, the first three of which I'm told--and I'm not a blood scientist--are routinely being taken home and held by the patient pending

administration. Immune globulin IV is a different question I'll get to shortly, and as I say, the way we would write the rule, if we did, it would cover all products that, one, have a potential for transmitting communicable disease, and, two, may be taken home by the patient. And there's a few that are under early stages of study that might fall under this and some theoretical products that we might have in the future. We don't intend to recodify each time a new product is licensed.

One of the very basic questions, why limit it one to these products and one to only those taken home? Well, right now we're only prepared to approach the question of having the patient who may possess those products know so that they can either return the product or take some other suitable action with that product. You can theoretically cover other products that may transmit disease, even blood and blood components, but the motivation would be different in that case. And so if you change the types of products, you would change the motivation. We do welcome comment on that, but right now our primary intent is to deal with those products that may be held in someone's home.

IGIV is of particular concern because we may have to handle those differently. According to our scientists, perhaps about 5 percent or so of the product may be taken home. The vast majority is, of course, administered at a

health care facility. So it may not be that the same system for notification would be suitable for IGIV as for these other products where you can perhaps generally notify all patients who received the product for those other products. That wouldn't be suitable for IGIV, notifying a huge number of people for which it would be unnecessary. But that also is something we ask for comment on.

[Slide.]

On the next slide, if you're going to have notification, you've got to know who to notify. I'm afraid that means tracking, record-keeping sort of exercise. Right now pretty much manufacturers know who are their direct consignees. They may not know every health care worker who may possess their products. So rules will also cover all consignees and also identification of all end patients.

Now, one of the very basic issues is who. The obvious choice would be the manufacturer, but there's some concern about that because many of the people receiving these products do not want the people that are making this product to know precisely who they are. I think they don't like mailing lists, but I'll let them speak for themselves. But they would prefer a third party or someone who already is directly involved in their care to be involved in gathering this data and actually engaged in the notification itself. So although the manufacturer undoubtedly would have

some responsibility, they may not be the primary notifier. They may not be the primary person that's holding the records of just exactly what patients have gotten their product. And the question is which system would work best, a third-party system, someone contracted to do this exercise, or I could be the consignees or the physicians that actually are administering or handing out these products that could be keeping the data and, if necessary, notifying.

A second area is, well, what do you track? You could simply track these are the patients that got this particular alpha therapeutic product, and you wouldn't care what specific lots each person got. If there's notification necessary, here's your list, and some people would get the notification unnecessarily. But that may be the most efficient way of doing it. Or you can have the other burden of keeping lot-specific records, and so if there is a recall or some other problem with a product, you could identify who got that specific lot which is found to have a problem to it and contact those persons.

There's a question of both which would be most efficient and which would be most effective, which is most likely to result in being able to identify the appropriate patients. We would like data and opinion on that tracking system, and by identifying the tracking system, you're also

identifying the means of notification. Should it be just simply by, oh, a company product or by persons who received that specific lot of the product that gets notified?

[Slide.]

On the next slide, I give our preliminary thoughts on the reasons for notification. As I said, it's a potential increased risk of transmitting a communicable disease. It would only apply to those products that are in date because the assumption is the product would not be held by the patient, or if it is, it should be discarded in any event. But while that looks nice, it really doesn't define a threshold. When would notification become mandatory? Because problems related to a product can be anywhere from speculative of a very maybe hypothetical situation where you're not sure. Records are lost of a couple of donors and you don't know on through to where indeed you know that a person that was infected with hepatitis was one of the donors and there might be a problem with the product where it's pretty self-evident. But what threshold of evidence is needed to trigger notification? And once we determine that, it would be very hard to define in the regulations where that threshold is so that both FDA and industry--I'm sure we want to agree on 100 percent, but to write it in a way that we know going in that we'll agree where that threshold is is going to be very difficult. We'd like your advice on it.

It could be a similar threshold as what industry is now using to determine when a recall or a withdrawal is necessary. I think that should be considered. There's some language in Part 7 of Title 21 regarding recalls that might be transferred and applied in this case, but that's only one suggestion.

I haven't noted it here, but this could be either a manufacturer or an FDA decision. FDA may gather information either through inspection or from hearing from physicians, patients, adverse experience reports where we determine that notification is necessary, and we would intend to issue the rulemaking so that we have that prerogative, if necessary. Certainly we wouldn't do it unilaterally. The manufacturer would be aware of it, but we would have that authority. Most times it would be the manufacturer that would initiate this exercise.

Now, one of the most difficult questions is why just communicable diseases. Well, if you expand it to include other problems with a product, then you have to say why only blood products. Why not any drug that's taken home? I'm afraid politically we're not ready to attack that. I mean, we can gather comments, but it would be very difficult to suddenly say for every drug in the world, if you take it home, people have to track, know who you are, be prepared to notify you in case there's a problem.

We have to draw a line in the sand somewhere, and we presented where we draw that line. If you want to move that line a little bit, please suggest to us a way in which it can be moved. But we're trying to avoid opening up Pandora's box entirely.

[Slide.]

Okay. Let's assume that we decided to notify. Timing. We have found historically we used to include in the regulations words like "promptly" or "expeditiously," and when we charted out the bell curve of response times, it was about this wide on any reasonable graph paper. And so now pretty much the higher-ups are asking us to be more specific as to what timing is reasonable.

Certainly this is something that is very tentative, but I put this in here simply to reflect the urgency we place upon it. If there's a problem perceived for a product, it's being held at home and could be administered at any time, a system should be in place to, as quickly as possible, let that patient know what is possible. We're in ivory towers here, please, so we need the data from you as to what is possible.

I note again, particularly for this part but for every part, we not only need to know the science, but we need to know the dollars and cents, the time, the dollars, how much do you think it costs, the number of people that

need to be notified in various cases. Facts and figures. It would be very helpful in defining our policy.

So we present the times there as only tentative. Notice we are considering the possibility--your first contact, obviously, isn't going to be nearly 100 percent effective. I know my girlfriend doesn't answer the phone if she doesn't recognize the number. So if you notified her by phone, forget about it. So you have to have a mechanism of multiple means of notification to try your best to notify this. We're suggesting three within one week, with the last one we're considering being in writing as the official documentation that you have attempted to notify. But that is all open to comment.

I've already mentioned what timing is feasible. Please, we need information on that.

Something I haven't included, if the consignee isn't notified or it becomes irrelevant, but if you have a third-party notified at the same time you'll be notifying all consignees down to the specific health care people that there's problems with this product. And I haven't put any figures regarding timing for notification of the consignee, but it could be something that we would consider for any regulation.

Okay, the next slide--by the way, I haven't covered just what the substance of such a notification would

be. It would be just the basis for such a notification. Why are we doing this? What are the problems? It wouldn't necessarily have to be telling the patient return the product. It could be that the patient and the patient's physician could then make a decision. Is this product still okay? Because we're covering a very broad realm, including some of the more theoretical concerns we've had historically with CJD-related issues, where it might be a reasonable option, if the patient is comfortable, to continue to take that product. It is simply to inform the patient. And certainly if the manufacturer decides that the product should be returned as unsatisfactory, they may do that. But it wouldn't be a mandatory element of the rulemaking as we consider it now.

[Slide.]

So things that didn't fit under individual slides. If you're going to have a system for notification, you have to be able to show how it works. Is it working through time? How is it functioning? We would expect that there be a system for quality assurance to make sure it works. And if so, what is "works"? You can't possibly expect 100 percent success rate notifying patients. Just when is enough enough? And this is particularly relevant because we have to compare--we have to know what is happening in the voluntary system so that we can compare is this system--once

it should get underway, is it working better as far as the percent of patients being contacted? We have to be able to get those figures.

I've already mentioned at the same time manufacturers will be doing a separate recall process. They don't need to be separate. They can be combined. How can they be combined? What's the best process to do so? They're in the best position to know because they're the ones that are doing the recall and product withdrawal process.

Finally, if you're going to have this complex system, it seems fair that the patient should know that this system exists so that if there is a problem, they may be notified. And the question is just what is the best way to let a patient who is starting to undergo care for hemophilia, for example, let them know that this may occur. We're suggesting by labeling, which simply means that there's some written documentation that accompanies the product. It's not necessarily integrated into the package insert, but it's nevertheless a written statement regarding notification that accompanies the product.

Okay. Well, I've covered some of the basic questions. It's nice to be able to just throw out questions rather than trying to answer them. What will happen from here? As I say, we'll issue an advanced notice, allow

opportunity for comment. We may be reconvening either with this group or some other public forum to discuss the information further. In fact, we can be entirely candid and start arguing numbers with you once the advanced notice issues. Right now basically it is confidential, and I've basically given you a background.

Then hopefully we'll get enough answers so that the little question dude will disappear and we'll be able to issue a proposed rule, which, of course, I'm sure you're all familiar with, will be another opportunity to offer your input, which will be entirely welcome. But in that case, we'll give you a non-moving target of what we think should be the appropriate plan. Here we're so flexible, you can't argue with us at all because we'll agree with anything at this point.

So that's my part of the presentation. I guess we're moving on to the voluntary part now.

DR. HOLLINGER: Thank you, Steve.

The next discussant, Jason Bablak on voluntary notification.

[Slide.]

MR. BABLAK: Good afternoon. My name is Jason Bablak. I am Director of Regulatory Affairs with the International Plasma Products Industry Association.

[Slide.]

I'm going to talk today about our voluntary notification system we've been working on for about the last year and have finally implemented. But first I'd like to just give you about a 2-minute overview of what IPPIA is, who our members are, and a few other things that we're doing that relate to this.

Our members are basically Alpha Therapeutic, Baxter Health Care, Bayer, and Centeon. They are the major commercial producers of therapies from plasma, and they produce about 80 percent of the supply for the United States and about 60 percent worldwide.

[Slide.]

This is basically an overview of plasma fractionation and the different safety areas that are involved in this. I'm not going to go through all of them right now, but you can see we have outlined basically seven steps where there's a chance to increase the safety of plasma-based therapies. What we're going to talk about today is Step 7, which is recall/notification.

[Slide.]

But before I go on to that, I'd like to review just a couple other things that we've done in the past and presented to this committee before, just kind of put it all in the perspective of this is an overall comprehensive safety plan that we're working on. The notification system

is one part of that.

In the past we've talked about the qualified donor standard where we're only going to use plasma from repeat donors; the viral marker rate standard, which will hold all the plasma centers that participate in this to a certain rate of viral markers; an inventory hold of 60 days, which basically allows us to assure that the testing has been done properly and we've had a chance to review the donor as they've come back again and again; PCR testing to increase the safety of the plasma that's being used; and we've also added a pool size limitation of 60,000 donors for a maximum ceiling for any final product.

[Slide.]

An overview of what I'm going to talk about today on the patient notification system. I'm going to briefly talk about the regulatory requirements in the system that we're currently operating in, and hopefully I'll be able to answer at least a few of the FDA's questions that they posed in the previous presentation and also some of our comments on that. I'll talk about some industry concerns and pressures that brought us to where we are now; the industry response, which is basically what we did to try to come up with a plan to address these pressures and concerns; talk about the system and its operation; and then wrap up and answer any questions that anyone might have.

[Slide.]

Basically, under the regulatory requirements, it's 21 CFR Section 7.40 to 7.59. Recalls are voluntary. That probably should be in quotation marks because there's no legal requirement that you have to do it because FDA has no recall authority except for a few--something like baby formula and medical devices. But the alternative that FDA has, which is seizure, recall, voluntary recall, is usually more appropriate by the firm standards.

[Slide.]

In the regulations, one of the things that's required is the recall strategy, and that has to deal with--one of the things is how far down in the chain of distribution do you have to go. There are different levels depending on the type of recall it is. If you have a Class I recall, which is the most serious, usually the FDA will want you to get down to the consumer or user level; whereas, if you have a Class III, they may only require a wholesale level.

[Slide.]

The problem with this is that there's difficulty with getting to the consumer. As you get further and further away in the distribution chain, the manufacturers don't have access to those lists of patients and other people who would be buying this product. There's also the

problem of interfering with the patient-physician relationship. Physicians are the ones that are prescribing this, and is there a concern that if we tell the patient something that the doctors don't want them to know, how does that interfere with their relationship between those two.

There's also a problem of desensitization. What happens if one year there's a whole lot of recalls, but they're all Class III recalls, and you notify everybody all the time. By the time you get to a Class I recall, people may just throw this in the garbage and think it's just another mailing I'm getting from those manufacturers.

Then, finally, there is a question of legal liability, and I pose this more in the effect of if we develop some type of system that's voluntary, what additional legal liability do the manufacturers take on if they somehow don't notify someone who otherwise would have been notified in a different way.

So these are all concerns that we have to think about, talk about, and come to conclusions on before we can move forward. And I think we've been able to answer some of these questions.

[Slide.]

Some additional difficulties with direct consumer notification. Basically there's no law or regulation that requires distributors to track by lot number. Also, there's

no law or regulation that requires direct patient notification. The discussion we had just a minute ago about the recall regulations, as was pointed out by the previous presenter, those are actually guidance--that is a guidance document even though it's in the CFR, and so there's some confusion about actually what's required and what's voluntary and what's not. So there's a lot of confusion in this area right now.

At some meetings we had previously on this issue, the IPPIA had a position where we had asked FDA to do a couple of things in the regulations because we felt they were the ones that could address the situation. One of those would be to require wholesalers and distributors to track by lot number, and also then to notify their direct sales so there would be a continuation down the chain of command. Right now it's assumed that that happens, but there's no oversight and enforcement by the FDA that it goes down beyond just the manufacturers.

Additionally, the other thing we would like to have done is have the final distributor, which would either be a home health care unit or a pharmacy or somebody of that nature track lot numbers to patients so that the patients--there's a direct connection between a lot number and a patient, include the lot number on labels so that the patients have that information because that doesn't happen

right now, and also notify affected patients in the event of a product recall. So these are some things that we think are needed to be done to change the existing system, and I think these are certainly comments we will make on the proposed rulemaking that's coming forward from FDA now.

But this is more a long-term fix. I think this is--to go through the notice and comment of a rulemaking is a lengthy period, and in order to address what we thought were some concerns of our consumers and other interested parties, we started having some discussions on this issue.

[Slide.]

Some of the discussions were brought to us by some of the patient groups that have basically had discussions prior to this, and they came up with some recommendations on their own. One was the Immune Deficiency Foundation and the Alpha-1 where they had a recommendation and came forward and wanted some sort of active system for notification.

There was another with the National Hemophilia Foundation; their Medical and Scientific Advisory Council had a recommendation that they adopted in October of '97, but certainly it had a lot of discussion and play time before that, and we had discussions with them.

Also, all of these patient groups have worked together, and they later became known as the Plasma User Coalition, and you'll hear from a representative of them

after I'm done speaking.

[Slide.]

There's been a lot of discussion on this, I'm sure. I don't need to go through all of this with you, but there was the FDA informational meeting. There was a discussion at this committee in March of '97 and some additional meetings. We talked about this Congressman Shays in the House of Representatives. And at the end of last year, we came before this committee and said that we had agreed in principle on some issues and that we were going to go forward with developing a system, and basically this is the answer to that.

[Slide.]

These are the members who are participating in our system. We have the four IPPIA members that I mentioned earlier, and we also reached out, because this really needs to be--to be truly effective for the patients and other users of this, we wanted to include as many of the distributors and other manufacturers that we could. So we reached out, and American Red Cross, Genetics Institute, and Novartis also have signed on. Certainly this isn't the end. This was the beginning of trying to get something in place. We will obviously have discussions with some of the smaller manufacturers and distributors as that becomes--as we become able to do that.

[Slide.]

As I said earlier, we also involved what later became the Plasma Users Coalition, and that's the Immune Deficiency Foundation, the National Hemophilia Foundation, Committee of Ten Thousand, and Alpha-1 Foundation.

[Slide.]

I'm not going to read all of this slide to you. This is basically what we presented last year at BPAC, which was the consensus that the industry had reached with those groups, with some FDA participation as well, and this just outlines our concept of what any kind of voluntary system needed to accomplish.

[Slide.]

And this is the time line. Again, I'm not going to go through all of this, but it's just to sort of lay out for you what was involved in putting this together. It wasn't something that you could just say, okay, we're going to do this and tomorrow turn it on. There was a lot of discussion. We had to go out and find a vendor that could actually do this for us. We had to make sure that everything was going right with them.

[Slide.]

By the middle of October, we had Phase I of our system fully operational, and we'll get into that in a minute of what that is. We intend to initiate Phase II

early next year, and we're also going to hopefully formally create our Advisory Committee. Right now we have a loose coalition of individuals participating in that, and we want to create that as a more formal unit.

[Slide.]

Going into it, this is kind of what we thought was the group of people that might be interested in this system. There's about 15,000 or so bleeding disorder patients who might be interested in this; somewhere around 40,000 primary immune deficient patients, about 5,000 alpha-1 antitrypsin deficient patients. The one unknown here was really the health care professionals and other, and that's one thing I wanted to mention about our system. This is not strictly for patients. We are actively encouraging physicians, other health care providers, anyone who has some interest in these types of therapies, to sign up for this so that notification can be sent to those individuals.

One of the things that we have included is we include all of our products on this, and for something like albumin where there isn't a patient population and there isn't a chronic use of this product, we really need to expand into the physicians and other hospital workers who might have an interest in this type of information on a more ongoing situation.

[Slide.]

Now I'm going to get into the operation of the system. Basically what we have are two different sections. There's a passive and active sections. In the passive section, it is basically a toll-free dial-in number which is 1-888-UPDATE-U, pretty easy to remember, and there are several things you can do once you call in to that number.

The first thing is you can listen to the recent actions that have happened on plasma-based therapies, and that's basically updated for the last six months, so it's a rolling--as six months go by, the new ones come on, the old ones come off. That's just if you hear about something and you want some quick information, you can call in, listen to this, and if there's something new on there, you can hear about it.

You can also register through a live operator. We have live operators, and we have extended hours for the first three months of the system. They basically go, I think, from 8:00 in the morning until 9:00 at night Eastern Standard Time, and then that will turn to more business-type hours as the system is in place for a longer period of time.

You can connect directly to a manufacturer, so one of the options is when you call in this number, if you have a company-specific question, instead of having to know all the 800 consumer hotlines from the manufacturers, you can just hear a list of manufacturers and, as the one you hear

comes up, you can just press that number and you'll be transferred directly to that manufacturer.

Also, basically this is going to be Phase II, check by lot number, so you will be able to call in, there will be an algorithm to punch in a lot number, and then that will search the computer contribution and it will come back and tell you whether or not there's been any action on that particular lot. So this would be useful for someone who's doing infusions from home to check something out right before they infuse.

[Slide.]

The active section is basically rapid outbound notification, and we chose 24 hours to mean rapid, and our goal is to reach 90 percent of the people in the database within the 24-hour time frame, and we have some standard operating procedures to address the ones that we aren't able to come in contact with in that quick amount of time.

When you sign up for this system, there are four ways that you can choose to be notified. That's phone, fax, overnight letter, or e-mail. And for all of those except the overnight letter, we will send a follow-up first-class mail letter. Basically what that does is ensures that someone gets a legible document in their hand, because I'm sure you all have heard things on the phone, and if there's three or four different lot numbers that are ten numbers

long, it starts to get confusing. Whereas, if you have the document in front of you in your hand, you're able to read that off in a much more legible fashion.

[Slide.]

The patient database, basically this is a voluntary system on both sides, so the manufacturers participate voluntarily as well as there's a voluntary system for patients or other interested parties to sign up. We can't mandate that people do. We can recommend, and we are working with the advocacy groups to ensure that we get a large number of people signed up for this. But the one downfall of this system is that it is voluntary on the patient side, and so we can only notify you if you choose to be so notified.

We have contracted with an outside third party to manage this system, and we did that for several reasons. One of them was confidentiality. There is a real concern about people knowing about you, about a disease that you may have, and, frankly, we don't need to know that type of information. So we have a third-party that keeps all that information in a database, off site, and we have no access to that. Also, the third party basically has the expertise to do this type of thing. The one thing we wanted to make sure, if we're going to put together a voluntary system, is that it would work and work well, and the best way to do

that is to find somebody who can manage this and do it on a full-time basis.

One of the other functions of the system is we will have checks on it every six months where we will send out just a notification by their chosen method for all the people in the system, which will just ensure that the system is working properly, that we can follow people as they move. One of the things that happens, I'm sure you understand, is you have a database of people and some people may move from one address to another; and if they don't call us to notify us, we have no way of knowing that. But if we check this every six months, one of the things we do is we follow up with a first-class letter if we can't contact somebody, and then the system will--you know, the mail system will move that forward under most circumstances.

That also gives us some credibility with the registrants if they sign up for a system and they actually see that they've gotten notified. Even if it isn't a particular instance of notification, it's just to know that, yes, the system works.

[Slide.]

This really is how we're going to go about trying to get people to register for this system. We're going to spread the word as much as we can. We're also going to have the patient groups who helped us put this together help

spread the word. So there are the four patient groups that we talked about earlier. There are some other ones that we're having some conversations with now that we will use to get to their members and say this is something that we think you should participate in, it'll get you some good information should the need arise. We're also going to be talking with physicians and other health care professionals. That's another good way to get access to the patient because there's a close relationship between the health care professional and the patient, and if we can get some help getting people to register that way, that will also be good. And then also the treatment centers where they're available.

[Slide.]

I just wanted to give you some information on the system itself. Basically we started this in October. As of the end of November, we had 586 people signed up for this. I was told as of yesterday there's slightly more than 650, so the number is rising rapidly. But this gives you a breakdown as to the way people would like to be notified and the type of registrant. We have it broken down into patient, parent, health care provider, and other. And as you can see, the majority here are patients and parents. So I think this shows that we're really getting to the people that we're trying to, and I think we're having some pretty good success with that.

[Slide.]

This is just some more information on the actual system, and this, once again, goes up through the end of November, and this just breaks down the type of products that people would like to be notified for. When you sign up on the registration form, you'll have a choice of what you'd like to be notified. You can choose all the products. You can choose a category, such as coagulation products. You can choose something more specific like Factor VIII. You can get even as specific as only recombinant Factor VIII. So there's a variety of ways to choose so that you're not overstimulated with recalls unless you so choose to be.

We also keep track of the dial-in section of the telephone, and as of the end of November, we had 384 people call in to use that as well.

[Slide.]

Pretty much the last thing I'd like to do is just go through--we've had use of the system two times. I just want to quickly go through a report from the second use, which was a recall by Alpha Therapeutics. And we intend to provide these summaries on a regular basis to all interested parties as events are completed just to give people an overview of what happened and give some credibility that the system is actually working like we said it is. So this is just--I had to break the report down into like three or four

slides because it wouldn't all fit on one slide and still be able to read anything.

So this is the first part. It just tells you who the manufacturer is, and for this one, because the lot numbers--there were quite a few, there's an actual attachment that includes all the lot numbers instead of listing them out on this page.

[Slide.]

Then you have here basically an event summary which is, you know, one paragraph of what happened, how it happened, when, why, and what the outcome was. That's the event results, and then there's a summary as well.

This is really more for people to read in their own time instead of me coming up here and reading the whole thing right now.

[Slide.]

Basically this is a summary of the event. We have it broken down by the type of method that people would like to be notified for, how many there are in each of those categories. The next column is basically the results within 24 hours, so, for example, for telephone there are 31 individuals in this system at that particular time that this event happened that wanted to be notified by telephone. The result is as of--within 24 hours, we reached 22 of those 31 people, and then the follow-up is we have standard operating

procedures of what to do in case we can't reach those people, and so we sent nine overnight letters to those individuals that we couldn't reach by telephone, and then we sent out first-class letters to the 22 people that we did reach. So this shows you the way the system actually works.

[Slide.]

The next slide basically breaks it down into the percentages of what happened. There's a little bit more detail on what happened with the ones that we didn't reach, and then some comments, if that's necessary, on those particular ones.

As you can see, for the telephone we had a 71 percent success rate of reaching the registrant within 24 hours. Hopefully we'll be able to increase that as we get some better use of the system and make sure. One of the things that happened here is people aren't necessarily familiar with this system, and when the system calls you to let you know that there's an event, you have to press 1 to hear the message. So six out of those nine that didn't get through were that people didn't press 1 to hear the message. So we just need to do a little better job of educating people on how to use the system. On the fax, we had an 81 percent rate, and I think probably what happens here is sometimes when people send in forms they're handwritten and we're unable to read the forms and you put a wrong number

in. We do have a way to verify when registrants fill out the form. We've sent out a notification to verify the information that they've sent us, but sometimes an event may happen before the verification is sent out, and we traced down the person because we couldn't reach them. Then e-mail, a much higher percentage, and overnight letter is 100 percent.

These percentages are obviously us reaching the person, getting information to them. We can't assure that someone actually read or understood the information. But this is the success rate of getting to the person.

[Slide.]

Basically, now we're just going to talk a little bit about some future considerations. In the near term, like I said, we want to create the formal advisory panel. We have now a loose coalition of individuals, both consumers and the manufacturers' representatives. We are encouraged that FDA is going to participate in this because we think we can get some valuable insight from them.

We're going to initiate Phase II, which is the dial-in lot checking, and we're also going to expand on to that to include Internet access so that we can have--the same information that's included on any particular recall notice will be up on the Internet so that people could just--similar to what you get at the CBER Web site, you'll get

that same information here.

Then expansion, we're talking about expanding the system to include Canada, which it doesn't include right now but it's not excluded either; and then also perhaps developing some type of system like this for Europe.

[Slide.]

More long term, one of the things that's going to be very important is evaluating the system performance. We have a system here, it's very new. There's really no experience with it, and I think evaluating over time how valuable it is will be good for both the manufacturers and the participants in the system.

I think we're going to look at covering additional products and consumer groups and adding additional features, perhaps lot tracking, having some additional notification options, and a greater sophistication of choices so maybe you can have a fax-back or adding other options in the future. So these are all things that will be discussed through the advisory panel to determine how well the system is working and what needs to be addressed.

[Slide.]

That's the end. I'd be happy to answer any questions anyone might have.

DR. HOLLINGER: Thank you, Jason. I think we'll go on, and then we'll come back to this issue in just a

second.

The last speaker is Bruce Ewenstein, who will talk about the patient notification system and the role of the FDA.

DR. EWENSTEIN: Thank you, Dr. Hollinger. I'd like to begin by thanking you and the other members of BPAC and the FDA for the opportunity to speak today on our experiences with the established patient notification system that you've just heard described and what we believe to be the appropriate role of the FDA in this important initiative.

My name is Dr. Bruce Ewenstein. I'm the Director of the Boston Hemophilia Center at Brigham and Women's Hospital and Children's Hospital, and I serve as the co-chair of the National Hemophilia Foundation's Blood Safety Working Group.

Today I'm here to speak on behalf of the Plasma Users Coalition, an umbrella organization representing the National Hemophilia Foundation, the Immune Deficiency Foundation, the Committee of Ten Thousand, the Hemophilia Federation of America, and the Alpha-1 Foundation, Alpha-1 National Associations.

We feel that the recent development and implementation of a patient notification system by which the end user of a blood product is directly notified by an

independent third party is a major achievement. Beyond the utility of the system itself, its creation demonstrates that consumers and industry can work together toward our common goal of improved blood product safety. We also believe that the FDA has made a significant contribution to this endeavor. The recognition by the FDA that it is the responsibility of industry to notify end users of an adverse condition in their product laid the groundwork upon which industry and the consumer advocacy organizations created the present notification system.

For the sake of time, I won't describe again but have put into the record what this notification system is, but I would like to just emphasize three particular points.

One, the system has been designed--and I hope people appreciate this--so that there is rapid communication to the end user, and yet confidentiality is maintained at all levels.

Second, the individual can select a particular product or class of products or the entire menu, and I know this was a question that was posed in the FDA presentations. We would feel that this is a desirable option.

And I would also like to emphasize, although it's been stated before, that we are encouraging both the consumers and the health care providers--physicians, nurses, pharmacists, et cetera--to register in order to maintain

both the good communication between the physician and the patient that you've heard was important to the FDA and to us, and also to reach additional unregistered patients through their providers.

We feel it's particularly noteworthy that this is an industry-wide effort, and we would like to thank the dedicated work of the staffs of IPPIA and the individual corporations, the plasma fractionators and the manufacturers of analogous recombinant products who have all now agreed to participate in this single unified system. I won't repeat the names of all the participants again, but I would like to just make special mention of Baxter Health Care and American Red Cross. I think their participation is noteworthy because they agreed early on to merge what was their previously established own systems into that of the IPPIA in order to achieve the efficiency and overall effectiveness that's only possible with a single communication network.

As you heard, the system underwent its first significant test a few weeks ago when the Alpha Therapeutic Corporation issued a particularly large recall of several products, including Factor VIII and IX concentrates and immune globulin. As Mr. Bablak presented, preliminary reports indicate that most registered individuals received timely reports. However, there were some problems noted.

Alpha initially omitted two lot numbers in its

report to the NNS and, moreover, had made the decision to not list products that had been distributed internationally and only list those that had been distributed domestically. And it's worth noting, I think, that the complete list of involved lots was provided to the FDA and accurately posted on the FDA's Web site and provided an important check that way on the system.

Now, the Plasma Users Coalition believes that regulations pertaining to recall communication require the timely and effective notification by the manufacturer to the end user of the product, and we believe that the FDA concurs with this position and has publicly stated so.

Now, we believe that the system now in operation is fully capable of meeting the manufacturer's obligation under the existing regulations and guidelines. We also believe that as the regulatory agency of jurisdiction, the FDA must and should provide the proper and necessary guidance and oversight to ensure that the effectiveness of the process of notifying individuals of adverse and at times potentially life-threatening situations affecting blood products goes forward.

The FDA's regulatory function might be accomplished in several ways. For instance, in establishing the current notification system, you've heard that there will be a formation of an advisory committee, and this committee is

to meet periodically to review the operations, make recommendations, and to confront any unforeseen situations that may develop. And we suggest that the FDA could work with this advisory committee.

In addition, the FDA, which necessarily works closely with industry in initiating recalls and withdrawals, could provide more immediate oversight regarding the accuracy and completeness of posted information.

The manufacturers, the trade organizations, and consumer organizations have each worked diligently to create what we think is an exceptional method by which to notify the end users of blood products. Nonetheless, the system is presently viewed by some as strictly voluntary, and therein lies what we perceive as a potential and real weakness. One or more of the participating manufacturers could withdraw at any time and for any reason. Moreover, the accuracy and the timeliness of the information provided is now not required to meet any officially promulgated standards. We strongly believe that FDA enforcement, through its participation and oversight, would ensure the long-term viability and integrity of the patient notification system.

The patient notification system is an important component of what we envision as a multi-tiered approach to blood product tracking and notification. Ultimately, such a system should be able to trace a product from the moment

it's created through the point of sale to the end user of that product. Moreover, the information chain should provide the ability for lookbacks from the end user back to the manufacturer. These additional components will ensure that all consumers of blood products are notified of withdrawals and recalls.

We believe that in order for the system to be completely effective, the FDA will need to provide regulatory guidance and mandate compliance. We fully understand the budgetary constraints and resultant manpower shortages at the FDA as potential obstacles, and the consumer organizations are prepared, therefore, to fully support efforts for greater funding of the FDA to ensure its ability to fulfill its regulatory role in support of a maximally effective system for blood product tracking and notification.

In closing, let me just restate our sense of accomplishment that a well-conceived patient notification system has been created through the hard work and cooperation of consumers working with manufacturers and with the helpful encouragement of the FDA. We believe that through participation in the system manufacturers are complying with their obligation to inform consumers of plasma-derived and analogous recombinant products of recalls and withdrawals in a timely and effective manner.

We have strongly urged our consumer and health care provider memberships to register, and today we call on the FDA to endorse this system and to provide the appropriate regulatory guidance and active participation.

Thank you.

DR. HOLLINGER: Thank you.

This completes the formal discussion of this topic. I'm going to open this up for public hearing right now, and there has been one person, Mr. Cavanaugh, who has asked to speak with the committee--the Committee of Ten Thousand, I believe it is--on this issue.

MR. CAVANAUGH: We endorse the statement that was given by our coalition, and we're very pleased that that coalition has come about, and we support the creation of the notification system.

But I just wanted to underscore the importance of connecting this system to the FDA's mandatory systems. We understand resource-constraint issues, but in an era of recalls of months of a company's output for serious contamination months after the fact, FDA should exercise every means at its disposal to alert every level of the distribution system and most especially patients.

We urge FDA, working with the notification system, to assume responsibility for providing information on potential contaminations to hematology and infectious

disease specialists, at a minimum, to assure that patients and at least several of the blood product user communities are being aided through provider alerts. In some of those communities, there is a lack of a central treatment structure, unlike with hemophilia treatment centers, and it is imperative that the treating physician, whoever that may be, be enrolled. It's vital to assure information reaches those whose health depends on receipt of this information.

Thank you.

DR. HOLLINGER: Is there anyone else that would like to speak to this? Yes, please state your name.

MS. HAMILTON: My name is Jan Hamilton. I'm with the Hemophilia Federation of America, and I support also everything that the Plasma Users Coalition, of which we are a part, said and echo what Dave Cavanaugh just mentioned.

There's one portion that I have mentioned with the people from National Notification System who are here, and I would just like for you all to be aware of it because it takes it one step farther of what has been said so far. We estimate that somewhere around 25 percent or so of, for instance, the hemophilia population is not seen in a hemophilia treatment center, and they are seen by primary physicians scattered out across the country in Podunk, USA. We hope that there's some sort of concerted effort to get to these primary docs to make them aware of the notification

system so that they can, too, be in on all the notifications and get to their individual patients.

Thank you.

DR. HOLLINGER: Thank you.

Is there anyone else? If not, this will--oh, yes, please?

MR. NAGLER: Rick Nagler. Coming from a legal background, what I would suggest is that there be incorporated in the system a strict trail of evidence, you might say. If the manufacturer produces is, who do they sell it to? Then they'll be responsible for notifying that person or that company. The home care company then has to keep records of who they distribute it to, and it would be their responsibility to notify them.

I have personal experience with this. About two years ago a product was recalled. I had just purchased a new batch of Factor VIII, and I was about to use it that evening. And thank goodness, due to the Hemophilia Federation and a home care company that's run by hemophiliacs, I was notified immediately. And they had kept the records strictly of what lot number went to whom, and it should just be a strict train of evidence straight down the line so you can track it from the source.

DR. HOLLINGER: Thank you.

MR. COLLINS: Yes, good afternoon. My name is

Patrick Collins. I'm Director of Government Relations at the National Hemophilia Foundation, and I just wanted to add to one point that Jason Bablak mentioned with regard to the number of people that have currently registered in the system.

Albeit we have only approximately 650 right now, the system was launched at the end of October at our 50th annual meeting, and what NHF is doing is in our monthly Community Alert, which is a newsletter that is sent out to our entire membership, for the upcoming issue we are included the actual notification form and our membership is some 23,000 people, so we anticipate that the numbers for the NNC enrollment should increase significantly.

I'm also aware that the other members of the Plasma Users Coalition are doing the same with their membership as well. So we anticipate a large blip upward in the numbers of people that are joining.

In addition, we are also hitting all the various industry meetings and trade meetings, such as the American Association of Blood Banks, the American Society of Hematologists, basically every possible way where we can get people to join the system, both consumers, providers, pharmacists, everywhere in the whole chain.

So thank you very much.

DR. HOLLINGER: Thank you.

If there are no further comments from the public, then that will close this part of the session.

We're going to take a break for about 20 minutes, and so we'll reconvene back here around 20 'til 4:00.

[Recess.]

DR. SMALLWOOD: We move to the committee discussion. Dr. Mary Beth Jacobson will make an announcement about an upcoming advisory committee meeting which may be of interest to the committee, as well as the audience.

Dr. Jacobson?

DR. JACOBS: Jacobs.

DR. SMALLWOOD: Sorry.

DR. JACOBS: Thank you, Dr. Smallwood.

Many of you are aware, but in case you aren't, we'd like to announce that FDA's Transmissible Spongiform Encephalopathies Advisory Committee is meeting a week from tomorrow, Friday, December 18th, at the Holiday Inn Bethesda at 8:00 in the morning. The committee will be asked to make a recommendation to FDA concerning possible deferral of blood donors based on possible foodborne exposure to the agent of BSE using geographical criteria in order to reduce the theoretical risk of blood-borne transmission of new-variant Creutzfeldt-Jakob disease. The committee will be asked to consider the recommendations in the light of

potential shortages of blood or blood products.

In order to incorporate the perspectives of this committee and also of the Advisory Committee on Blood Safety and Availability, we will have Dr. Hollinger, Dr. Nelson, Dr. Hoots, and Dr. Gilcher there either as temporary voting members or as guests.

Anyone who would like to make a comment at the open public meeting or also in written form can contact the Executive Secretary of that committee, who is Dr. William Freas, F-r-e-a-s, and his telephone number is (301) 827-1295.

Thank you.

DR. HOLLINGER: Thank you.

Well, we want to open up discussion about the end user notification initiative, and I'd like to just open it up for the committee for any comments. Dr. Boyle?

DR. BOYLE: In order to understand what we're dealing with in terms of this proposed mandatory notification, could somebody--Jason Bablak or somebody--explain the chain of distribution that occurs between the manufacturer and the end user so we have some sense of who we're going through and how that works?

MR. NAGLER: Basically, it's my experience that there's a middleman between fractionators and the user, usually a home care company. Sometimes there are buying

clubs that form. So basically it's purchased from the manufacturer, goes to a home care distribution company, and then to the patient.

MR. BABLAK: Just to expand on that a little bit, basically all of the manufacturers sell through wholesalers and distributors and then sell to either smaller distributors, specialty distributors, home health care companies or hospital pharmacies, that type of thing. So there is at least, you know, two or three intermediates between the final person who's selling the product and then the person buying it and then the manufacturer. And what happens is the people further down the line don't want to give the lists up to the manufacturer because then there's a potential they can be bypassed. So the manufacturers do not have access to those lists, but yet they have a responsibility for the product the whole way down through the chain. So right now it becomes difficult to get all the way down there because you have no control over your distributors down the line, but you still have responsibility for your product.

DR. BOYLE: So you have the responsibility in terms of the discussion of the chain of evidence but you have no way to compel the distribution or to evaluate whether or not it's actually occurred.

MR. BABLAK: Exactly. There are understandings

that companies are supposed to follow through and the manufacturer gives instructions on what to do. But you have no direct control over those people. So, therefore, you can't assure that that's actually going to happen.

DR. BOYLE: One more question, and this would be directed to the FDA, and I'm not sure who can answer it. But does the FDA have the authority to require the registration of persons or entities that sell, distribute, or dispense a biologic product? In other words, if the manufacturers can't reach down to that level, can the FDA require the registration of the people who handle those products to the end user?

MR. COLBURN: I might be able to shed some light on that. Donald Colburn, President and CEO of AHF, which is a hemophilia disease management company.

There actually are a number of checks and balances, and, unfortunately, some of them are not the checks and balances we would like to see. But as an example, with the exception of hospitals, who can dispense many of the biologicals that we're talking about from their blood banks, outside of that arena they have to be distributed through a licensed pharmacy. That licensed pharmacy has to be licensed in the state that it does business in. It is not uncommon for my company to receive multiple notifications of recalled drugs that we have never

even considered purchasing.

As most of you know, hemophilia is primarily a male disease, and we have often gotten birth control pill recalls.

Now, I think the interesting thing about that is we get that because we are listed as a pharmacy within the State of Connecticut, and as that notification system goes, that's how they do it. But there is also--from manufacturers, they actually sell directly to me. I then resell to the client base. In addition, you have hospitals who will oftentimes buy the product, put it up, and then dispense it to a home infusion company. And so, you know, it's not always multiple layers. It's just oftentimes two.

I have a legal liability if I break a chain of a recalled product. It just doesn't make sense--I would have to venture to say that I would be very surprised if any of the major players in home health care do not track by lot to patient. I can take a lot recall--for instance, the last recall that we had from Alpha--and we literally within the space of 30 minutes can determine who's received it, how much of it they've received, and be able to, you know, start contacting, if that helps you.

DR. KOERPER: Things get more complicated because hospitals often borrow factor from each other, and I don't know to what extent the hospital pharmacies keep track of

those lots and who they've lent to someone else. Larger hospitals such as my own, where we have a large hemophilia treatment center, our pharmacy and pharmacists know that they must keep track of the lot numbers. But oftentimes if this is sent off to a small hospital that doesn't deal with hemophilia patients on a regular basis, they don't appreciate the importance of noting the lot numbers that they dispense to specific patients.

Moreover, frequently patients borrow factor from each other. Since hemophilia is an inherited disease, oftentimes there are a number of family members--brothers or uncle and nephew--who are using the same product; and if one of them runs out, he'll just borrow his brother's or his uncle's product.

So even with the best intentions, you can't always assure that if you simply track by lot number that you're getting to the person who ultimately used the product. And I bring this up for an answer to someone's question about whether to track specifically by lot numbers. And I think it's more important that this general notice go out about a brand of product and that everybody who potentially may have used that brand gets the notice. Our patients are also instructed to keep their own records of their lot numbers so they can then reflect back and see whether they may have used or open their own refrigerator and see if they happen

to have some of that lot in their refrigerator that they borrowed from somebody else.

But I think the notice has to go out generally rather than specifically only to the people who on paper are the ones who got that lot.

DR. HOLLINGER: How many--any one patient, for example, how much might that person have at home and for how long does it sort of stay there before it's used? Can you give me a feeling?

DR. KOERPER: Yes. Patients with severe hemophilia are treating themselves every other day, so they will routinely get a month's supply, which is 15 doses. And if they've just gotten a shipment, then they'll have 15 doses, and this month being the end of the year, maybe their insurance is going to change, they may get an extra shipment toward the end of the month to make sure they have plenty to carry over while they're changing insurance companies and getting things ramped up with their new insurance company. So anywhere between 15 and 30 doses, and that would be used up in one to two months.

Other patients with mild hemophilia may treat themselves only once or twice a year. We generally recommend that they keep two or three doses in their refrigerator in case of emergency. But those two or three doses may sit there for a year before they're used. So even

though theoretically we're close to an expiration date, there may still be people who have some still in the refrigerator that's unused.

DR. HOLLINGER: The expiration date is usually how long?

DR. KOERPER: Well, when it leaves the manufacturer, I believe it's around two years. But by the time it gets through the chain of distribution into the patient's refrigerator, usually there's about a year left on it.

DR. HOLLINGER: And do the patients, by and large, usually get their material from one manufacturer primarily, and could there be more than one lot within that two months of stuff they have? Or could it be whatever is there, they might get it from Alpha, they might get it from Baxter and so on? Do they usually say I want this product or something?

DR. KOERPER: Most patients have a brand preference that they feel works the best for them or does not cause allergic reactions. So most patients will have only one brand in their refrigerator at one time.

DR. HOLLINGER: Yes?

DR. OHENE-FREMPONG: The system as it was described seems to be somewhat high-tech-dependent at the moment, and I think as Ms. Hamilton said earlier, not all

patients may be at the end of a computer to get e-mail or get a fax. And I'm concerned a little bit about just notification being not viewed as the end, but also monitoring to make sure that the right action was taken based on notification. What sort of follow-up monitoring is taken to make sure that, in fact, the person understood either the fax or the e-mail or a letter message and that, in fact, they returned the particular lot?

MR. BABLAK: At this point there is no actual follow-up action. What we do is we provide information to the patients through the system, and in that information packet is a list of things to do: return it to the place you bought it--there's a whole list of things that need to be accomplished. But we do not follow up, say, a week later and make sure the people have done that. I don't know that there's much that the manufacturers can do once we notify someone of that, much more we can do, except to encourage people to follow the directions as they come in the packet.

DR. OHENE-FREMPONG: Do you have in the system a network of local agents of the system that would follow up for you? If you are sitting far away as the manufacturer, but you're going through a distribution system, at least the treating agencies or associations, consumer groups--

MR. BABLAK: I think what you're asking here is beyond the scope of the system. This is more the

manufacturers themselves and how the product gets distributed through the chain and then how it might come back up through. And it's my understanding that basically the local distributor would then take that back and it would go back up through the chain just the way it came down. But that's really the only way that this can be accomplished, as I understand it.

DR. KOERPER: The treatment centers usually serve that function of, A, being the person--the people available that the patients can call locally for questions if they don't understand the nature of the recall or if they don't understand how to return the product. And we also get a list of all the patients who have been dispensed the implicated lots that we contact personally as well so that at that time--but it may be a day or two later, but we'll have a personal conversation with them and make sure that they understand what to do.

Now, occasionally there are instances where the patient will elect not to return the lot. This Alpha recall, for instance, the problem was with contaminated diluent from IGIV, and most patients had already either used up all their factor or had used several vials already without getting sick. The factor is in short supply, if not impossible to get, and many patients chose to continue using it rather than to return it.

DR. OHENE-FREMPONG: I'm a little concerned about the little bit of feedback. I mean, I just traveled for about three weeks and came back to about 200 piece of e-mail waiting for me. And to the sender, the job was done. They sent it to me, but they don't know that I read it. They don't know that I didn't open it. They don't even know that I was there to receive it. So if there is no quick way of checking--those who depends on centers, there are sort of checks and balances. The centers will take the responsibility to follow them. But somebody who is not at a center and who is depending on outside, distant agent to notify them, if there is no way of checking to make sure that, in fact, the information was received handled, you know, you have in your records that you performed the notification, but it may not have been received.

MR. BABLAK: I guess the answer to that is twofold. One, in certain cases, depending on how the patient is treated in such--like the hemophilia patient, the home health care company may do some of that follow-up work. But our view here also is that we're dealing with patients who have come to us and asked for a certain amount of information, and we assume that if patients sign up and want this information that they will be responsible and do what they feel is right once they have that information. So there has to be some level of responsibility on the patient

as well as on the manufacturer, and we think by getting them that information they can then make a responsible decision as to what they want to do at that particular situation.

DR. HOLLINGER: And, in reality, they tell you how they want to receive the information. Is that correct?

MR. BABLAK: Exactly.

DR. HOLLINGER: And can they say I want six different ways of receiving it, or do you say, you know, give us one way that you would prefer to have it? They say I want telephone, I want e-mail, and I want fax?

MR. BABLAK: We ask them for one choice, but for all of those choices except for the overnight letter, they then get a follow-up letter. So if you say you want e-mail, you will also get a first-class letter. So there is some follow-up there with that as well. You have a document in your hand.

DR. HOLLINGER: All right. I want to give Mr. Falter a minute.

MR. FALTER: I just wanted to respond to your earlier question regarding legal authority. While certainly we have control of the product throughout its movement, the product itself, and control over the manufacturer and immediate distributors, if the system we decide to put forward in an actual rulemaking, proposed rule, is of such a type that it would involve extensive involvement of health

care facilities, we would meet with the Health Care Finance Administration and there would be consideration whether they would cross-reference our standards and their standards. And, therefore, they would share in surveillance and enforcement of the provisions.

DR. BOYLE: But, specifically, since the real problem--one of the reasons why a lot of us are thrilled with the development of this voluntary system is in the case of immune deficient patients who are not normally treated through a center, but it's widely distributed, the bottom line is patients say they were never notified, the doctors say they were never notified, the pharmacies say they were never notified, so there was a breakdown somewhere in the existing system. And so there was an attempt to try to get to the end user.

If a new system is put in place to try to do a notification, a mandatory notification that involves multiple levels of consignees, one way to achieve that is to create a unified list of consignees by some kind of registration process, mandatory registration process, through the FDA so they would know who to send these notifications to. And the question is: Do you have the authority to require registration as you do require registration for medical device manufacturers and so on?

MR. FALTER: I don't think that active involvement

of FDA has been contemplated as yet. We're asking the industry and the patient groups for the best system, and then we'd codify it. But that active role of actually functioning as the people to whom you register hasn't been considered, so, therefore, the legal authority to do so has not been considered.

DR. BOYLE: Thank you.

MR. NAGLER: You have to treat it like a deadly product, like the legal system treats drug screen samples. Everyone who touches it has to keep records. And whatever system is developed, there's going to have to be time limits set for their reaction to notification. That way you can trace back or you can trace down from the manufacturer or you can trace up from the client. Basically, I think the legal liability ends once the client receives the product in regards to giving it to somebody else or whatever. If that were to happen, then it would be a legal matter.

But having been the product of military medicine and several different home care companies, a strict train of evidence has to be maintained. Everybody who touches it has to keep records, and that way you can go from step to step to step.

MS. HAMILTON: One thing that I'd like to mention that might be something that falls through the cracks on this, and at some point somebody mentioned only notifying

the people who you know got that particular lot. And I would like to encourage us to make it some kind of way known that everybody knows what the lot numbers are because people share product. They get in a bind. Their shipment is not in. They have an emergency. They know Johnny across town has what they need so they go borrow it. It may not even be the same product line that they normally use, but they have something they can have in an emergency.

So they would not have been notified, you know, if that lot had been recalled that they went and borrowed from Johnny cross town. So, you know, that needs to be taken into consideration in this chain of notification.

DR. HOLLINGER: How would you do that?

MS. HAMILTON: I think blanketly, you know, just making sure that every kind of way you can think of--on the Web, which doesn't reach everybody, but through chapters, through home care companies, through treatment centers, and ask them to let everybody know, too, you know, so that it doesn't just stay with the individual that was sent that lot from the manufacturer through whoever.

DR. HOLLINGER: Currently, I mean, the FDA, just on this Alpha-1, if you looked on their page there, there is a whole list of all the--

MS. HAMILTON: All the numbers--

DR. HOLLINGER: --recalled products, and anyone

can look at that.

MS. HAMILTON: But part of it, I think, is training the consumers, and that's part of our situation. We need to train the consumers to look for those things.

DR. HOLLINGER: Dr. Koerper?

DR. KOERPER: Is Mr. Bablak here still? One concern I have--and I don't know if it's been addressed yet--in California we have maybe 40 percent of our patients who are Spanish-speaking. Are the materials available in Spanish? Are the faxes or e-mails or phone calls and the letters going out in Spanish? Is there an option that patients can request Spanish language materials as opposed to English?

MR. BABLAK: At this time it's only in English. That point was brought to us actually at the NHF meeting that we attended and rolled this out, and so we are looking at ways that we can add additional capabilities, either by putting something on the notification that says in Spanish it's very important, ask somebody to translate this for you, or making it more sophisticated. And when I put up the signs of things we're looking to do in the future, that would certainly be one of them. And as we look to expand this in Europe, you know, language capabilities will be important. So that's something that has been brought to our attention, and we're looking at the best way to solve that,

and we will, both through our contractor and also through the advisory panel we have, try to work through that particular issue.

MS. KNOWLES: I think this is great that this is happening. It's probably well overdue. I have a couple points.

First, in terms of the people, to reach the people who are not treated by big centers, I think what you have to do is you have to use the media. You have to use the media--any of it, all of it. And I'm not trying to say to scare people, but just use it appropriately. I know FDA has used it before with other kinds of drug recalls and stuff.

Then in terms of the folks who do have access to computers and Internet, I think that it's important to post those international units, lots, companies, because there are U.S. citizens who travel abroad who turn on their computer and log onto the Internet. They might like to see that. Plus there are people in other countries who also turn on their computers and log onto the Internet, too.

DR. HOLLINGER: Yes, Dr. Ohene--

DR. OHENE-FREMPONG: That was going to be my question. I know you said you were not addressing the international patients yet, but I was asking whether you have plans to do so. They pay for their products.

MR. BABLAK: Well, like I said, we have had some

earlier discussions about moving this into Canada, and we're also working through an affiliate organization, EAPPI, European Plasma Products--Association of Plasma Products Producers, and we will work to expand it to Europe. Obviously, there are certain constraints that you can do with systems right now. The 800 number is only available for Canada and the United States. Certainly things we could do would be to post a regular dial-in number that wouldn't be toll-free that people could access from anywhere in the world, things like that.

So, obviously, suggestions that people have, you're welcome to give those to us, and we will see what we can do to improve the system.

DR. OHENE-FREMPONG: Is it possible to have an insert with a product that a consumer can fill in the form and return it and say I'm registering my name, address, and e-mail even if I live in Sao Paolo so you can contact me if there's a problem?

MR. BABLAK: At this point the registration forms are not distributed actually with the products. There has been some discussion of that, but that obviously involves going through an FDA process. Right now they are distributed through the patient organizations, through the physicians, and other means. But certainly that's something we could look into as well.

DR. HOLLINGER: Yes, Mark?

DR. MITCHELL: I still have some basic questions. How far down do you know--how far down the chain are you aware of who has your product?

MR. BABLAK: As the manufacturer, you mean?

DR. MITCHELL: As the manufacturer.

MR. BABLAK: As the manufacturer, you know who you directly sold it to, and that's it. So once it leaves your hands, you know who you sold it to, your direct consignee, from there those people can sell it as they see fit. And that is not shared up the chain because one of the reasons is that's business information that they don't want to give out.

DR. MITCHELL: Again, I think that the industry needs to be applauded for the efforts of having this voluntary system and also the consumer groups. I think that it's a very important and very good first step, and I think that--and it's clear that a lot of work has gone into it and a lot of time and a lot of money. So I don't think that you can be thanked enough for doing that.

But, again, I think that there does need to be, as has been pointed out here, more of a passive system where people will be notified of problems. And I also think that it should be--that blood products in general should be looked at as the ultimate recipient of notification. And,

you know, we can start with this, but I think that the issue is the risk of infection. I think that risk of infection from drugs and also the risk of people getting infected I think is very, very important. And I think that blood products are by their nature more likely to have people become infected by that, and so I think that it would be good for the FDA to ultimately go toward the goal of notifying all recipients of blood products, including the whole blood, which is probably the most risky type of blood product that there is as far as spreading infection.

DR. McCURDY: It seems to me--and whole blood was just mentioned. Blood banks have, for as long as I can remember, which is longer than I'd like to admit, they've had it necessary for them to track from the donor to the end user--that is, to the ultimate patient. And there are--in major cities, there's a lot of trans-shipping of blood from one hospital to another, particularly when blood is short. And yet you always are able--or should be able, and usually are able--to tell if you shipped it to Hospital A and Hospital A transferred it to Hospital B and on to C and so forth, you can track that down the line. And I'm not quite sure I understand how it can't get to the pharmacies or the ultimate dispenser to the patient.

It's probably a little more complex than blood when you're dealing with blood banks, but it would seem to

me that tracking any of these products to the person who gets the ultimate material to take home with them--I guess if they get it from Johnny across town, Johnny across town ought to make a phone call.

DR. HOLLINGER: Could they use systems like Smart Cards or some sort like that, you know, where people would have a card with the data that's imprinted on it where it could be swiped and so on when they pick up material that would be put onto the computer and so on, that kind of information? A lot of information goes on just regular credit cards, and certainly they can point out very quickly in the credit card industry the end user. You know, if you purchased gasoline the same day by somebody else, things like this, they call you up and they say, did you really do that?

The point is that a lot of that is very rapid. They haven't thought anything about that, I imagine, have they?

[No response.]

DR. HOLLINGER: Yes, Dr. Koerper?

DR. KOERPER: Is Mr. Falter still here?

DR. HOLLINGER: There he is.

DR. KOERPER: Good. Okay. Just a couple more points. I personally think that the users of IGIV should be notified because they are keeping the product at home and

using the product at home, analogous to the patients with hemophilia who are keeping the product at home. So I just wanted to make that point.

The other thing, just in general to the members of the FDA, I think--well, to start off with, I think that this is a very good first start in getting this vitally needed patient notification system. I think that it's vital that this momentum be continued and that ultimately the FDA devise a set of rules or regulations--I don't know what the appropriate terminology is--to ensure that this system continue. There's a lot of momentum to do it right now, but if everybody feels like, okay, now we've got our system and become complacent, then the system may gradually fall apart again. So I would encourage the FDA to continue your efforts to codify some rules and regulations as to the best way to maintain this system. I realize it make take a couple of years to get it through all the steps of the process, but I would encourage the FDA to continue with that effort.

MR. FALTER: We agree with the IGIV. The only point I was trying to make is that the system for tracking notification may differ between that product where 95 percent, we estimate, would be held at some health care facility until the time of use compared with the other products where--I don't have the percentage, but the

preponderance of the product is taken and held by the patient. And we're willing to consider treating the two differently as far as the means of achieving notification where we do believe that notification should take place.

DR. HOLLINGER: Yes, Dr. Stroncek?

DR. STRONCEK: I'm a little bit confused. It sounds like as far as anti-hemophilia factor and IGIV pharmacies are keeping track of lot numbers on who they dispense it to. But my interactions with pharmacies in the past concerning IGIV was they didn't necessarily know which lot numbers went to which patients.

And related to that, how about albumin? Albumin is very safe relative to these other products, yet it still a plasma derivative, and there may be reasons to recall that. Is there any discussion on keeping track of who gets which albumin or recalls for that?

MR. COLBURN: You just might find this interesting. One of the first CJD recalls--

DR. STRONCEK: State your name, please?

MR. COLBURN: Donald Colburn. One of the first CJD recalls that we had--I'll word this politely--a large east coast teaching institution called us and asked, hey, how do we figure out who got the albumin that we bought? We said, well, obviously, you track that with lot numbers, who it goes to, patients. No, no, we don't do that. Albumin's

a commodity. You know, we never know whose product we're going to have.

I think basically what we're dealing with here is just a couple of things, and I don't know how complicated this gets for the government, but every distributor, every pharmacy is licensed by the state where they do business in. I don't know what the difficulties would be for the Federal Government to mandate that for a certain class of products, such as biologicals or something, something injectable, that folks have to start to keep track of that. I mean, it is beyond my belief that that's not a requirement today. So if there's anything that this group can do to stimulate that type of activity, I would highly encourage you to.

The other option that is available, which, you know, gets close to that, quote, 100 percent notification issue, is really one that is very difficult to tackle. And when I say this, the CDC is going to cringe, but you could make certain of your conditions mandatory reporting, as they do with many other disease states, so that you actually have tracking of the people. We actually came close to that in the world of hemophilia in about 1978, but then everybody got worried about who's going to have the records, and so we didn't have it. And I think it would have helped if we had.

DR. HOLLINGER: Yes, Dr. Koerper?

DR. KOERPER: One simple thing that might

facilitate tracking is if there were bar codes on all the boxes or on the labels of the bottles themselves. Somebody asked about whether the unit number should be on the bottles, and the answer is yes, because patients take the bottles out of the box and stick it in the refrigerator, because that's the only part that has to be kept cold, and then they have no idea which bottle goes back in which box if they happen to have more than one box.

MR. COLBURN: The lot number is on the bottle.

DR. KOERPER: Is it on? Okay. But bar codes would be a simple way for pharmacies to scan and keep track. No, Don? Why not?

MR. COLBURN: We actually have designed a customized piece of software, and we initially thought we were going to do everything with bar codes because, you know, that was the coming thing, everybody was doing it.

The difficulty with the bar code is four-fold: The larger you get, the more nightmarish that becomes because you have to bar code every item that you've received, you have to bar code every item you dispense, and then you have to bar code every item that you have when you have an inventory. And if you are small, there is no problem doing that. If you grow to any substantial size, you are talking a logistical nightmare. It's not quite the same as doing the bar coding of widgets and guesstimating

that, you know, the hardware store, this guy says, okay, here's the bar code, I've got eight boxes. You literally would have to do each one because you oftentimes have different lots. You might have, you know, a Baxter shelf, a Bayer shelf, or something like that. But for the purposes of tracking to the patient, you've got to do each individual box. So it becomes a real nightmare time-wise.

DR. HOLLINGER: How do grocery stores do it?

MR. COLBURN: Somebody was kind enough to invent a universal system for them that all the manufacturers adopted, and at the same time allow them the opportunity to buy those cut little scanners. We don't have that. I suppose it could be developed.

DR. ELLISON: I think if we're going to go to a requirement for recording everything, a bar code system would be--you know, it's going to be an expensive investment, I guess, but I think it would be an easier way than recording it by hand or typewriter every lot number for every bottle of albumin and every bottle of AHF.

DR. KOERPER: And factor is often dispensed in an unbroken case. You could bar code and scan the box, the case.

MR. COLBURN: We didn't find it practical when we explored it because oftentimes the dose for a person is not like, you know--I mean, you would have to--you're doing

double bar coding. You might have a thousand size and a 250 size. And I'm not saying it's impossible. All I'm saying is that at least available to us, the technology was cost-wise prohibitive and then the time to administer that, since we don't really have a supermarket checkout, if you follow what I'm saying, when you're in the pharmacy situation, it's a little bit different.

DR. HOLLINGER: How are you recording your lot numbers now?

MR. COLBURN: When inventory is received, they're entered into a computer. When inventory is dispensed, it's dispensed from the computer, which automatically subtracts it. Obviously, you do your checks at the end of the month for what--you know, everything should equal.

DR. HOLLINGER: It's entered into the computer by hand?

MR. COLBURN: Sorry?

DR. HOLLINGER: It's entered into the computer by hand initially?

MR. COLBURN: Yes.

DR. MITCHELL: Is it trackable by individual patient?

MR. COLBURN: Yes. Anything that gets assigned to a patient when you're making up--at least our system, anything that goes to that particular patient goes into

their record, and that's what makes it easy for us when there are recalls to--

DR. MITCHELL: But that includes the lot number?

MR. COLBURN: Yes.

MR. BABLAK: I just wanted to make a statement regarding what people are talking about here with lot numbers and tracing that by patients and then also getting the information out to everybody, because I think that's sort of an apples-to-oranges comparison, and it's two different ideas that I think we need to talk about distinctly. The first one is something like our system which gets out the information to everybody who wants it. That's one thing, and that's something that's in place now.

Tracking lot number all the way to the patient is something different, which we support wholeheartedly, and that involves tracing all the way down through the chain of command and doing something like what Don was saying where they have it in the computer and it goes out with the patient. That may be done in some areas. I think in hemophilia treatment centers they are pretty good about keeping track of lot numbers, but a lot of the other patients do not receive that information.

Certainly it's my understanding for the IGIV patients, they may get several lots mixed up into a bag when they go in and get treatment, and then that's never conveyed

to them what those lot numbers are. So one of the things we're doing is trying to educate people that they need to make themselves aware about what lots they are receiving, but I think also the FDA has a role to play here in requiring lot number tracing all the way to the end user so that it's required all the way down the chain and this type of information is made available to them.

DR. HOLLINGER: Yes, Dr. Linden?

DR. LINDEN: I just wanted to echo some of the comments that others have made. I agree that theoretically we should be able to trace to the ultimate recipient for all these products, but the fact is that the standard of practice for blood banks is to have a disposition, either a computerized or manual log of where all the components went.

But in pharmacies, for a lot of the other derivatives, that is simply not the standard of practice. In our state, we actually tried to introduce a mandatory disposition for all plasma derivatives, and the pharmacists initiated a massive letter-writing campaign in opposition saying particularly for albumin the hospital pharmacy ships huge amounts down to the OR and then the OR dispenses it to individual patients, so the pharmacy has no idea, and that basically for, you know, immune globulin and a lot of these other products, they claim it is simply not possible for them to do that.

And while I don't believe that, I believe there would be enormous opposition to any system that were very broad, and I think focusing on the chronic users who depend on these products for their lives and use them time and time again, it seems to be an appropriate first place to start. And that's what the voluntary system does. These patients are motivated to find out for themselves, and I think also in any mandatory notification system that that would also be a first place to start. I think anything massive for all plasma derivatives simply would not work.

DR. HOLLINGER: Yes, Mark?

DR. MITCHELL: I have several things. First of all, I am surprised that it's not currently required that we keep lot numbers and that it be traceable by lot number. And I know that people complain that it's not possible and so on like that, you know, on an individual basis. But, I mean, they can bill for their products on an individual basis. And if they can come up with a system for billing, they should be able to come up with a system of making sure that the person got what they were billed for.

One of the things, getting specifically to the wording that's being proposed, I think I don't like the idea of a tracking system. I think that it's not really a tracking system. I think it's a system where it's traceable, where, if necessary, you can trace--when I say

tracking system, I expect that the manufacturer is going to have control over where it's going and is going to know who has it. And that's not necessarily what this system is--what I would expect that a system would be set up to do. I would expect that the system would be set up to make it traceable so that you could find out who had it if the need arose.

The other thing is that I think that the burden of this should actually be at the local level with the local distributor, be it a pharmacy, be it a center, because I think that they're in the best position to contact the local people, to know the local language, to do the things that need to--and hopefully they have an established relationship, and they'll have better addresses. Those kinds of issues I think can be better handled on a local level. So I think that the FDA, again, should put in place a trackable system where the manufacturer can reach the end distributor, not the end user necessarily but the end distributor. The end distributor could notify the patient.

That's it.

DR. HOLLINGER: Yes, Dr. Boyle?

DR. BOYLE: Just one question that might resolve a lot of what we've been discussing here, because it's sort of like our opinion or what we think is going on.

Are the dispensing pharmacies--this is a question

to the FDA. Are the dispensing pharmacies required to keep patient records by lot number of what was dispensed? And has compliance--if that is a rule, has compliance with that ever been done on a sample basis of pharmacies to tell what kind of situation actually is out there?

DR. HOLLINGER: Can somebody respond from the FDA?

MR. COLBURN: Donald Colburn. It's state-regulated, John, and each state has their own peculiarities, and, yes, they sometimes--some states inspect pharmacies. Lot numbers is not a big thing, though, because--I mean, it sound terrible. See, our operation is not typical of a retail pharmacy. If they don't do 300 prescriptions a day, they're in trouble. And I would be overwhelmed to do 300 a day. So, you know, it's a big difference.

DR. LINDEN: The State of New York is probably the number one most heavily regulated state in terms of health care in the country, and lot numbers are not required in New York State for plasma derivatives except for factor concentrates.

DR. HOLLINGER: Mr. Falter?

MR. FALTER: I'm tempted to ask if there's a lawyer in the house. But it's true that as far as directly regulating the pharmacy, FDA has, in large, not done that. The pharmacy has been asked to cooperate in some rulemaking, and in some cases as far as pharmacies associated with

health care facilities, they've been regulated through HCFA. But that is an issue that inevitably will be a problem to FDA of what do we do if a given pharmacy fails to cooperate.

DR. HOLLINGER: Okay. Thank you.

If there are no other questions, I think I'm going to adjourn the meeting for today. Now, there are two sessions tomorrow. We'll start at 8 o'clock. The first one is on inadvertent contamination of plasma pools for fractionation. We're going to revisit that again, and then discuss it with some different algorithms. The second one is going to be on recombination B-domain-deleted antihemophilic factor.

So with that, then--do you have anything?

DR. SMALLWOOD: Would the committee members remain for just a second? I need to distribute some information to you.

DR. HOLLINGER: The committee will remain.

[Whereupon, at 4:25 p.m., the meeting was adjourned, to reconvene at 8:00 a.m., Friday, December 11, 1998.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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