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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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BLOOD PRODUCTS ADVISORY COMMITTEE MEETING

Thursday, December 12, 2002

8:10 a.m.

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

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Donna M. DiMichele, M.D.
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Lori A. Styles, M.D.

Consumer Representative

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Temporary Voting Member

Liana Harvath, Ph.D.

Nonvoting Industry Representative (Acting)

Toby L. Simon, 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

Welcome, Statement of Conflict of Interest,

Announcements

DR. SMALLWOOD: Good morning. Welcome to the 75th meeting of the Blood Products Advisory Committee, the longest running series in the FDA history.

I am Linda Smallwood, the Executive Secretary. At this time, I will read for you the Conflict of Interest Statement that applies to this meeting.

This announcement is part of the public record for the Blood Products Advisory Committee meeting on December 12th, 2002.

Pursuant to the authority granted under the Committee Charter, the Director of FDA's Center for Biologics Evaluation and Research has appointed Dr. Liana Harvath as a temporary voting member.

Based on the agenda, it has been determined that there are no products being approved at this meeting. The committee participants have been screened for their financial interests. To determine if any conflicts of interest existed, the agency reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration has prepared general matter waivers for the special government employees participating in this meeting who required a waiver under Code 18, Section 208.

Because general topics impact on so many entities, it is not prudent to recite all potential conflicts of interest as they apply to each member. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

We would like to note for the record that Dr. Toby Simon is participating in this meeting as the Acting Non-Voting Industry Representative acting on behalf of regulated industry.

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

For the discussions on bacterial contamination, Dr. James Aubuchon has reported that he is a researcher on bacterial contamination. He has spoken on behalf of Pall Corporation and he is a member of the Medical Advisory Board for Verax.

Dr. Stephen Wagner is the Director of Cell Therapy, American Red Cross, Holland Laboratory. He also received a research grant from Organon Technika for the detection of bacteria in platelets.

In addition, there are speakers making industry presentations and speakers giving committee updates from regulated industry and other outside organizations. These speakers have financial interests associated with their employer and with other regulated firms. They were not screened for these conflicts of interest.

FDA participants are aware of the need to exclude themselves from the discussions involving specific products or firms for which they have not been screened for conflicts of interest. Their exclusion will be noted for the public record.

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

Waivers are available by written request under the Freedom of Information Act.

At this time, I would like to ask are there any declarations that need to be made before we proceed with this meeting.

Hearing none, I would just make a brief announcement that outside you should have found a sheet that listed the tentative dates of the Blood Products Advisory Committee meetings for the year 2003.

I hope that you will make a note on your calendar to hold these dates, but we will advise you when we have confirmed them.

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

Dr. Kenrad Nelson, Chairman. Dr. Lori Styles. Dr. Paul Schmidt. Dr. Harvey Klein. Dr. Liana Harvath. Dr. James Allen. Dr. Sherri Stuver. Dr. Robert Fallat. Dr. Toby Simon. Dr. Donna DiMichele. Dr. Mary Chamberland. Dr. Samuel Doppelt. Dr. Fitzpatrick. Dr. Judy Lew.

As you may have noticed, we have a very full agenda today, very full. We will try to keep on time and we will ask everyone's cooperation in doing so.

At this time, I would like to turn the proceedings of the meeting over to the Chairman, Dr. Kenrad Nelson.

DR. NELSON: Thank you, Dr. Smallwood.

The first item on the agenda are some committee updates.

First, Dr. Hira Nakhasi is going to summarize a Workshop on West Nile Virus that was held in November.

Committee Updates

Summary of Workshop on West Nile Virus

November 4-5, 2002

Hira Nakhasi, Ph.D.

DR. NAKHASI: Good morning. Thank you, Dr. Nelson. Since Linda said there is a full schedule today, it will be 6 o'clock is the regular time, I don't know how long we will be here, but I will try not to contribute to the delay and go right away into giving my update.

[Slide.]

This update is on the workshop which we held on November 4th and 5th, and many of you attended that workshop, and this was on the Development of Donor Screening Assays for West Nile Virus.

This workshop was in response to the recent epidemic in the epidemic 2002, and we wanted to see how we could understand what the epidemic is and how we can get the methodologies in testing soon developed and to screen the blood for the West Nile Virus.

[Slide.]

The goals of this workshop were as such, as pointed out here, we wanted to know what is going on with the current status on the West Nile pathogenesis and epidemiology in the U.S., and wanted to know what are the methodologies suitable for blood and tissue donor screening, and wanted to know from the industry perspective are they ready for testing in a large-scale screening mode.

Also, we wanted to hear from the manufacturers about the inactivation process in the blood products. We also wanted to hear from the proposed studies on prevalence and donors, and how this test would be licensed and FDA's expectation from that, and issues relevant to the implementation of the West Nile Virus.

It was a two-day full agenda, very interesting. There were a lot of discussions, but before I go to what we achieved from that meeting, I just want to give you a little bit of background for the people who may not know about West Nile Virus.

[Slide.]

The West Nile is a mosquito-borne flavivirus. It has a positive strand RNA and primarily infects birds, but horses and humans are incidental hosts.

About 80 percent of the infected persons remain asymptomatic, and the rest, 20 percent, develop mild febrile illness, flu-like symptoms. In that, approximately

1 in 150 infected people develop meningitis or encephalitis.

The viremic period can occur up to two weeks, but it is sometimes a very short period, but can also last for almost a month.

[Slide.]

Blood transmission of West Nile has been confirmed in the recent U.S. outbreak, and I will go into a little later about the cases. However, the magnitude of the risk of West Nile from transfusion is unknown at this time.

Again, the problem with this virus is that it is a very low titer virus compared to other viruses like HIV and HCV, 10^3 copies/ml. It is, as I said, viremia is transient, however, in some of these encephalitis patients, the viremia can be as high as 10^6 copies/ml.

The viremia resolves rapidly after seroconversion to IgM, and IgM can persist as long as one year. West Nile infection does not become chronic.

[Slide.]

The current status of West Nile as of last week, what we saw from the CDC/MMRW report, in 2002, the total number of West Nile cases reported was 3,775, of which 216 deaths have occurred.

The whole of the U.S. is practically endemic except in a few states in the West even though one case was found in L.A., but the majority of the United States is endemic.

[Slide.]

Viremia begins one to five days before the onset of symptoms and can last an average of six days. As I said earlier, you can go up to two weeks or 14 days.

The estimated risk at this time, Lyle Peterson from CDC had published a paper this year of one and two infections per 10,000 donations nationwide, however, in highly endemic regions where the activity is very high, 16 at the peak of the epidemic, was 16 per 10,000 with a mean of 68, because as I will say here, it can go from late August to late September, and that is the range there.

So far, 47 possible transfusion-transmitted cases have been reported. Out of that, 13 have been confirmed, 14 were not transfusion related, the rest are under investigation still going on at CDC.

[Slide.]

Then, people presented, researchers presented data on the methodologies which are suitable for blood and tissue donor screening.

Both serological and nucleic acid based tests were discussed. Basically, the serological or IgM antibody

assay, people have used recombinant antigen, but these are all research assays at this time, so mind you that they are not being used in a clinical setting, in a trial setting.

Some of these serological assays use recombinant antigen, can cross-react with other cousins of West Nile, like St. Louis encephalitis, dengue, and Japanese encephalitis, that is what we heard, however, this test could be used in a high throughput assay, low specimen volume, and can be multiplex, short turnaround, and can be adapted to the platforms which are existing already for serological testing for other components.

The nucleic acid tests, there are many PCR based, there are standard PCR, Taqman PCR, and NASBA, but what came out of the meeting, that Taqman, real-time PCR is the most sensitive at this time and equal to NASBA.

It could be used in the high throughput setting and detection limits are 15 plaque-forming units/ml to 15,000, however, in some of the cases, we heard also it can go 0.1 plaque-forming units/ml.

The caveat here is these tests so far, what we have is the human viremia is around 18 PFU. It is basically towards the tail end, and the lower limit of it, but then we recently heard, which I will maybe talk about down the road, that CDC has come up with a much more sensitive test, which is 10-fold sensitive and can, by

making such a modification concentrate, increase the volume of the sample and also making other changes in extraction.

But we heard that minipool NAT, detection rate is only 50 percent, and need to adapt smaller pools. Sue Stramer and ARC pointed out that even smaller, eight pools could be better, but maybe it may go to the usual NAT also.

[Slide.]

Again, there were some other issues. I don't want to go into detail of these things basically, because what we were told earlier, what we knew, that the West Nile Virus, once the virus is resolved, the antibody comes out, the viremia is resolved, but there are cases where RNA can be detected in the presence of antibody.

Again, under the caveat is that West Nile IgM can remain positive for one year longer without any infective, and whether there is infective, people do not know.

It looks like NAT could be the preferred choice for testing, however, IgM assays have also a role to play, the serological assays may have a role to play in confirmation of NAT results or seroconversion studies.

Also, it was discussed that if we screen blood, it will have a strong impact on tissue and organ donation and screening it.

Again, there was emphasis, which I will talk a little later, that we may have to have developed tests

which are suitable for cadaveric samples. Then, there are some activities going on in the panel development, I will talk a little bit later.

[Slide.]

The industry presented their data, which was basically plan and not much information. NGI presented some data where they have a NAT test which has sensitivity of 100 copies/ml with the range of 10 to 200 copies.

We heard that they had screened a large number of some samples, and the prevalence rate was 1 in 8,000, and one of the samples was very high titer donation and could result in pools of 64 and 512.

We also heard from GenProbe that they have a test development validating their tests using synthetic RNA, and the detection was 7.6 copies/ml. They are still working, we may hear maybe they have some information during the open discussion, that they are working on selecting the primers where they can use it. They are still in that mode.

Roche presented some data, which is basically the plan, no data, and then basically the development of tests, everybody agreed that it will be IND/BLA mechanisms. The validation of these tests will be at the beginning of 2003 and IND by the middle of 2003.

[Slide.]

We heard about the virus inactivation process strategies and several manufacturers presented data on using the currently used inactivation processes like psoralen, riboflavin, Inactine treatment of various blood components, and they also tested in West Nile, inactivation in that process, and they could inactivate more than 4 logs.

Therefore, on that basis, some people felt that they may not need to demonstrate West Nile Virus specific inactivation, however, other people, an equal number have held that it will be having showing West Nile Virus specific inactivation would also add a layer of safety similar to like HIV and HCV.

It is known that whenever there is an agent which we can culture and show that it can be specifically inactivated, it is FDA's understanding that we should use and show specific virus, specific inactivation.

However, there are caveats to these inactivation processes, such as adverse events which will be due to the products have been treated with such, such as immunological reactivity, increased sensitivity of blood cells to other drugs, specificity of inactivation between pathogens and hosts.

It was agreed upon that studies are needed to assess the risk of this inactivation process on blood products.

[Slide.]

Then, we heard about the proposed studies. There were several studies talked about, and there have been changes going on since we heard about studies. Now, we have heard that the ARC is conducting a linked study of a large number of samples, of 85,000, out of which 7,000 are going to be tested under the CDC, and will be tested by CDC's sensitive method which I described just a few moments ago.

Then, those samples will be tested by GenProbe's test, and these samples are linked.

Also, there is a research study under RADAR, which is REDS/TRIPS, but the samples are small. This is mostly going to be IgM sero problem studies, and finding out from that, sero problems in their samples, those seropositive samples will be tested for NAT using several NATs.

Then, the other study is the Roche samples. Roche has a large number of samples again collected through moderate, low, and high epidemic areas, and we have not heard anything about what is going on with that.

But the objective of all these studies was to really see the prevalence of viremia, compare minipool versus individual NAT, confirm viremia by IgM and RNA testing of donor follow-up samples, and then develop analytical-sensitive panels, compare West Nile, RNA, and IgM assays, and also incidence rate of transfusion-transmission of West Nile, and exposure to recipients by testing autologous donations for IgM reactivity.

These prevalence studies, we were told that it will be done in two phases, Phase I, where the performance of candidate West Nile RNA assays will be validated against the benchmark, which is the CDC NAT (50 geq/ml at 50 percent detection limit), which will be 100 geq/ml at 100 percent detection levels. We were told that the completion will be in the first quarter of 2003, that is to perform validation of these tests.

Then, Phase II is testing the samples by the middle of 2003 under IND.

[Slide.]

Here, we at CBER-FDA also have some effort going on with, first of all, there is several efforts actually, not some, several efforts going on. One is the development of reference panels for lot release testing, and these we are taking the virus from the CDC, culturing that, and then spiking into the naive blood and then that panel will be

distributed among different groups and tested to see how these tests will perform.

Then, we are also developing an in-house Taqman PCR and IgM assays to basically compare with CDC's, because many times we have to do investigational tests in-house, too, so we want to have the capability of the testing in-house, too.

The objective is basically to study viral dynamics, infection dose, distribution in the blood components, viral tropism, correlation between viral strains and infectious outcome.

[Slide.]

Then, we discussed about the regulatory pathway for these assay developments, and a few of these slides are directly stolen from Jay's presentation to AABB. The donor screening and supplemental tests will be reviewed as biological products under the PHS Act, and will be through IND/BLA process.

The instrument part and the software portion of this application will require separate 510(k) submission. You have heard in a couple of BPAC's earlier that a licensed test used for screening donors has been determined to be a major level of concern, so we need whatever is necessary for the submission to 510(k) has a major level of

concern which is given in this guidance, has to be part of that.

Also, last October, we used an FDA guidance, which talks about the current thinking on management of donors and products.

[Slide.]

Obviously, to the audience, I don't have to teach all this, what is needed for the validation of these tests, and also what are the needs for the clinical tests, so I don't want to go into detail there.

[Slide.]

There has been transmission through organ donations. There was quite a bit of discussion about what tests would be needed and how would we protect the organ donations. Again, this slide has been taken from Jay's slides.

The screening of tissue donors will come under FDA regulation after publication of a final rule on donor eligibility as proposed FDA rule would require approved donor screening tests for organ donations, and therefore, a need exists to show the effectiveness of West Nile Virus screening in the cadaveric blood samples.

Even though the solid organs and bone marrow are regulated by HRSA, FDA approves the tests which are commercially available.

[Slide.]

So, FDA's current thinking is to recommend routine use of licensed donor screening tests to detect donor infections, possible use of donor screening tests under IND. It would be built on existing platforms, validation in donor screening environment, adequate sensitivity to detect low level of viremia, and possible need for individual unit NAT.

Again, will encourage the technologies, such as viral concentration, which CDC is doing, because as I told you, the virus load is much, much lower, so to increase the sensitivity and then the development of reference panels to standardize different tests.

[Slide.]

Then, there was quite a bit of discussion on the implementation, rightfully so, from industry, how would we implement these tests, and there are a lot of issues which are relevant to that, logistic issues, and again, some of these have been taken directly from ARC's, Sue Stramer's presentation, which she described that there is the need to SOP modification, process qualification, space is a problem because there has to be enough room for other tests by medical information systems, which transfers the information, it is getting overloaded, how do we do that, and impact on the scheduled release of other tests because

there are also other tests, which you will hear this afternoon, Parvo B19, Chagas, and other tests, individual NAT, so how are we going to implement all this on top of the other things.

The other issues that were discussed, the testing, how will the testing be done, because we heard this epidemic is during certain period of the year, and will testing be done seasonal versus year-round, geographical versus national testing, individual versus minipool, do we need to test other related viruses because SLE, JE, and other infections have been also shown to occur and are related, transmitted through the blood, do we need to test those guys, and what have we learned from the past, for example, St. Louis encephalitis epidemic and what happened, can we think about that model and applied to this one.

Those are all hypothetical questions and we need to think about it and apply estimated risks to determine the need for donor screening. So, these were the issues in the implementation section.

[Slide.]

So, the general conclusions obviously were that we need to have specific tests, we need to determine what is the infectious dose of the virus. We need to know what components of the blood transmit this infectivity. We also

need to know how these infectious agents survive in blood banking storage conditions.

We also need to have confirmatory tests because this will be screened, we need to have a confirmatory test. How does it cross-check with other flaviviruses, or if there is a cross-check, do we need that type of test, multiplexing of these tests.

We also need to find out the estimated risk and then the cost of implementation. Obviously, FDA is not obligated regarding the cost, but obviously, we need to think in that direction, too.

[Slide.]

So, the general conclusion was that really, you know, I was very much impressed by the close cooperation between FDA, PHS, device manufacturers, and blood organizations, which they came all together in a very positive way to say that we need to develop NAT screening tests for the West Nile Virus, whether it is nucleic acid based or whether it is serological.

Testing will start under IND by the next West Nile Virus epidemic, I hope so, and meanwhile, the safety of the blood supply can be ensured in procedures which are in place in blood banking practices, and currently, FDA has issued a guidance for current thinking on management of donors and products.

Hopefully, we will see an outcome in the middle of next year about this testing.

Thank you very much.

DR. NELSON: Thank you, Dr. Nakhasi.

Any questions, comments? Judy.

DR. LEW: I just wanted to ask, can you clarify when you say 1 in 150 infected persons develop meningitis or encephalitis, is that 1 in 150 symptomatic or overall?

DR. NAKHASI: Yes, 150 infected people.

DR. LEW: Well, infected is different from symptomatic.

DR. NAKHASI: I think it's symptomatic, is that correct - no, infected, yes.

DR. SIMON: On the presentation that we heard at the last meeting from the CDC, they indicated that we were, at that time, thought to be about halfway through this particular epidemic, and I wonder, is there consideration that we might be at a point when this test is introduced that the risk has fallen to a low level, and how do you assess that risk going forward?

In other words, we will be introducing the test after the time period during which it might have been useful.

DR. NAKHASI: I am sorry, I didn't get the exact question.

DR. SIMON: What I am wondering is by the time the test is introduced, will we have passed through the period of risk and be at a point where the risk is so low, that there will be little value to the test.

DR. NAKHASI: If we are aiming at around maybe hopefully in June or so, and I think the epidemic which we had, the peak is between late August to late September, so I think the test, if it is introduced around that time, if we have a test available, it will not be past that time, so it will be before that even though there are some cases as early as in May sometimes. I believe that we will have a test which may be before that.

Jay, do you want to say something?

DR. EPSTEIN: Toby, I think you are suggesting that we may have had our epidemic, but no one can really predict what will happen in the next mosquito season, but the expectation is that we may see another epidemic of West Nile Virus with human infections in 2003, so the whole concept is to try to have a test available at least at the investigational level prior to or at the onset of that season, but no one can predict what that season will look like.

DR. NAKHASI: I hope that there is not, you know, we will see how the things are going, but if the predictions are that, you know, since 1999, the epidemics

have ranged in the summer months, so even though in 1999, it was much more localized in the New York area, but then, 2000 and 2001, it was less, but in 2002, it took off. Who knows what will happen?

Again, that is the reason I suggested that we need to think about from our past experiences, like SLE epidemics, it was 1977 or 1976, there was a higher epidemic than the following year, there was very little, so you are right, we hope, we think that if the trend continues, at least we have a test available at that time.

DR. ALLEN: In your background information, you pointed out, as the CDC did earlier, in your presentation, that the viremia is fairly low, only about 10^3 copies/ml. Then, under the Review of Methodologies with NAT testing, you noted under the caveats that the average human viremia is 18 plaque-forming units/ml.

Can you reconcile those?

DR. NAKHASI: The plaque-forming units and the copies, you know, the data is not really very well established at this time, so we and our laboratory and CDC is also really trying to figure out exactly how one plaque-forming, how many copies/ml, so the copy numbers we do not know exactly the numbers yet.

DR. NELSON: I guess the point is it is probably too low to just simply add this test to the current pool, minipools or maxipools.

DR. NAKHASI: Exactly.

DR. NELSON: Whatever the exact numbers of virus are in the average case.

DR. SCHMIDT: Thank you for your very complete report. One piece of information that is not in there, is in a CDC publication, saying that the incubation period of the disease can be as short as two days.

When we are dealing with something with an incubation period of two days and talking about the viremia one day after, we just have to look at this differently, I think, in our planning from our look-see at other diseases that we are used to dealing with.

DR. NAKHASI: Yes, I just actually in one of the slides, I mentioned it can range from one to five days, so you are right, I think that is very important.

There are a couple of things. One, the viremia is very low, and the second, the duration can be short, so it is a very tricky situation.

DR. KLEIN: Do we know whether antibody confers long-term protection or can you be reinfected two years from now with variant viruses?

DR. NAKHASI: I don't know. Any West Nile expert around here? I don't know how long the protection is. Mary?

DR. CHAMBERLAND: I think the sense is that there is long-term protection, that once you are infected, you are likely not susceptible, but how well that has been studied, I don't know.

DR. KLEIN: And that may have implications for the overall epidemic, not just the seasonal epidemic.

DR. NAKHASI: Also, there have been some reports which I remember that there is some cross-protection from other infectives, you know, like if you have some other infections, you may have some cross-protection.

DR. FITZPATRICK: You did say in your presentation that the whole of the U.S. is endemic, but there are states where there is neither animal or human evidence of West Nile, so I think it might help if you would clarify those states that are non-endemic or those areas that might be as opposed to. That statement might be construed as being a bit misleading.

DR. NAKHASI: Maybe from AABB presentation, you may hear that there are some states which are non-endemic and which are endemic, but actually Lyle Peterson's chart, which showed the last time, there were some of the states

which were not, but I think the AABB presentation will clarify that.

DR. ALLEN: I think the problem with trying to clarify is we don't know what is going to happen in the future. If we had tried to predict based on what happened in 1999, what would happen in 2001, we probably would have been quite wrong. I think we just haven't looked at the spread yet.

So far Arizona hasn't had any cases except imported cases, but we are absolutely certain that within the next year or two, we definitely will.

DR. FITZPATRICK: I agree. I think it would be more truthful to say it is most likely that the whole U.S. will become endemic, but it isn't yet.

DR. ALLEN: Right, and what is going to happen in terms of endemicity five years from now in terms of an established recurrent pattern once this first burst of it, the epidemic has passed across the nation, I think is anybody's guess at this point.

DR. NELSON: Yes. I guess that deals a little bit with Toby's concern. The St. Louis encephalitis epidemic in '75 was a large epidemic, equivalent to the current West Nile, but subsequently, there were just handfuls of cases in the subsequent years, even decades.

But I think the way West Nile is sort of spreading and the fact that the West has been spared so far except for one case in Los Angeles and an isolate I guess from Washington and Montana, the likelihood is that the West well could have an epidemic next year, but it is hard to predict.

We could put all this effort into developing a test and then have 10 cases next year. This is such a complex disease that it is hard to predict accurately.

I think AABB wanted to make a statement. Kay Gregory.

AABB, ABC, and ARC

Kay R. Gregory

MS. GREGORY: Thank you. Actually, this is a statement on behalf of the American Association of Blood Banks, America's Blood Centers, and the American Red Cross.

As of December 10, 2002, we know that 13 persons have been identified who acquired West Nile Virus infection from infected blood components from eight blood donors. These eight donors resided in states where mosquito-borne West Nile Virus infections to humans was documented by surveillance during the 2002 epidemic.

Transfusions of red blood cells, platelets, and fresh frozen plasma have been implicated. Persons with

transfusion-associated West Nile Virus infection were aged 7 to 75 years with a median of 47 years.

Four persons had hematological or other advanced malignancies; three had stem cell or organ transplantation; and four persons, all 70 years or older, received transfusions associated with other medical problems or a surgical procedure.

In addition, transfusion-related infection was documented in two women who received transfusions post-partum, and transmission to a breast-feeding infant from one of these women was documented. Nine patients developed West Nile Virus meningoencephalitis and three died.

As a result of this information, the American Association of Blood Banks, America's Blood Centers, the American Red Cross, and the Department of Defense are recommending a voluntary market withdrawal of selected frozen transfusable in-date products in inventory in an effort to mitigate the risk of transmission of West Nile Virus through blood transfusion.

The frozen products affected are products that were collected in areas experiencing mosquito-borne transmission of West Nile Virus to humans in 2002. This withdrawal includes both products that were in the blood collect facility and products that have been shipped to hospitals for transfusion.

The identified periods at issue will vary from state to state and were developed in consultation with the Centers for Disease Control and Prevention after review of the relevant epidemiologic and national surveillance data. The Food and Drug Administration has been briefed on this issue and is fully aware of this industry recommendation for the voluntary withdrawal of these products.

First, quarantine of frozen products collected during the defined risk periods.

Blood Centers and hospitals should immediately quarantine all frozen products collected during the defined risk period. The risk period is generally defined as seven days prior to onset of symptoms of the first reported meningoencephalitis case and ending with the seventh day after onset of the symptoms of the last reported meningoencephalitis case in the respective state. We are providing a table listing this information for each state.

Blood collection facilities will inform their hospital customers of the applicable defined risk period, including the peak incidence reached and expiration dates of the products involved. Blood collection facilities and hospitals should assess the available supply of frozen products as soon as possible after the initial notification.

Next, we considered the replacement of quarantined frozen products. As soon as feasible, and consistent with the need to maintain inventories critical for patient care, blood collection facilities will prioritize replacement of units collected during the week of peak incidence, followed by replacement of units collected during the antecedent and subsequent weeks.

This voluntary market withdrawal is intended to apply to all at-risk frozen product inventory collected in 2002, with the exception of frozen rare red cell products, which are to be handled in conformance with existing protocols for emergency release and transfusion of red cells.

Finally, prioritization of use of the quarantined product. To the extent that quarantined products must be transfused during this time period due to medical need, transfusion services are strongly advised to manage inventories in a manner that avoids transfusion of blood products collected during the peak incidence week for each applicable state.

If it becomes necessary to transfuse quarantined products, a prudent strategy would be to use those products that were collected as near as possible to the beginning or the end of the defined risk period.

Transfusion services are also advised whenever possible to avoid transfusion of products collected during the entire risk period for each relevant state to any of the following groups:

1. Immunocompromised patients (particularly organ and stem cell transplant recipients, patients on immunosuppressive drugs, and patients with hematological malignancies and myelodysplasia and other advanced malignancies);

2. Patients over 65 years of age; and

3. Pregnant, immediate post-partum and breast-feeding women.

Transfusion services may also want to give special consideration to neonates.

Let's talk about supply. To the extent possible, all blood collection facilities will make every effort to assure that adequate supplies of frozen products with lesser or no ascertainable risk are provided to areas where frozen products are at higher risk for West Nile Virus transmission through transfusion.

Under existing regulations, withdrawn plasma prepared from collections of whole blood may be relabeled as recovered plasma. Blood centers with existing short supply agreements may continue to ship recovered plasma for

further manufacture under their existing agreements, provided that temperature storage requirements are met.

However, blood collection facilities that wish to convert frozen plasma collected by apheresis during defined risk periods to recovered plasma prior to the frozen plasma out-date, must request a variance from the FDA. We want to stress that FDA will need to act on these variances expeditiously.

It is anticipated that cryoprecipitate, and frozen plasma converted to recovered plasma, that cannot be shipped for further manufacture under existing agreements will be destroyed.

Blood collection facilities have committed to make and stockpile frozen blood components during non-endemic months to minimize the need to make these products during defined risk periods for human West Nile Virus, until such time as a licensed test for West Nile Virus or other intervention (including testing under IND) is introduced.

We also have provided a list of states for which product retrieval is not necessary because West Nile Virus is not considered a problem for those states.

Then, we provided a list of all other states that are considered to have periods of risk for transmission of human West Nile Virus for 2002.

Thank you.

DR. NELSON: Thank you, Kay.

Comments or questions?

DR. DiMICHELE: I was wondering if you had an estimate of what percent of transfused patients your deferral requirements comprise. In other words, prioritization of the use of quarantine product under that, you have actually prioritized groups of patients who should not receive these products.

MS. GREGORY: That is correct.

DR. DiMICHELE: What percentage of patients who are transfused would this group comprise, do you have any idea?

MS. GREGORY: No, I really don't.

Celso, do you have any idea?

DR. BIANCO: No, we don't have an exact idea how many patients will be affected. We do not have an idea how much product is still available in hospitals at the present time, but there was a lot of thought into that and we were trying to do the best and to predict that in some situations, we may have to prioritize. Hopefully, most of it will be replaced by product outside.

This will be more difficult for states where the epidemic has been very intense and very long - Louisiana,

Michigan, and in Texas, and we hope we will be able to replace that product as soon as possible.

DR. DiMICHELE: The reason I was asking is that one group that is not included here is the chronically transfused group of patients, the patients who are receiving blood every two weeks.

Is there any reason that they were sort of excluded from this prioritization list?

DR. BIANCO: The prioritization, Donna, was made, they don't seem to be immunosuppressed, was based on the cases that were observed. There was a lot of transfusion during the period, so probably a lot of infected units were transfused, but those were the cases that were identified and reported, and that constituted the patient population. There were no neonates, but it was thought that it was prudent to do that.

DR. DiMICHELE: Thank you.

DR. PAGE: Peter Page, American Red Cross, Arlington, Virginia.

Pertinent to your first question, one could say that for every 100 units of whole blood collected, almost 100 red cell units are prepared and transfused, but only about 20 of them result in a plasma product for individual transfusion to a patient. The rest are essentially fractionated.

So, on the average, as far as number of units, not number of patients, it is about 20 percent has got red cells.

DR. NELSON: Thank you.

Next, is Dr. Mary Elizabeth Jacobs talking about medical device user fees.

Medical Device User Fee and

Modernization Act Of 2002 (MDUFMA)

Mary Elizabeth Jacobs, Ph.D.

DR. JACOBS: Thank you, Mr. Chairman, and good morning.

I am here today to tell you about the Medical Device User Fee and Modernization Act of 2002, which was signed by the President on October 25th.

[Slide.]

I would like to cover an overview of MDUFMA, the law itself and how it was developed, the user fee provisions, the performance goals that are related to the user fees, third-party inspections, which is one of the major provisions in the law under the modernization part of MDUFMA, some additional provisions, and then implementation, where we are now.

I have titled this part MDUFMA and CBER because there is one provision that applies to CBER in particular

that I want to mention and another provision which as a practical matter applies less to us.

However, I want to emphasize that all of these provisions apply to any center in FDA that regulates medical devices. CBER has been very committed to making this work and we have been involved in all stages of the analysis and negotiations.

First of all, we regulate at CBER up to 10 percent of the device workload in any given year. That comes primarily under blood-related devices, such as the blood screening tests which are used to screen donated blood.

We also are involved in combination products, which is specifically mentioned in the law, and combination products are products that have a combination of a biologic, a drug, and a device, two or three of those. For example, there are hemostatic agents which include device components and thrombin.

We are in a very active implementation state and you are going to be able to get information as it is developed, and I want to tell you the two places you can get that.

First of all, most of you probably know that our web site is fda.gov. You can then go to the Biologics Center or you can go to the Device Center. We anticipate

having one web site for all FDA centers related to devices, however, right now, as an interim measure, you can go for general information to the Devices Center, which is CDRH, and go to their web site, and you can send general inquiries to them at mdufma@cdrh.fda.gov.

For CBER-specific information, you can go to our web site, which is CBER under the FDA web site, go Devices, and under that, MDUFMA, and you can send in inquiries, as you always can to us. For manufacturers, it is matt@cber.fda.gov. For consumers and health care professionals, it is octma@cber.fda.gov.

[Slide.]

First, what is the background? The law was developed in consultation with the industry, the Congress, FDA, and with input from other organizations including consumers and patient groups.

The two major industry groups are AdvaMed, which used to be HEMA, and MDMA, Medical Device Manufacturers Association, and it had bipartisan House and Senate support.

In addition, during the negotiations, we invited in all the people who belonged to our BPAC mailing list. That includes the AABB, ARC, ABC, and all the consumer and patient groups, and we had a separate session with them.

Most of them came, and we went through all the provisions with them.

The law explicitly recognizes the need for additional medical device resources, and the basic idea behind user fees is that FDA will commit to faster review times than we are required to under the law.

This represents approximately 25 percent improvement in our review times. It isn't 25 percent for every single kind of application. For example, the expedited, which are very novel products, have a greater improvement time than some of the ones in which we had better times.

In exchange for this, the firms agreed to pay user fees, which will give them greater predictability. FDA, prior to having this, has already had 10 years of successful experience with what is called PDUFA, which is user fees for prescription therapeutic drugs. So, this MDUFA is building on that experience although it differs in certain ways.

It explicitly recognizes the need for additional resources and this has an appropriations piece. This law is not just user fees, it also has appropriated funds from the Congress, and it was signed, as I said, by October 26th, so the implementation clock is ticking.

[Slide.]

What are the key provisions? First of all, there are medical device user fees and, as I said, additional appropriations from the Congress. It includes third-party establishment inspections, which I will discuss, and that is covered by approximately 25 percent of the law.

It has greater oversight of reprocessed single-use devices, and this is the provision which I mentioned which doesn't, as a practical matter, come through CBER. These are primarily surgical instruments which are manufactured by what we call OEMs, original equipment manufacturers.

They are labeled for single use. They then are frequently reprocessed and resold and redistributed. As far as we know now, those will go through CDRH. It has provisions for supplying labeling electronically.

It has modular review of PMAs in the law, and we at CBER have already had modular reviews of PMAs, but that has been a matter of policy, and this is the first time it has been in the law.

Then, it has oversight by the Commissioner's Office of the combination products to which I referred.

[Slide.]

Now, what are the user fees? First of all, they apply to the major classifications of submissions, but not to all of them. For example, for PMAs which are the more

novel devices, for the BLAs which would be the licensed tests for blood screening, and to 510(k)s which, for those of you who know these, these are in general lower risk products in which you deal with the substantial equivalence to products which were originally on the market.

However, we have committed to maintain our performance on other kinds of submissions for which there are no user fees. For example, the investigational device exemptions in which we have 30 days to tell a firm no, you cannot start a clinical trial. We are maintaining our performance on those.

The structure is that we anticipate that there would be, beginning in 2003, this is the first year, $25.1 million in fee revenues, rising to $35 million in FY 2007. Then, there are workload compensations and other things which I would refer you to the law on those.

Then, we have $15 million in additional appropriations, to bring the total by the end of 2007 up to $50 million.

Now, one of the questions we are asked is do you have that appropriations passed yet, and the answer is not yet passed, the Congress will be coming back after the first of the year, however, we are actively implementing this and assuming it is going to be passed.

[Slide.]

The first year fees range from $154,000 for a premarket application, to $2,187 for a 510(k). There are reduced fees to protect small businesses, "small" meaning sales and receipts less than or equal to $30 million.

For small businesses, the fees are 38 percent of a standard fee for a PMA, except for 510(k)s, in which case they are 80 percent. The small business fee for 510(k) starts in 2004, and it sunsets October 1, 2007.

The device industry includes a wide range of corporations, some of which are extremely large global corporations, and some of which are almost amazingly small corporations. This was to have a structure that was appropriate to all of them.

The sunsetting in five years is similar to PDUFA. That also has had two, five-year cycles. We are now in the third cycle PDUFA 3, so this will sunset in five years unless it is renewed in some form as MDUFA 2.

[Slide.]

There are some waivers. There is no fee if the applicant is a Federal or State Government, unless it is going to be marketed. The first premarket application by a small business is free.

The first premarket report for a reprocessed device is free. There is no fee if there is a third-party review of a 510(k). We do have a provision in which

certain third parties can review 510(k)s. That is actually not very widely used. They are then submitted to FDA for concurrence or nonconcurrence. Finally, there is no fee if the device is solely for pediatric use.

[Slide.]

Now, what are the performance goals? Overall, we are aiming to improve our performance by 25 percent. These goals are defined in a letter from the Secretary of HHS, Secretary Thompson, to the Congress.

It differs from PDUFA in this. We have a combination of cycle goals, which means a firm sends us a submission and we respond to them. That is one cycle. For PMAs and 510(k)s, decision goals, meaning the time in which FDA finished its review and telling a firm it is approved, it is denied, or what it has to do exactly to get approved. That could be a nonapprovable or approvable decision.

The goals are measured in FDA days, so they are independent of the time that it takes for a firm to respond to us.

[Slide.]

The performance goals are very detailed, but I want to just go through with you what is the basic structure on all of these performance goals, so that when you read the goals letter, it will be more clear.

First of all, for BLAs, the licensed screening tests, as we said, the law takes effect October 26, 2002 for Fiscal Year 03. The first goals start in 2005, and that is because the initial funds are going to be used to hire additional people. That is why the goals are starting in 2005.

However, we are having an annual report with our stakeholders. We fully intend substantial progress on these, but formally, the goals come in, in 2005.

Secondly, the goals ramp up from 2005 to 2007, so for BLAs, the goals would go from 75 percent in 2005, to 90 percent in 2007.

The third thing is, as I said, we are reducing the time frame which is in the law for all of these categories. For example, for the initial submission on a BLA, which we call our response review and act on, which includes the complete review, the inspection, and going to an advisory committee if that is necessary, instead of doing those in 12 months, we will be doing the goals in 10 months. That is the basic structure.

Secondly, for BLAs, we now have a new category of resubmission. That means after we respond to you from your first cycle, the firm then responds to us unless they are licensed in the first cycle.

If their response has a substantial amount of data, for example, a completely new study, we have six months to respond. If they have less, for example, if they are providing updated stability information, we have two months to respond.

Those categories have already been used in PDUFA and I would anticipate the criteria we would use would be very similar to those that are used for the PDUFA guidance which is on our web site.

Finally, our manufacturing supplements again will go, instead of being done in six months, they will be 75 percent to 90 percent of the manufacturing supplements, that is, after licensing, would be done in four months.

[Slide.]

Let's go to PMAs, which would be used for the HIV diagnostics, which have been handled by CBER because of all of our work with HIV as it relates to the blood supply. These are handled by PMAs again. The target goals go from 2005 to 2007. They have cycle goals and they have the decision goal.

For example, a cycle goal would mean your first letter would be if you have major deficiencies, you would get what we call a major deficiency letter. Instead of doing that in 180 days, the goal is for 70 to 90 percent,

ramping up again from 2005 to 2007, you would get the letter in 150 days.

For PMAs, the decision goal, when we finished our review, the goal is that by 2007, we would have 50 percent completed in 180 days. That is quite a challenging goal for FDA.

Another provision in the law, which applies to this, and the next category I am going to talk to you about, is that because that is such a challenging goal for us, we have a provision in the law that says we will notify the Congress following a public meeting in 2006 if we think that that would be a problem for FDA to meet that goal.

[Slide.]

Let me now go to 510(k)s. The 510(k)s are the ones that are the more abbreviated kinds of applications which we call "substantially equivalent."

Here, we have instead of 90 days for our first letter, which we call "additional information," it is like a deficiency letter, you would get that in 75 days instead of 90 days, again changing the statutory deadline.

This also has a total time for the decision of 75 percent within 90 days, again a very challenging goal for FDA, and because of that, we again have the structure of a public meeting and a report to Congress if we believe that we can't meet that by 2007.

[Slide.]

The next provision is for third-party inspections. I mentioned to you that we do have a provision for third-party reviews for what are called "510(k)s."

Third-party inspections, I am only hitting a few of the points, 25 percent of the law covers third-party inspections. There was interest by a number of firms which market globally and which have inspections for other standards, for example, ISO, to be able to schedule all of their inspections together by paying a fee.

There was also some interest because at times FDA inspectors, because of the international situation, cannot go into certain countries although European inspectors are there. So, this would potentially solve some of the problems of companies which are in those countries.

These have the most complex provisions. In order to be accredited, the third party has to have the same conflict of interest provisions as we do internally at FDA. For example, people who would be third-party inspectors for medical devices cannot own stock in companies that are regulated by FDA, for example, food companies. So, they are just as stringent as those for FDA employers. That is only one of those.

These are all going to be spelled out in guidance to you, but there are already many of them in the laws.

The inspections are permitted only for quality systems in GMP. If it is pre-approval, BiMo, which is our monitoring of studies, and "for cause," those are exclusively for FDA.

[Slide.]

We must publish our accreditation criteria by next April. Those will, of course, be on the web site. They will cover establishments that market in the U.S. and abroad and where the other country accepts FDA inspection results.

The most recent FDA inspection must be classified as No Action Indicated or Voluntary Action Indicated, which means that the firm is already in good compliance before this happens, and FDA must periodically inspect, and this is anticipated to be one out of three.

Again, I have only hit some of the major points in this. If you are interested, please refer to the law and to our web site.

[Slide.]

Here are some additional provisions which would be of interest to our group here.

First, combination products. Those reviews are going to be coordinated by a new office in the Office of Commissioner. This is because firms were concerned because frequently, one center is the lead, another firm is very active in consultation. They want to make sure that there

are adequate tracking systems, so we are going to be having and are developing new tracking systems for this.

We already have a courier system between the centers. We had a meeting on November 25th, which we call a Part 15 hearing, which means we solicited input from firms and from other groups, and they made a number of provisions.

I already mentioned to you that under some circumstances, there will be electronic labeling.

Finally, I want to mention the provision which is specific to CBER, but could be also for the Center for Drugs if they have device reviews. Under Section 205, there will be a one year report to Congress on the timeliness and effectiveness of premarket reviews by centers other than the Center for Device and Radiological Health.

That means CBER will be developing a report which will go to the Commissioner's Office and to the Department about our timeliness and effectiveness, and our regulation of these devices.

[Slide.]

Next, let's go to implementation. We are very actively working on this now. We are developing the basic reference materials. You can look on the web site. We

have a kind of plain language version of the Act and frequently asked questions.

We have implementation teams for all of these major provisions and CBER is very actively involved in those. I just want to mention to you that there is one specific to stakeholder education. We have active training, for example, tomorrow, we have required training for everyone involved in reviewing these.

[Slide.]

Finally, I want to mention how can you make your views known to FDA. I already mentioned that we are opening a docket. That means you can send them in there. There will be annual public meetings starting in FY 2004 to review our progress.

The law specifically mentions consultation on certain specific policies including bundling of submissions and modular PMA.

Please look at our web site, send in your questions, and I would be happy to address any questions you have.

Thank you.

DR. NELSON: Thank you, Dr. Jacobs.

Any questions?

DR. FITZPATRICK: I just had one. You exempted State and Federal agencies. What about nonprofit corporations?

DR. JACOBS: That is a good question. I would have to go back and check the law to see if that is in there, and let me bring that to people's attention. I am not sure if that has been addressed.

Thank you.

DR. NELSON: Thank you.

Next, is an update on the approval of the OraQuick Rapid HIV-1 Antibody Test.

Approval of the OraQuick Rapid HIV-1 Antibody Test

Elliot P. Cowan, Ph.D.

DR. COWAN: Thank you, Dr. Nelson.

[Slide.]

The purpose of this update this morning is to inform you that on November 7th of this year, FDA approved the OraQuick Rapid HIV-1 Antibody Test.

The intended use of the OraQuick Rapid Test is to detect antibodies to HIV-1 in fingerstick whole blood specimens, as a point-of-care test to aid in the diagnosis of infection with HIV-1, and this test is intended to be suitable for use in multi-test algorithms designed for statistical validation of rapid HIV test results when such algorithms have been evaluated and approved.

[Slide.]

OraQuick is approved as a restricted device. Sale is restricted to clinical laboratories, number one, that have an adequate quality assurance program including planned systematic activities to provide adequate confidence that requirements for quality will be met; number two, where there is assurance that operators will receive and use the instructional materials.

It is approved for use only by an agent of a clinical laboratory.

[Slide.]

The test subjects must receive the "Subject Information" pamphlet prior to specimen collection and appropriate information when test results are provided.

The test is not approved for use to screen blood or tissue donors.

In addition, a customer letter will be included with all kits that are shipped, which has the provision that "By purchasing the device, you are doing so as an agent of a clinical laboratory and agree that you or any of your consignees will abide by the...restrictions on the sale, distribution, and use of the device."

[Slide.]

What I would like to do now is just run through the device, to describe it for you and how the test is performed.

It consists of several components including the main device itself, as well as a vial of buffer solution, the stand to hold the buffer solution, and a specimen collection loop.

[Slide.]

The first step in the procedure is to provide the test subject with a Subject Information pamphlet. This information pamphlet, it is a multi-page pamphlet containing such information items as what are HIV and AIDS, how does someone get HIV, to what is the OraQuick device, to the interpretation of the results, to where can I get more information about HIV and AIDS.

[Slide.]

A fingerstick is performed and the sample is collected within the specimen collection loop.

[Slide.]

That is then added to the vial that contains the test developer solution. The sample is mixed in the vial.

[Slide.]

The device is then inserted into the vial and then a time period of 20 to 60 minutes later, a result is read.

[Slide.]

The last step of the procedure calls for following CDC guidelines to inform the test subject of the test result and its interpretation.

Let me just show you what some of these results look like. Before I do that, let me just point out that there are two lines that could appear on this test. Number one, there is a line at the C position, which is the control, and at the T position, which is the test.

The C position will detect antibodies to human immunoglobulin. Therefore, this serves as a procedural control to ensure, number one, the specimen has been added, and, number two, that all the components of the test are working properly. All valid tests will have a line at the C position.

The T position, on the other hand, contains peptides to HIV-1, and a line here will indicate a reactive result. So, in this case, I am showing you a nonreactive result which is interpreted as negative for anybody as to HIV-1.

[Slide.]

Here are some examples of reactive results. The intensity of the lines may vary relative to one another, but any appearance of color at the T position is considered

to be a reactive result. Reactive results are interpreted as preliminary positive according to CDC guidelines.

[Slide.]

Finally an invalid result will occur if there is no line at the C position for the control. Even in the presence of a line at the T position, this would be considered an invalid result also.

This is invalid because of high background and the inability to see lines, this is considered invalid because the line does not appear in the proper position. Invalid test results should be repeated.

[Slide.]

OraQuick kit controls consist of a negative and a positive sample. The positive is low reactive. These are provided separately as an accessory to the kit.

In the product package insert, it is stated that kit controls should be run under several situations, number one, by each new operator, prior to performing testing on patient specimens, whenever a new lot of OraQuick is used for the first time, if there is a change in the conditions of testing, for example, new location, lighting, temperature, that sort of thing, and also a periodic interval specified by the quality assurance program of the laboratory doing the testing.

[Slide.]

I would like to now run through some of the clinical trial data used to support the approval of this test. For sensitivity, there were three groups of specimens that were studied, AIDS, known HIV-1 positives, and high risk specimens, a total of 1,146 specimens, of which 538 of those were determined to be true positives.

The OraQuick correctly identified 536 of these. Two specimens from known HIV-1 positive patients were not detected.

The sensitivity in these studies, it was therefore determined to be 99.6 percent with a 95 percent confidence interval of 98.5 percent to 99.9 percent. I would like to point out that this is within our minimal performance criteria for the performance of a rapid HIV test for sensitivity, which is 98 percent as lower bound of the 95 percent confidence interval, and that criterion was discussed at several BPAC sessions.

[Slide.]

Also, in support of sensitivity, analytical sensitivity studies were done looking at 11 seroconversion panels and 2 low titer panels. The performance of OraQuick was similar to licensed EIAs for the specimens.

In addition, unrelated medical conditions and interfering substances specimens were spiked with an HIV-1

positive specimen to give low positive reactivity. Again, in this case, all spiked specimens gave reactive results.

[Slide.]

For the specificity, a total of 1,250 low risk specimens were looked at, as well as non-reactive specimens from the high risk study, making a total of 1,856 true negative specimens that were examined. OraQuick correctly identified all of them. There were no false positive specimens in this study.

So, again, in these studies, specificity was determined to be 100 percent with a 95 percent confidence interval of 99.7 percent to 100 percent. Again, these are in line with our minimal criteria for performance for specificity as discussed at BPAC for a rapid HIV test, which is also 98 percent is the lower bound of the 95 percent confidence interval.

[Slide.]

Also, in support of specificity, unrelated medical conditions were examined, a total of 321 specimens, as well as 119 specimens with interfering substances. There were a few specimens that gave false positive results in this case, but the caveat here is that all of these specimens or most of these specimens were frozen repository specimens.

I would like to remind you that the intended use specimen type for OraQuick is a fresh fingerstick whole blood specimen. If anything, a repeatedly frozen and thawed specimen would be expected to give a false positive result if there is a problem at all.

[Slide.]

For reproducibility, reproducibility studies involved three sites, three lots, three different days, and three operators per site, making a total of nine operators who examined the blind-coded panel of five contrived whole blood specimens. Four of these were anti-HIV-1-positive and one was anti-HIV-1 antibody-negative.

The results for the 20-minute read time were 99.8 percent agreement, and at 55 to 60 minute read time, 100 percent agreement.

[Slide.]

I would also like to touch just very briefly on CLIA issues since this is something that we have talked about at BPAC before.

This test on approval was categorized as moderate complexity. The Company stated publicly on September 11th of this year that they will apply for CLIA waiver.

On November the 7th, at the time of the approval, Secretary Thompson made a statement at the OraQuick approval press conference, "I strongly encourage OraQuick

to ask the FDA for a CLIA waiver... if the company's data prove that the OraQuick test is safe and easy to use, it can get a CLIA waiver."

[Slide.]

Finally, I would like to point out that there are a number of things on the CBER web site. The approval letter for OraQuick is listed, as well as the package insert, the summary basis of approval, and an FDA talkpaper. I have listed the web site for you here. That could give you some more detailed information.

I would like to close by saying that we are continuing to actively work with additional manufacturers to approve more rapid HIV tests, so that we can move toward multi-test algorithms.

Thank you very much.

DR. NELSON: Thank you.

Questions or comments?

I noticed it is not approved for use in blood banks at this time, and it may not be terribly useful in that setting in the U.S., but I think in many developing countries where it is very difficult to follow and recontact donors once they leave the blood banking system, I know that it can be a real horrendous problem.

I can see where in some settings and at some blood banks, a rapid test could be very useful.

DR. COWAN: We have actually approached the company to provide us with data to support the use of OraQuick in this country as an emergency blood donor screen. In the absence of any data, though, we couldn't do that at this time.

DR. NELSON: I imagine that maybe Celso or somebody knows that there is probably very close to 100 percent success in finding a positive donor once all the tests results are available in this country, but it may not be 100 percent everywhere.

When that result goes down to, as in Northern Thailand, maybe 50 or 60 percent, that can be a real problem.

Thanks very much.

The next topic is Bacterial Contamination. We will start with Dr. Alan Williams.

DR. SMALLWOOD: I would just like to inform you that there is an electrical problem in the surrounding area, and Pepco is working on that, so we may have some intermittent interruptions, but I hope it won't be permanent.

I. Bacterial Contamination

A. Background and Introduction

Alan Williams, Ph.D.

DR. WILLIAMS: Thank you and good morning.

What I would like to do with this introduction is give a very brief overview of what is admittedly a very complex topic, and in the course of that, try to emphasize some of the key points that are in need of discussion and deliberation and emphasize those that are the topics for this meeting and others that might be appropriate for future discussion just to help provide focus.

I will then finish up by outlining the list of speakers for this session and the questions that are being posed to the committee.

[Slide.]

The first slide deals with the frequency and importance of bacterial contamination in the transfusion setting. Sepsis is, in fact, the second leading cause of transfusion-related fatalities. It follows a group in type and compatibility fatalities. It is the second cause in transfusion-associated acute lung injury is the third cause.

There are actually five to nine recognized fatalities per year associated with sepsis.

The most comprehensive study documenting clinical cases is the CDC-sponsored multi-center bacterial contamination BACON study published recently which documented that for single-donor platelets, clinical case

rates were 9.98, close to 10 per million, of which 1.94 per million were fatal.

Among random donor platelets, the rate is just slightly higher, 10.64 cases reported per million random donor platelets, 2.2 per million fatal.

Among red blood cells, refrigerator temperatures, case rates were 0.21 per million, of which 0.13 were fatal.

A conclusion was made that among the fatalities, most of them appeared to be related to gram-negative organisms and also related to units containing high levels of endotoxin.

Those are clinical cases. A different consideration is the amount of contamination in units that may result in a spectrum of outcomes in the recipient from no effect up to fatality.

The generally accepted figure for platelet units which are stored at room temperature is between 1 in 1,000 and 1 in 2,000 contamination risks per unit, but reports vary widely among institutions and among different studies that are published.

I think relevant to this is a study by Dr. Leiby with the Red Cross which looked at outdated platelets, studying close to 5,000 units. They found 4 to be positive, for a prevalence of 0.08 percent in that published study.

[Slide.]

Where does the contamination come from? In many cases, it simply isn't known, but due to the nature of the organisms and other criteria, it is known that skin contamination logically is the source of much of the product contamination.

This can occur by bacteria that are on the surface and are incompletely disinfected by the pre-phlebotomy decontamination process or because blood units are drawn with a large needle, there can, in fact, be a tissue plug that is caught up in the needle and makes its way into the collected blood product.

There also can be occult bacteremia in a donor who appears otherwise healthy, but may, in fact, be circulating bacteria in the blood. As mentioned, the contamination prevalence and incidence as measured by patient outcomes varies by site.

I think it is important that because this does vary, there may be room to control some of these extrinsic control points. One would expect that bacteremia in a donor for the most part might be a static level and that extrinsic contamination may contribute to some of the different levels of contamination that have been reported.

[Slide.]

A brief description of platelet components. Apheresis components, this is where the donor is hooked up to a machine for a period of time and one or more components is removed. It is also known as single donor platelets.

These products may, in fact, be split and the split units are then counted to make sure that they contain a minimum platelet count. In the country, about 6 million units per year are transfused, and these products had a five-day shelf life.

The other class of platelet products are pooled random donor platelets. There are the products derived from whole blood collections. Approximately, 3 million units per year are transfused, and these are pooled together from individual platelet concentrates derived from the whole blood units in different quantities, typically 4 to 6 platelet concentrates from allogeneic donors are pooled to make a dose of random donor platelets.

This pooling procedure, because it involves connecting up to individual platelet concentrates, currently requires a four-hour hold after the pooling procedure, and this is typically done in the transfusion service.

[Slide.]

Detection methods that are currently available. Clearly, the most sensitive and most widely available at this point is culturing, and there are variables related to the time the culture is taken, the volume, and source of the sample, how long the culture is incubated, and what type of detection system is used to monitor the culture. You will be hearing a lot more of that in the course of the session.

There are other techniques available. For the most part, without going into great detail, they tend to be considerably less sensitive than the culture mechanism, but may serve as a very quick read on an individual unit of platelets prior to transfusion as to whether there is moderate to gross contamination.

These other methods include urine dipsticks to measure pH less than 7 or a glucose level, Gram or other types of stains, swirling, and a technique that shows promise in terms of sensitivity, but needs further development is actually doing polymerase chain reaction looking at RNA content of different bacteria.

[Slide.]

Now, two automated or semi-automated culture devices were recently cleared by the FDA for quality control purposes, and I think a major issue that we will be dealing with today is that they are cleared for quality

control, not for pre-release testing. This is not a screening test which allows labeling of the product.

These two tests are the Biomerieux BacT/ALERT System, which is cleared for quality control of leukoreduced apheresis platelets, and there is a specific labeling indication in there that it is not designed for pre-release testing.

This system detects both aerobes and anaerobes although the latter appear to be infrequent causes of clinical sepsis in recipients. The system produces continuous monitoring and it is a calorimetric sensor.

The second system, made by Pall Medical Corporation, is a bacteria detection system, or BDS. It is cleared for the quality control of both leukoreduced random and apheresis platelets. The system detects primarily aerobic bacteria, and the sample could be taken as early as 24 hours after the platelet unit collection.

[Slide.]

Now, two issues are going to be recurring throughout the discussions today, but I want to point out that these are areas where there are data needed, and FDA is very interested in reconsidering the issues based on available data, but not specific topics for today's question consideration to the committee.

The first is the four-hour hold for pool random donor platelets, should that be extended and particularly should it be extended if we have procedures for culturing these units to determine sterility.

This is actually a regulation CFR 606 122. It raises a concern in terms of platelet pools in terms of trying to culture or do quality control because of the four-hour hold with the pool, it provides insufficient time for sampling that pool and developing a culture result before the pool actually would be transfused.

The techniques used for creating pooled random donor platelets are typically sterile dock welding of the individual platelet concentrates. There has been a lot of experience with this procedure. As you will hear today, there is one paper published in Europe in I think 1997, which called into question the sterility of the tube welds and whether, in fact, when the sterile docking device is used to create pooled platelets, whether sterility of the final product could be compromised. There will be specific discussion about that.

Also, FDA feels that to extend the four-hour hold, it would also create considerations beyond contamination, such as measuring in vitro platelet function, in vivo efficiency, and concerning the fact that

mixed leukocyte response to the set may take place when allogeneic units are pooled may stimulate cytokine release.

The second issue is extending the five-day platelet storage. This is based on an FDA memo issued in June of 1986. Clearly, extending platelet storage would be dependent on an approved pre-release bacterial detection system, not upon the QC systems currently cleared, and also would require data related to platelet efficacy when held seven days.

[Slide.]

Now, the four key elements that we are going to focus on in today's session regarding reduction of bacterial contamination risk is effective arm preparation, an update on the diversion pouch. This would be an integral pouch that would potentially capture the first 30 ml or so of blood, as well as any skin plug and hopefully pull off any bacteria that might be associated with that early volume.

It would be a discussion of FDA current thinking in terms of quality control mechanisms and data that might be needed to establish pre-release screening approval.

[Slide.]

On the arm preparation subject, which will be next, there will be a background review of the literature by John Lee in our Division of Blood Applications.

There is a question associated with this, and I will note that all of the questions are going to come at the end of the session because of the need to integrate the public hearing.

The first question is: Do available scientific data support preferential use of an isopropanol/tincture of iodine procedure for preparation of the donor's phlebotomy site?

[Slide.]

The second subsection will be an update from Dr. Jaro Vostal of the FDA on the diversion pouch and current FDA thinking. There is no question associated with this.

[Slide.]

The third subsection is the discussion of quality control. I am going to introduce some concepts, as well as current FDA thinking, on a quality control approach. There will be a data presentation by Dr. James Aubuchon from Dartmouth University on sterility of plastic tubing welds, as well as transfusion service experience with universal bacterial culturing of apheresis platelet units. We are representing published experience with these two procedures.

[Slide.]

Thirdly, data on the sterility of the plastic tubing weld by Tracy Manlove with Terumo Medical Corporation.

[Slide.]

Questions related to quality control.

Question No. 2. Do available data on the sterility of the sterile connecting device procedure support the use of this procedure to collect samples for bacterial detection from in-date platelet products?

Question No. 3. Does the committee concur with FDA's proposed statistical approach to providing quality control for platelet contamination?

[Slide.]

The final subsection, a discussion of data that might support pre-release screening. There will be a presentation by Dr. Steve Wagner with the American Red Cross Holland Laboratory on design of clinical trials for clearance of devices intended for screening of platelet products prior to transfusion, so it will be a background talk.

Again, Dr. Jaro Vostal will then present FDA's current thinking about a study design.

[Slide.]

A question related to this.

Question No. 4. Does the committee concur that data derived from FDA's proposed clinical trial design would be appropriate to support clearance of devices for pre-release screening of platelet products for transfusion? Yes or No.

So, it will be a packed session. I tried to establish some context for you. You will hear more about each of these topics as the session proceeds, but with that in mind, I would be happy to entertain questions.

DR. NELSON: Toby.

DR. SIMON: As some people may be aware, there is two prevalent systems in the laboratory industry for doing these kinds of cultures with rapid results - one, the BacT/ALERT, which you have approved for quality control of platelet screening, and the other, the Bactec system manufactured by Becton Dickinson.

My understanding is that as a result of litigation between the two companies, BD is unable or has agreed not to sell the Bactec system to blood centers.

Is the fact that you have cleared two devices for the quality control of platelets mean that non-cleared systems, such as the Bactec, could not be used on any FDA scheme for quality control by licensed and registered organizations?

DR. WILLIAMS: I am going to defer the answer on that to someone else if I can.

DR. EPSTEIN: Well, use of those systems would be off-label use because they are not indicated for quality control monitoring of platelets, so it becomes an issue of enforcement discretion. I can't tell you that that is permitted.

DR. NELSON: Any other questions?

DR. FITZPATRICK: Alan, it might be a little confusing. You used the term "four-hour hold" for the pooled random donor platelets. Actually, it is a four-hour expiration after pooling meaning that they have to be transfused within that four-hour period, right?

DR. WILLIAMS: That is correct. I think "four-hour hold" is kind of a term in common use, but that is correct, they do expire after four hours.

DR. NELSON: The next presentation is by Dr. John Lee on Skin Preparation of Phlebotomy.

B. Skin Preparation of Phlebotomy

John Lee, M.D.

DR. LEE: Thank you, Dr. Nelson, and good morning.

As Dr. Williams pointed out, effective donor arm preparation is a key step in preventing bacterial contamination of blood, particularly platelets.

[Slide.]

Up to this point, whenever we mention blood safety, we have typically meant viral safety, and much of our effort has been directed at improving viral safety towards zero risk. Bacterial safety has been in relation somewhat neglected, but nonetheless, a very important area for further study and concentration.

As Dr. Williams pointed out, platelet transfusion and particularly platelets have been implicated in many transfusion-associated problems, even fatalities, and contamination rate in platelet concentrates has been generally accepted to be about 1 unit in 1 to 2 per 1,000 units collected, and the actual rate of contamination depends on storage duration.

As you all know, platelets are stored at room temperature and the longer you store at room temperature, the higher the risk, and this is due to the fact that bacteria, unlike viruses, multiply within the collected blood after a brief lag phase.

When these causative organisms are identified, they turn out typically to be--well, I wouldn't say typically--but they often turn out to be a member of the skin flora. So, it is a reasonable conclusion that inadequate donor skin antisepsis is a major contributor to bacterial contamination of blood.

[Slide.]

The current most widely used technique in the U.S. in preparing the donor arm is the method outlined in the AABB Technical Manual. This is a two-stage procedure where at least an 8 cm diameter area is selected for phlebotomy.

As a Stage 1 procedure, that area is first scrubbed with a 0.7 percent iodophor preparation for at least 30 seconds. That area might be wet. It is actually written in the manual that you need not wait for it to dry and move on to the second step, where the second step consists of applying a 10 percent povidone-iodine, which has a 1 percent availability of free iodine.

This is to be applied beginning with the site of phlebotomy, the needle entry point, and move outward in a concentric spiral. After covering all of the at least 8 cm diameter area, that area should be allowed to stand for a minimum of 30 seconds.

[Slide.]

Now, this method has been in use at least in the U.S. widely for many years. There has been a recent challenger to that method, and that method has been described by two authors, the studies by those authors I will describe in a few minutes.

This is a method I believe widely used currently in Canada and also in UK. I will refer to this as the IPA/TI method, isopropyl alcohol, tincture of iodine method, but in the literature, it is more commonly referred to as the "Medi-Flex" method, because it comes in as a kit manufactured by a company as a Medi-Flex kit.

That also is a two-stage procedure where the first stage consists of applying 70 percent isopropyl alcohol in an up and down motion. The second stage is to apply 2 percent tincture of iodine again starting at the point of needle entry and moving outward in a concentric spiral. This should also be allowed to let stand for an adequate time for drying.

You notice that in both methods, two stages are involved. This is consistent with sort of the general accepted thinking in the surgical literature where if you apply two different antiseptics, they may work by two different mechanisms and therefore have a complementary, if not synergistic effect, in knocking out the bacterial flora on the skin.

Although that has been a general thinking, first of all, it is not clear whether that is true, and secondly, it is not clear whether that thinking applicable to patient care is necessarily applicable to phlebotomy at blood collection.

The second point that I would just like to insert at this point is that tincture of iodine itself is an alcohol solution. By "tincture," what we mean is iodine dissolved in alcohol, and to increase solubility of iodine, an iodine salt is added, something like potassium iodide, and it is suspended in roughly a 50 percent alcohol solution. Most typically, it is the ethyl alcohol for increased solubility.

[Slide.]

Now, this method has been a recent challenger and the reason for that is because of two out of the three available studies on donor arm preparation for blood collection.

The first of these studies was performed by Goldman et al. It is entitled, "Evaluation of Donor Skin Disinfection Methods," and it appeared in Transfusion in 1997.

The second of these studies was performed by McDonald et al in the UK. The Goldman study was performed in Canada. McDonald's study is entitled, "Evaluation of Donor Arm Disinfection Techniques," a very similar title. It appears in Vox Sanguinis in 2001. Both of these studies focused on the IPA/TI method, in other words, the Medi-Flex method.

The third study did not address the effectiveness of the Medi-Flex method, however, it is a study of a somewhat larger scope and relevant to this discussion, and again only the third available study in this area, so I included it here.

That study is entitled, "Impact of Donor Arm Skin Disinfection on the Bacterial Contamination Rate of Platelet Concentrates." It also appeared in Vox Sanguinis in 2002.

Each of these studies recognized the previous study. Dr. McDonald built on the results produced by Dr. Goldman, and Dr. Lee built on results obtained by Goldman and McDonald although he did not study the Medi-Flex kit per se. Dr. Lee's study was performed in Hong Kong.

[Slide.]

To describe these studies in a little more detail, Dr. Goldman compared four methods in three paired experiments.

The povidone method, which is the AABB method, that method was used in all three experiments as the common comparator to which the next three methods were compared, the first being the Medi-Flex IPA/TI, the second being a sponge followed by an ampule application, both of those applications involving 0.5 percent chlorhexidine in 70

percent isopropanol, and the last method being green soap followed by 70 percent isopropanol.

I might as well just point out that green soap is a method recognized in the Technical Manual by the AABB at this point as a method to use if donor proves to be allergic to iodine.

Dr. Goldman transferred the residual skin bacteria after arm preparation to culture plates by direct skin contact, so this was not a study about actual units collected or any kind of a clinical study. She simply enumerated bacteria in colonies appearing on culture plates after that culture plate has been directly pressed onto the donor's skin after arm preparation.

[Slide.]

These are the results that she obtained. In the first of these studies, a comparison between the AABB method, povidone-iodine, and the Medi-Flex method, IPA/tincture of iodine.

She did not produce a quantitative estimate of the relative effectiveness, but more of a qualitative result in that the Medi-Flex method resulted in a significantly higher number of procedures where the bacterial colonies, residual bacteria as measured by colony count was reduced either to zero or 1 to 10 in a

significantly higher proportion of donors than with povidone-iodine method, the AABB method.

Conversely, the percent of donors with a high residual bacterial count was associated with the AABB method in a higher percentage of donors than with the Medi-Flex kit. So, this gave you some indication in a qualitative sense that the Medi-Flex kit method might be more effective than the currently used AABB method in the U.S.

[Slide.]

In a similar way, she compared the other two agents to the povidone method, and in somewhat smaller studies the comparison between AABB method and the Medi-Flex method was performed in 126 subjects with a high statistical significance.

The povidone method was compared to the green soap, in other words, the AABB standard method was compared to the AABB back-up method, and that also indicated that the standard method is more effective than the back-up method with a high level of significance.

When the chlorhexidine method was compared to the povidone method, statistical significance was not achieved, and she concluded that the two methods are about comparable.

[Slide.]

So, based on these results, Dr. McDonald performed the next study, which also concentrated on the Medi-Flex kit. In this study, five techniques were compared, actually, five techniques were expanded to 12 variations.

The isopropanol/tincture of iodine method had four variations associated with it, and then also the standard AABB method was compared. The povidone-iodine method followed by 70 percent isopropanol was compared to it. A Cliniswab Alcohol method, which is a one-step method involving 70 percent isopropanol, that was studied.

Then, the North London method, which happened to be the prevailing method up to the point of performing this study, was also studied, and that involved applying 0.5 percent chlorhexidine in a 70 percent alcohol solution.

After arm preparation, instead of direct skin contact plating of culture plates, the investigator used moist saline swabs to transfer the residual skin bacteria from the prepared donor arm to the culture plates.

Which of these enumeration methods are better, it is difficult to say.

[Slide.]

These are the results that were obtained by that study. The Medi-Flex adapted method, and by "adapted," it is adapted because the second stage application of tincture

of iodine is applied in a straight up and down motion rather than a concentric spiral, and that proved to be or at least appeared to be the most effective, resulting in 99.8 percent reduction in 29 subjects.

The next best was the povidone method or the AABB method which had an effectiveness of about 90 percent reduction, and this was comparable to iodophor application followed by alcohol of again approximately 90 percent effectiveness.

The Cliniswab alcohol method was close behind with 87.4.

Now, it is difficult to say if the differences among these results are all that significant, particularly among the last three.

[Slide.]

Based on that initial study, a higher number of subjects were selected for a more in-depth study, comparing the existing North London method at that UK blood center to two variations of the Medi-Flex method which appeared to be promising.

One is the adapted method where the tincture of iodine is applied in straight up and down motion rather than spiral as the kit originally intended, and another variation being the IPA/TI Medi-Flex method as a two, double alcohol application variation where the isopropanol

component is applied twice rather than once. You would expect that to be a high performer, as well.

The results actually indicated that applying the alcohol once is as good as applying it twice, maybe even better, and applying the tincture of iodine suspended in 50 percent alcohol is applied in a straight up and down motion rather than in a concentric spiral.

Again, the significance of these results is difficult to make a statement about, but it seems clear that both of these variations are more effective than the then existing North London method, which only reduced to about 78.5 percent of the donor skin flora.

[Slide.]

So, these are very suggestive results and basically, that is all there is. Because of the lack of data in the blood collection literature, that became a major challenger to the existing AABB method, but several points need to be further considered before we widely accept that as the replacement method.

First of all, in the ways that the investigators counted the amount of residual skin flora, the way that they collected the sample either by moist saline swab or direct skin contact of the culture plate, certainly it was targeted at identifying the surface, but not the resident bacterial skin flora.

It is well accepted that the skin flora consists of basically two components, a transient component which resides in the skin surface which can easily be removed by simple hygiene and washing methods, and a more deeper resident flora which is down in between epithelial cells, which is difficult to remove mechanically, but has to be sterilized by an antiseptic method.

So, the enumeration method is targeted at the surface, a transient flora only. Further, it has been a concern that with every phlebotomy at blood collection, there is a small core of skin that may be generated by the needle that is difficult to remove and just stays with the blood component.

Certainly, that core of skin will contain the resident flora in deeper layers of the skin which has not in any way been measured by these two studies.

[Slide.]

Even if these counts truly reflected the skin flora levels, it is difficult to say what it means in the clinical arena. This is a laboratory study using culture plates. What it means in terms of contamination of the actual platelet units is only to be speculated about.

Even if the correlation were to prove to be present with the correlation between the laboratory results and the clinical outcome, one has to bear in mind that

neither of these studies, at least to my knowledge, through a close reading of the published articles, has been blinded in any way, and you might suspect that the care with which the arm was prepared with a particular agent might have great result on the results of obtained, as well as the care in setting up the cultures with either agent.

So, even though both investigators concluded a high statistical significance with the results obtained, it is difficult to say whether the studies had been set up in a way to allow an interpretation of high statistical significance, so it is not clear how to interpret the results despite the p-values obtained.

[Slide.]

Also, even if all of these prove to be concerns only, and not real worries to ponder over, you have to keep in mind that there are other intervention mechanisms being considered, such as the diversion pouch, such as the QC system, and such as the unit release testing system.

So, in the context of a multi-pronged approach to reducing bacterial contamination, what changing from one agent to the other agent means, that is difficult to know.

On the other side of evaluating a potential switch from one arm preparation method to another, what about the down side of things. The currently available

method seems to be well accepted by donors. Will the tincture of iodine be similarly well accepted?

It causes more of a skin irritation and staining than does the povidone. In terms of tincture of iodine, it is more readily available for absorption into the system at circulation. Now, where this is probably not much of a concern in the donor setting, it has been a concern in the patient setting.

So, all of these, how will it translate to donor acceptance and ultimately the effect on donor availability or blood availability, that has not been addressed at all.

[Slide.]

Further, the multiple variations of the Medi-Flex method that Dr. McDonald studied, it is difficult to say much about the small differences obtained in the results.

Furthermore, the tincture of iodine component is a high alcohol solution to begin with and what kind of results would you obtain with the same study if you were to include one more antiseptic solution of simply applying 70 percent isopropanol multiple times? That is another question to think about.

Lastly, the results obtained in these two blood collection studies conflict with results, parallel results available in the patient care literature where two investigators, Little and Wilson, studied that particular

antiseptic kit, the Medi-Flex, consisting of the same components, 70 percent isopropanol and 2 percent tincture of iodine.

They compared that to the povidone methods and other methods, but povidone being one of them, for their effectiveness in reducing contamination of blood cultures at patient sepsis workup, and either the results were only marginally better with the Medi-Flex kit or actually comparable as studied in the patient care sector.

So, these seemingly conflicting results have to be at least reconciled.

[Slide.]

Now, those are some critiques on these two studies supporting a transition over to the isopropanol/tincture of iodine method.

A third study is available in the blood collection literature, as I mentioned earlier, and this involved a comparison between 0.5 percent cetrimide and 0.5 percent chlorhexidine followed by 70 percent isopropanol application.

That method was compared to a povidone-iodine method, which is not the AABB method, but it is a method of applying povidone-iodine with 1 percent available iodine, which is like the prep solution of the AABB method, but that is used more as a scrub rather than a prep, and the

actual prep solution in this case was the 70 percent isopropanol.

What they did was just a study, not performed as an experiment, but tacked onto the actual transfusion service requirements. Over two, 10-month periods, these two studies were compared one after the other.

Over these two, 10-month periods, over 170,000 platelet units were cultured. The samples from these platelet units were injected into an aerobic bottle of the BacT/ALERT system culture bottle, and results were obtained that way.

So, although this does not address the Medi-Flex kit, currently, the one that has raised the whole point about potentially switching to a different solution, it does point out that it is possible, readily doable to generate data that is more applicable to a clinical interpretation.

As obtained by Lee et al, the cetrimide-chlorhexidine followed by isopropanol method resulted in 0.072 percent contamination rate.

When that was switched to povidone-iodine and isopropanol, in other words, basically, the scrub component of the method was switched from cetrimide-chlorhexidine to povidone-iodine, obtaining the same prep solution component isopropanol, when that switch was made, the contamination

rate fell to 0.042 percent, for approximately a 42 percent reduction. But again, I present this only to point out the possibility of performing more studies in this area.

[Slide.]

At this point, I would like to present five points to consider and show you some examples of supporting evidence from the clinical care literature.

Point No. 1 is that the following antiseptics listed here may be comparable in their ability to reduce skin bacterial flora - 10 percent povidone-iodine, 2 percent iodine tincture, 2 percent chlorhexidine, 70 percent isopropanol alcohol, or any combination of these, one step or two step.

[Slide.]

Why would this be? This is based on my reading of the literature. A study performed by Calfee et al, the article entitled, "Comparison of Four Antiseptics in a Randomized Trial," published in the Journal of Clinical Medical Biology in 2002, a very recent large-scale clinical study, where four antiseptics were compared in over 12,000 blood cultures - 10 percent povidone-iodine, 2 percent tincture of iodine, 70 percent isopropanol and povidone-iodine, and 70 percent ethyl alcohol or the kit called Persist.

No significant differences were seen in the contamination rates of the obtained blood cultures using these four different arm preparation methods.

The contamination rates ranged from 2.5 percent to 2.9 percent, and the preparations that contained an alcohol component tended to be more effective although no statistical significance could be derived.

[Slide.]

I list three additional studies here. The Calfee study I just described is listed in the first slide, a randomized study in over 12,000 blood cultures, but there are other smaller studies which support a similar conclusion - Trautner's study in 2002 where 2 percent tincture of iodine was compared with 2 percent alcoholic chlorhexidine or 2 percent chlorhexidine suspended in a high concentration of alcohol. In a blinded, 215 paired blood culture study, there was no significant difference between the two preparations.

Wilson's study in 2000, an iodophor/alcohol method was compared to the Medi-Flex method, isopropanol followed by a 2 percent tincture of iodine in over 12,000 blood cultures. Again, no significant difference.

An interesting study by Shahar in 1990 where this investigator was not convinced that the arm preparation methods of any kind made much of a difference, and he

compared 70 percent isopropanol followed by 10 percent povidone-iodine, and this is sort of the state-of-the-art at the time accepted method of collecting blood cultures or maybe you might call it good clinical practice before obtaining a blood culture sample.

That method was compared to a method used for just obtaining a blood sample for laboratory measurement, such as obtaining a CBC, where you take an alcohol swab, just briefly wipe the patient arm one or two times, blow on it a bit, and go right to needle insertion.

He compared the results, after comparing these two studies, in 181 paired blood cultures, and there was no significant difference. Something to think about.

A second point to consider. Washing with soaps is effective in removing transient surface skin flora, but has little effect on reducing the resident flora in the deeper layers of skin. In fact, the soap residue, if not completely removed at washing, may interfere with the activity of subsequently applied antiseptic.

[Slide.]

This is based largely on a close reading of an article published by Lilly, et al, where the article is entitled, "Detergents Compared with Each Other and with Antiseptics as Skin Degerming Agents."

The authors used the word "degerming" to indicate removal of both surface bacteria and removal of the more deeper layers of skin bacteria since the surface bacteria is felt to be more of a mechanical removal and the deeper layer removal being more of an actual microbial killing.

This was published in the Journal of Hygiene in 1979. Basically, this was an enumeration of hand bacteria before and after hand washing with a particular degerming agent in six subjects.

The way they measured the residual bacteria on hands was much more elaborate than was performed by either Goldman or McDonald, where what was described as a standard method was used.

A hand was first washed in some kind of basically a saline solution. The washing was performed and then also, subsequent to that, a hand washing was performed in the identical solution and an aliquot of that solution is then incorporated into a culture medium, into pour-in culture plates. Then, the bacterial colonies are enumerated.

So, it was more than a simple transfer of saline swab, more than a direct skin contact plating, was much more elaborate and felt to be superior in that it better measures the overall skin flora, not just the surface.

In any case, basically, the investigators compared three types of degerming procedures - one using a combination of antiseptic and a detergent, which the one used here was Hibiscrub, which is 4 percent chlorhexidine gluconate in a detergent base.

That was compared to detergent alone. For that, only the detergent base of the Hibiscrub solution was used, without the 4 percent chlorhexidine gluconate. Those two were also compared to an antiseptic, which was 0.5 percent chlorhexidine gluconate in 95 percent ethanol.

There are all kinds of critical comments that can be made about the enumeration methods, and so forth, but the results are rather largely spread out in that the antiseptic method, which she achieved 96 percent reduction--I think I switched the numbers here--the antiseptic method achieved 96.0 percent reduction, whereas, the detergent alone achieved 4.6 percent. A combination of antiseptic and detergent achieved 81.2 percent. So, the first two figures under the column Percent Reduction is switched. I apologize for that.

Basically, it tells you that antiseptic is much more effective than soap, and that is consistent with common sense, but what is somewhat surprising is that if you were to use a combination of soap plus antiseptic, it

may be no better, and, in fact, probably worse than applying the antiseptic alone.

[Slide.]

This Lilly study in 1979 is consistent with the results obtained by the Goldman study, which I described earlier, where the results obtained with the green soap method as compared to the standard AABB method of using two different concentrations of povidone-iodine, when that was compared with the green soap followed by isopropanol alcohol, it was clear that the povidone-iodine method, which did not involve a detergent, was superior to the green soap method, green soap being a soap.

[Slide.]

A third point to consider is the following. In the donor setting, iodine and chlorhexidine may not offer an advantage over isopropyl alcohol. These are the reasons why. Iodine and chlorhexidine is felt to be advantageous in the clinical care setting because, although it achieves antisepsis more slowly than does alcohol, it maintains it for a longer duration.

So, for instance, if you are concerned about catheter sepsis where the catheter will remain in the patient for prolonged periods of time, it is much more important how well maintained the initial site is. It is

just as important to maintain it as to achieve antisepsis to begin with.

Of course, the same applies for any surgical procedure. So, maintenance of antisepsis is important in clinical care, but in the donor setting for blood collection, rapid antisepsis is probably much more important than maintenance of antisepsis since phlebotomy is initiated and terminated quickly and there is no reason to really maintain antisepsis, and donors are probably not willing to stick around for long periods of time, and probably being able to achieve antisepsis rapidly is probably much more important.

Most of all, isopropanol is readily available, is inexpensive, and is well accepted by donors and patients alike. The same cannot be said about tincture of iodine.

[Slide.]

Two more points to consider. Repeat application of 70 percent isopropanol may be more effective than a single application. This is contrary to the result obtained by McDonald, et al, where the double alcohol variation of the Medi-Flex method proved no better and suggestively slightly worse than the standard method, than the adapted method where the tincture of iodine was applied in a concentric circle, in a straight up and down method rather than a concentric circle.

The second of these two points is that two-page antisepsis is not necessarily more effective than a single-step procedure. The reason for that comes from the following.

[Slide.]

Lilly et al also performed a second study entitled, "Limits to Progressive Reduction of Resident Skin Bacteria by Disinfection," that appeared in the Journal of Clinical Pathology in 1979, where two experiments were performed under this study.

First, the effect of repeat applications of an antiseptic and an effect on limits to progressive disinfection, where 12 hand disinfections were performed over four days, bacterial counts were measured after each handwashing and 4 different solutions were compared - soap, Hibiscrub, 0.3 percent chlorocresol, and 95 percent ethanol.

Also, a second experiment for evaluating the effect of a two-phase disinfection. Six hand disinfections were performed over two days with 95 percent ethanol as the first agent, and then an immediate seventh disinfection was performed after the sixth with a phase 2 agent.

The agents compared there were Hibiscrub base and Hibiscrub, 95 percent ethanol alone, and 0.5 percent chlorhexidine in 95 percent ethanol. So, 95 percent

ethanol was the first scrub, first phase in all of these methods followed by different second phase methods.

[Slide.]

These are the results obtained. This is for repeat application of an antiseptic or what the author described as "progressive limit" to disinfection.

With 0.3 percent chlorocresol, there was some initial reduction in bacterial count. That continued to be true to about seven or eight washings, but then it leveled off and no further benefit was derived from continuously repeatedly washing with this solution.

Hibiscrub, which is again a chlorhexidine/detergent combination, performed better than that. There was a more rapid initial reduction after first hand washing and good additional benefit was obtained by subsequent hand washing to about six procedures, but then it also began to level off and no benefit was derived beyond about seven or eight washings.

With 95 percent ethanol, achieved the greatest benefit with the first washing. Then, although there are some blips there, you generally get the sense that you got additional benefit from each hand washing, all the way down to 12 washings. It is not clear whether the benefits stop there. It is possible that additional washings could even produce more favorable results.

So, by this experiment, it appears that at least with repeated washing, 95 percent ethanol works best. Now, the reason for the 70 percent isopropanol being the most commonly used alcohol based antiseptic rather than a higher concentration, is that it is a balance between concentration and volatility, so the higher concentration, the better antisepsis, but it evaporates on the skin quicker than at lower concentration and the duration of contact is important for antisepsis, as well as the concentration itself.

So, 70 percent concentration appears to be the best compromise between strength and volatility. As a single application agent, 70 percent is most appropriate or most effective, but if you are evaluating multiple washings, then, a higher concentration could also be used.

[Slide.]

The second experiment, which evaluated the role of the two-phase method, which was generally accepted in the patient care arena, two phase more effective than one phase presumably because it used different mechanisms of pathogen reduction.

Whether or not that is true was looked at in the following way. When a Phase 1 solution was used, 95 percent ethanol, you got a certain reduction. Then, when it was immediately switched to a second phase agent,

presumably having different mechanism of action, the results obtained were rather surprising.

With a Hibiscrub base, which is actually the detergent-only component of the Hibiscrub solution, the reduction obtained by 95 percent ethanol was reversed in that the bacterial count actually rose.

With Hibiscrub or the detergent/antiseptic combination, the results were largely maintained, but were not improved. That was also true for 0.5 percent chlorhexidine and 90 percent ethanol. It was maintained, but not substantially improved. With 95 percent ethanol alone, you seem to get a further reduction.

So, the differences between Hibiscrub, chlorhexidine and ethanol, and ethanol, they are rather small, so again it is difficult to say much about that, but it seems clear that a soap is not a good thing to use after using an antiseptic.

The authors made the following comments about these results. They postulate that there is kind of a balance when you remove the surface bacteria, the bacteria residing in deeper layers of skin somehow make its way up to the top, and with repeated washing, you continuously knock that off.

An effective solution will knock it off every time used to the full potential of that particular

solution, so if 95 percent ethanol is able to reduce it to a certain level, it will keep knocking it toward that level with repeated washing.

But if you stop using the most effective solution, but use a less effective solution, then, the emerging flora from the deeper layers of skin are now faced with a less effective solution, so it is able to maintain a slightly higher count on the surface. This seems to be a reasonable postulate, but whether or not that is true is debatable, but at least these were the results obtained.

[Slide.]

As a summary, I have these five points to consider in evaluating whether or not the isopropanol/tincture of iodine method is more effective than the double povidone- iodine method, and/or points to consider in possibly selecting a most effective, most practical agent method to use for donor arm preparation and perhaps points to consider in designing further experiments to arrive at that information.

First, the major antiseptics appear to be rather comparable. Second, the use of soaps may interfere with antisepsis. Third, in the donor setting, iodine and chlorhexidine may not necessarily offer an advantage over simple isopropyl alcohol.

Fourth, repeat application of 70 percent isopropanol may be more effective than a single application. Lastly, two-phase antisepsis is not necessarily more effective than a single-step procedure.

[Slide.]

So, with those points in mind, I will present you with this question to be voted on and discussed about.

Do available scientific data support preferential use of an isopropanol/tincture of iodine skin preparation procedure for preparation of the donor's phlebotomy site?

I thank you for your attention.

DR. NELSON: Thank you, Dr. Lee.

Questions or comments?

DR. STYLES: You mentioned early in your report that the Medi-Flex system is already being used in Canada and the United Kingdom.

Is there any data on their relative contaminated unit incidence compared to ours, and/or is there any data--they must have changed at some point--if the change for them resulted in any reduction in contaminated units in their blood supplies?

DR. LEE: If it exists, I am not aware of it. There may be someone in the room that may be more current on that topic than I am. It hasn't been that long that the switch was made in their centers, so the data is probably

accruing, but I don't think those studies have been performed or published.

DR. STYLES: I would just imagine that they would have that same kind of surveillance data. I would hope that they would have that, just like we would, so that you might be able to get some indication in a "real world" setting of, you know, what sort of benefit that is going to give you.

DR. LEE: I agree.

DR. NELSON: Mary.

DR. CHAMBERLAND: Do you even know if these data are being collected in these countries, because I don't think we can assume that it necessarily is?

DR. LEE: That is quite true, no, I don't know that.

DR. SCHMIDT: Certainly, some of the complexity of this has to do with the human element, and you were only able to mention the care in arm preparation, and investigators of these studies I think don't see.

It has certainly been my experience in inspecting many, many blood collections to see often, frequently, no numbers, that the phlebotomist performs the correct preparation of the site and then, at the last minute, the index finger goes out to make sure that the vein is still there.

Now, these people are doing repetitive things, over and over again, but each one is kind of different because each site is different, each vein is different, et cetera.

If you ask the person who has been doing this for two weeks or two months why they did it, they will say, well, I just touched the edge of the site. If you ask the person who has been doing this for maybe two years or 20 years, they would say I didn't do it. In their minds, they didn't do it because they actually don't know that they are doing it.

Some of this I think is influenced now by the fact that they may be wearing gloves, and there is this instinctive thing that although they are not wearing the gloves for that purpose, that it is giving some protection.

I think that those of you who have hospital samples drawn for friends or yourself, if you pay attention to that, it is a different setting and they are drawing the sample for a different person, but in the hospital, this happens very frequently in the outpatient lab.

I have talked to hospital pathologists about it, and they think it is fine. Maybe it's fine, but we are not talking about that.

The second point I would like to make is with the tincture of iodine, I think nowadays it comes in prepared

individual cellophane-wrapped swabs. The old problem, which I would think would exist in developed countries and maybe some undeveloped states, is the jar of 50 percent alcohol/iodine sitting out there for hours and days, and sometimes a week, is certainly no longer 50 percent. That was one of the reasons everybody was so happy to see the other things come along.

The final point I would like to make, because maybe we won't come back to it, is the problem of pooling the platelet concentrates, of course, happens because of the timing in the hospital setting, the hospital blood bank or hospital transfusion service, and those people I don't think are exposed to many of the things we in this room are exposed to, and the care and attention given the training of the hospital technologist person in performing the pooling, how much space, what the facility is that the hospital administrator has given them to do this properly is something we don't see, but I can assure you it is not managed with the same care as we look at the preparation of the drugs, as we call them.

Thank you.

DR. ALLEN: I know we have got a very packed day, but let me ask one question and than make a couple of comments.

I was intrigued as I went through the papers that you provided at the difference between the observed rate of platelet contamination which generally is well below 1 percent and the false positive blood culture rates in the studies cited, which often were somewhere in the range of 2 to 4 percent.

Do you have any explanation? I mean I have got several hypotheses as to why that may be.

DR. LEE: I think it depends on the care with which you perform the procedure, and blood cultures are likely to be obtained by multiple people whereas, in blood collection, the same trained staff is repeatedly doing the same thing.

What is measured is different. In blood cultures, you are measuring blood cultures, but in other studies, at least the Goldman and McDonald studies, you know, they measured something quite different, so the contamination rates are not really transferrable from one area to the other.

DR. ALLEN: Similar types of hypotheses.

It has been a number of years since I have looked at this kind of literature although at an earlier point in my career, I looked at it fairly intensively. I am a little surprised at the relative paucity of data just looking at actual skin culture results.

There was a little bit presented here and there, but I think that this difference that you talked about between the transient or the surface bacteria, which are relatively easily removed and killed, versus the residual flora is extremely important.

Another of the issues that hasn't been adequately discussed is the extent of the scrubbing. As I remember from earlier literature, too intensive scrubbing may actually promote the release of some of the residual flora shortly after the completion of the cleansing process, which goes on for perhaps a minute or so, and that if one were to sample immediately after the antiseptic has dried and then 10 to 15 later you would find actually a very sudden rebound of the release of some of the deeper residual flora that is there, that if you don't have a residual antiseptic agent, may not then be killed at that point.

So, I disagree a little bit with the point that you made that donation is a fairly short-term process and you may not need a residual agent. Certainly, you don't need it to the extent that you do when you have an intravascular device, but certainly, donation can go on for 15 to 30 minutes or so, and I would just question whether perhaps having some degree of residual activity may not be preferable.

DR. LEE: Actually, apheresis donations go on for hours, so your point is well taken.

DR. ALLEN: I also would have liked to have seen much more study of 2 percent chlorhexidine and 70 percent isopropanol. It was mentioned in three of the papers, Calfee, Trautner, and Mackey, and to me, that certainly seems like a very promising alternative combination.

Finally, I think we do need some information about donor acceptability of iodine and chlorhexidine in the donation process, and that hasn't really been addressed at all.

DR. LEE: I don't know if there is much information other than experience type anecdotal information. I don't know if there is any published information about donor acceptance of those agents.

DR. DAVIS: In my own practice, which involves indwelling catheters, we prepare the skin using alcohol first, then, the povidone-iodine, and then we wipe off the iodine with alcohol again. That may address some of the donor concerns about residual iodine on the skin. It works very well for us.

DR. FITZPATRICK: John, first, I want to thank you for a really extensive review. We still seem to be needing to know what the source of the contamination is, whether it is the skin plug or the residual flora on the

skin. You addressed the flora on the skin. Previously, we have heard about the skin plug as the source.

In your opinion, which do you think is better to address?

DR. LEE: I tend to look at skin plug as an extension of the flora depending upon how you define flora. It is well accepted that there is a surface flora and a deeper flora, and if you make the deeper flora go pretty deep, then, you have a skin plug.

So, I think it is probably a continuum and not a separate skin plug issue to consider.

DR. FITZPATRICK: Just one other. Back in ancient history, we were required to culture a number of prep sites monthly in order to meet quality control criteria, and the recommendations were that you culture individual technicians, so that you could identify those techs that prepared the site properly as opposed to those that did not.

Personally, I found that very beneficial in my sites because we were able to identify individual phlebotomists who were the core of the problem and not doing the prep properly.

I think if we go to root cause, maybe we should relook at what we were trying to determine, which is who is doing the prep properly and who isn't, and maybe more of a

recommendation to examine the technique of each phlebotomist might even be beneficial.

DR. CHAMBERLAND: I just had a couple of sort of historical background questions. As I understand it, currently, what is out there is an industry standard, namely, the AABB standard, extra skin prep?

DR. LEE: That is my understanding, too.

DR. CHAMBERLAND: So, there is no FDA-related guidance in this area?

DR. LEE: True.

DR. CHAMBERLAND: With the release of these two studies and with the Medi-Flex procedure in two countries, adaptation or adoption of these methodologies, has there been any utilization of this methodology in the United States or are collection agencies pretty much committed to the AABB standard?

DR. LEE: I see some hands in the audience. I think Dr. Dodd might be more--

DR. CHAMBERLAND: I guess what I am trying to get is an appreciation of what is driving this, posing this question to the committee. Maybe in a subsequent presentation, this will become clearer, but is AABB, is FDA signaling that you are going to try and have a role in this vis-a-vis guidance development?

I guess I am just trying to get a better understanding of these data are out there, so what is driving the question to the committee and what might happen.

DR. LEE: I think I understand your question.

I think it occurred like this. There has been a number of national and international meetings about bacterial safety of collected blood. In every workshop/conference, skin site preparation is an issue, and in every one of those settings, these two studies by Goldman and McDonald are described either directly or by the investigators themselves.

There has been little critique at these workshops as to why not to adopt or switch to something that looks better, and there doesn't seem to be a huge down side. So, if there isn't a huge down side to this, and there is some reason to believe that it is more effective, then, shouldn't we move ahead and adopt this on a precautionary principle rather than wait until all data are available.

That is the concern that was raised within the FDA. We are hearing information that this is better, we are not hearing much information about why not to do it, then, shouldn't we move ahead.

DR. DODD: Thank you very much. Roger Dodd speaking right now as AABB president.

In fact, the method that is being discussed is not an AABB standard. It appears in the Technical Manual, which is recommendations. But, in fact, as you will hear later, the AABB is proposing a standard to move to a tincture of iodine approach with chlorhexidine as a backup.

At that point, it would become mandatory on the membership to employ that method, so that may muddy the waters, but it is important to recognize that povidone-iodine is a commonly used procedure which is recommended, but isn't listed as a standard.

DR. NELSON: We are going to discuss this further in the questions for the committee. If there aren't any other questions for Dr. Lee, I wonder if we could take a break now.

Other questions or burning comments? We will come back to this I guess at the end when we consider the questions.

Let's take a 20-minute break until 11:20.

[Recess.]

DR. SMALLWOOD: We have a very full agenda and we are grossly behind. That is an overstatement. However, we are going to try to do the best that we can to move forward quickly, and we are going to be enforcing the time frames for speakers.

We know that a lot of you are here because you wanted to participate in this meeting fully and particularly this afternoon's presentation on parvo. I also am aware that some of the committee members will have to leave, so we will have to make an adjustment and sacrifice, and I will ask your cooperation.

Thank you very much.

DR. NELSON: Continuing on Bacterial Contamination, Dr. Vostal.

C. Update on the Diversion Pouch

Jaro Vostal, M.D., Ph.D.

DR. VOSTAL: Thank you very much. I will try my best to sacrifice myself.

I will just give you a very brief update on an issue that was discussed with BPAC about a year and a half ago, and that is the issue of having a diversion pouch in the blood collection sets.

[Slide.]

As has been already mentioned a couple times during the day, the needle cutting through skin can make a skin plug, and this skin plug could be contaminated due to a poor skin prep or due to passing through a pocket of bacteria that is hidden under scar tissue.

The thought has been that if you could take the skin plug that probably is in the first couple cc's of the

blood that is coming through and divert it away from the main product bag, you might be able to reduce some of the contamination rate.

[Slide.]

When we were here the last time, we presented two studies that sort of addressed this option. One study was done by Steve Wagner, and this was a model of how a diversion pouch or diversion concept would work.

What he did was he intentionally contaminated a sample site coupler of a blood bag. He then sampled that with a large bore needle and collected the 7 ml fractions and looked at the bacterial content of these fractions.

He observed that within the first 21 ml, he was able to recover about 88.5 percent of the bacteria, and if he collected up to 40 ml, he was able to recover 95 percent of the total bacteria that he collected.

So, this in vitro model demonstrated that this concept would be possible.

[Slide.]

The second study we talked about last time was a clinical study done by Dr. Bruneau. They were collecting actual blood samples and then they had a special collection set which had two small pouches, each one holding 15 cc, and they diverted the initial blood, first, 15 cc in the

first one, and then the second one, and then collected the main product.

They measured the contamination rate in the bag 1 and bag 2. They found out that in 76 out of 3,300 donations, that both bags were positive, either bag 1 or bag 2 were positive, and that was a contamination rate of about 2.2 percent.

They also noticed that the first sample was positive and the second sample was negative in 55 out of the 76, so a potential reduction of contamination of 1.6 percent. So, they argued that you could reduce the contamination rate from 2.2 percent to 0.6 percent.

[Slide.]

Those were the studies that we discussed last time. This is a study that has been published since then, and it is a study by Dr. de Korte, and he actually measured contamination rate in standard collection sets. He has a relatively large number of units collected.

He compared the standard collection to a collection where the first 10 cc of the blood was diverted away from the final container. Under these conditions, he had 7,000 collections.

They observed a reduction from 0.35 percent contamination rate down to 0.21 percent, a reduction of about a third was achieved using only 10 cc diversion. Of

interest was specifically contamination by Staph species. In the standard collection, they had a 0.14 percent contamination with Staph, and if they diverted the 10 ml, they had 0.03 percent contamination due to Staph.

This is an actual clinical study that shows that using this diversion approach, you can actually reduce the contamination rate of the final product.

[Slide.]

So, when we were here last time, we talked about the kind of design that we would like to see for a product that is coming to the U.S. market. We stressed that it should be a closed system, that the diverted blood is separated from the final blood product by a unidirectional flow, and this would be usually achieved by kind of a breakaway closure.

First, the blood would flow into the bag. This would then be sealed permanently. Then, this would be opened, so the blood can flow into the final bag. Finally, that the volume of diverted blood would be sufficient to achieve the potential benefits that were sort of suggested by those clinical trials.

[Slide.]

In summary, what we discussed last time, we came to the conclusion that there do not appear to be any negative aspects of using a diversion system to collect

blood. The preliminary trial suggested that a diversion of a small volume of blood away from the main storage bag may be beneficial in decreasing the contamination rate.

An additional benefit could be of using the diverted blood for testing, and this could save units that are lost to inadequate sample collection at the end of phlebotomy. For example, if you collect a full unit and you lose the venous access at the end and you cannot collect the testing samples, that unit will usually be discarded, so collecting those samples upfront may be able to avoid this problem.

[Slide.]

The question that the FDA asked the BPAC Committee back then was whether manufacturers could claim a significant reduction in bacterial contamination of the blood product if the diversion pouch was included in the collection set.

The committee concluded that the available data did not support such a labeling claim, however, the committee supported the FDA position that a diversion pouch would be beneficial because of the potential reduction in bacterial contamination and reduction of lost products due to inadequate sample collection.

[Slide.]

So, to bring you up to date where we are right now, several manufacturers have submitted to the FDA blood collection sets. They are modified with a diversion pouch. These submissions are currently under review and we are hoping to clear these in the near future.

Thank you very much.

DR. NELSON: Thank you.

Questions?

DR. ALLEN: Of the manufacturers that have submitted products that are under review, do they provide clinical data that document the reduction in bacterial contamination similar to the studies that you presented, or is that proprietary information?

DR. VOSTAL: They actually do not provide clinical data. They provide the design that we suggested, and we have taken that as being sufficient.

DR. NELSON: Thank you.

Dr. Williams is next. Quality Control Approaches for Detection of Bacterial Contamination.

D. Quality Control Approaches for Detection of Bacterial Contamination

Alan Williams, Ph.D.

DR. WILLIAMS: Thank you.

[Slide.]

I think in understanding this situation, there needs to be some understanding of the current environment. As mentioned, bacterial sepsis is recognized as a second leading cause of transfusion-related fatalities.

Now, with the availability of automated culture devices which are cleared for quality control testing as early as 24 hours after collection, there is sort of a tug between trying to put out the safest products possible, as well as stay within the labeling associated with those cleared products.

It has been well publicized that there are industry initiatives to, in fact, test all in-date platelet products for evidence of contamination.

With the apheresis platelets, the cleared products will allow this to be done with the semi-automated systems as soon as 24 hours after the product is collected and have a culture result possibly before issue, so as not to hold up the product and make it done on a pre-release type situation, there potentially are mechanisms for retrieving that product should a problem be found with it.

As mentioned earlier, random donor platelets are a little more difficult or a lot more difficult because of the pooling procedure which takes place at the transfusion service and necessarily any monitoring of these products needs to be done by the less sensitive methods.

[Slide.]

In considering the first two issues, the first is just to ensure that no harm is done by undertaking quality control schemes that may be statistically based or might be done universally on all products.

Sampling of in-date platelet components for culture requires use of either a closed system, i.e., an integrated satellite bag which one can then clamp off and use to collect the sterile sample or a tubing weld made through the use of a sterile connection device.

Sterile connecting devices are considered functionally closed systems and obviously, with the platelet component, if you draw the sample, you want to be able to maintain a five-day shelf life.

[Slide.]

Now, the sterile connection procedure itself, there are a lot of data, particularly in the U.S. supporting the sterility of that procedure when the weld is, in fact, intact. This normally would include as part of the blood center's SOPs a visual inspection for leakage of the weld joint.

The data that exist include the original data submitted for the device review. A study, which will be described by Dr. Aubuchon in a few moments, published in Transfusion, and I think an observation, although not

specifically reflecting data collection, an acknowledgment that the sterile docking procedure is, in fact, commonly used on platelet products because when a platelet product is split, a sample needs to be drawn to actually count the content of the splits.

It would be potentially feasible to look at contamination for split platelet, apheresis platelet products versus non-split products, but I have not seen data that looks at that, but, in fact, the procedure is in place for a room temperature product.

[Slide.]

The reason for bringing the subject to the attention and a vote is, in fact, there is a single study of pooled platelet concentrates that reported 15 of 1,105 contaminated units among pools that were connected by tubing welds. As a control, they looked at cultures on 378 apheresis platelet concentrates.

The 15 contaminated units, in fact, they went back to the buffy coats of those products and did not find evidence of contamination, and the study concluded that quite possibly those contaminations were due to the sterile docking device itself. This was published in 1997 from the Belgian Red Cross.

I think subsequent speakers including Dr. Aubuchon and probably the Terumo speaker will have further comments about that study.

I think the bottom line in terms of policy development is that any extrinsic contamination rate of this magnitude would clearly negate any benefit of large-scale culturing.

[Slide.]

The other aspect of quality control is to identify strategies that facilitate the direct reduction of bacterial risk given that no current detection systems are approved for pre-release testing, and balance that with what is typically considered quality control, reducing bacterial risk by assuring that blood collection and processing procedures conform to a defined standard of some sort.

[Slide.]

There is a proposal currently under consideration by the Council of Europe, and I believe public comments have been received, and modification of this represents FDA's proposed current thinking on a statistical quality control procedure.

What this would involve, would be at least 5 percent or depending on facility size, a minimum of 1,500 platelet products annually are subject to quality control

testing for bacterial contamination at 24 hours or later when the product meets a labeling criterion for which one of the automated devices could be used, that is a possibility for random donor platelets or products that could not be used within the labeling requirements, it might be reasonable to use outdated products or other criteria to produce the culturing to meet this quality control method.

The second portion of this is that standard statistical methods should be used to identify significant deviations from a baseline contamination rate, and we are proposing that baseline contamination should not exceed 0.2 percent. So, in other words, 0.2 percent is the standard. The implementing facility needs to predefine a scheme which will establish a trigger point when that standard is surpassed on a statistical basis.

[Slide.]

The chosen method should be based, as I mentioned, on a predetermined level of confidence to exclude a maximum tolerated contamination rate, and an action limit should be established.

Now, there is an example in the handout that you received. I am not going to go into that in detail, but basically, the scheme that is laid out is that this

represents the activities of a small collection facility that is doing the 1,500 cultures per year.

In the course of the year, if they realize three cultures for 400 attempts at culturing, it would, in fact, put the background prevalence of contamination over the action level, but the statistics wouldn't be supportive of the fact that this sample accurately represents that level of contamination in the entire process.

However, if that site designated that within the annual sampling period, they found 7 positive units, this would not only constitute an action level that was exceeded simply based on the prevalence of the contamination, but also statistically within defined confidence and power limits would be shown to exceed that 0.2 percent standard.

This is based on a binomial distribution. Other statistical considerations may apply, but I think this is one fairly straightforward way to reach that sort of statistical control scheme.

So, the bottom line take-home message is a facility would be required to test either 5 percent or 1,500, whichever was greater, assign inaction limits on a statistical basis that would call for investigation and revalidation if that limit was exceeded.

[Slide.]

A second element of that is as with any good quality control system, any instances of a positive culture should be investigated promptly to facilitate identification of a correctable cause. As discussed earlier, this could be related to arm preparation procedures, an individual phlebotomist who had unacceptable technique, or things that might be occurring in the component preparation laboratory.

Simply by trending some of these results, one might get a clue as to what problem exists in the processing procedures.

There are other actions which are not specifically part of current thinking, but, for instance, if culturing is being done and a product is released, there are issues related to whether the individual contaminating bacteria should be identified, whether sensitivity testing should be done, and whether the recipient physician should be notified.

Clearly, this has implications if the product has been received. Some of this is easier to decide than if it is to be done on a routine basis without knowing the actual disposition of the final product.

[Slide.]

The FDA recommendation regarding quality control would incorporate examples of what would constitute an

acceptable quality control strategy, such as what was mentioned earlier for a small facility, could also give examples for large facilities which would be done on a similar statistical basis.

The current thinking is that the FDA recommendations would not inhibit what might be occurring at the industry level, but would actually serve as a minimal standard and that industry standards may well be defined to be more stringent. As you will hear, some of this is currently being proposed by the American Association of Blood Banks for culturing at a somewhat higher level.

So, FDA's thought is just to institute a minimal standard that can be exceeded.

That basically outlines the quality control issues. Again, you will hear more about the European study and the sterile connecting device from the next two speakers.

DR. NELSON: Questions or comments?

DR. ALLEN: Since the committee will be considering the question about the proposed statistical approach, do you have any other information from blood centers or other published literature that suggests that that kind of quality control mechanism is useful in terms of keeping the contamination rate low, that it is a good

check on procedures in use at all steps of the collection and processing?

DR. WILLIAMS: Within the blood center environment and specifically culturing related to contamination, I am not aware of practical data.

I know to suggest a statistical approach to quality control, this is the first attempt to do this was with respect to leukoreduction and residual white cell content, and it has, in fact, been a rather difficult scheme to reach balance between what is practically possible in an individual collection site and what would meet a statistical criteria. So, I think those are considerations.

As far as the actual practicality of a sampling approach, I am not aware in a blood center situation.

DR. ALLEN: Going back to the other use in terms of the leukoreduction, how easily has it been adapted by QC staff in blood collection centers as you have worked with them to implement this?

I am saying this simply because for most physicians and others who aren't coming out of a manufacturing background, this kind of statistical quality control, it is a foreign concept, and is part of the issue one of education and training, do current QC managers at

blood collection centers have that kind of skill and facility, or what are some of the obstacles here?

DR. WILLIAMS: I think my observation would be in most circumstances, probably not. The best way to approach it is in the context of FDA guidance to propose schemes that the FDA would consider appropriate, and if a center has more sophistication, can make other quality control approaches that might be distribution dependent, for instance, they can propose those and have them reviewed for prior approval.

But it appears that the best way to approach the issue is to be as prescriptive as possible in defining the simplest system to be put into place and work with that as a minimal system.

DR. NELSON: Did you want to make a comment?

DR. KUNERT: Yes. Matt Kunert at the CDC.

First, I just wanted to say I think any step forward is a good step. I do have a question about what essentially looks to be a benchmark of 0.2 percent contamination was determined.

In my experience with health care facilities and looking at, say, nosocomial infections, usually, benchmark is determined after looking at what the overall rate is among a group of facilities, for instance, and this, I think is more based on previous studies, but I am just a

little concerned that it seems high, 1 in 500 seems a little higher than, although there is variation, what I have seen in the literature, in some of the real-time data, for instance, some data forwarded on from Japan where they looked at 10,000 units and got 1 positive.

Aubuchon had a paper where they had a bunch of false positives, at least that is what they have determined them to be. But I didn't have any positives in two years, so I am just a little worried that this might be a little high to use as a benchmark.

The other comment I had is considering about those positives that you might see, might not be those that are pathogenic, and how that will be addressed, because you mentioned about clinician notification.

You have something like a corynebacterium species that is very different from a Klebsiella species, say, in terms of clinical significance, and whether you might want to consider having different benchmarks for different clinical significance as the numbers of organisms that have questionable clinical significance are likely to overwhelm those that are really significant, and those are the ones you really want to prevent, like the gram negatives.

DR. WILLIAMS: I agree. Again, I think there is a balance to be reached between working up those that are clinically significant and those which, while maybe not

clinically significant, do represent some breach in procedure, and that has value in the workup itself, but clearly, you need to reach an approach that is realistic and feasible.

As far as the 0.2 percent, Jay may wish to comment further since this is part of the European standard. From my approach, I think it is felt to be a standard that can be reached and reasonably approximated by a statistical approach. If you get too much more ambitious than that, you simply can't get there with a sampling approach.

I guess one final comment is that statistical approaches in sampling really don't come under consideration if you are doing universal culturing because clearly, then you have the results, 0.2 is the standard and optimally, you would want to stay within that.

DR. EPSTEIN: First, let me just reiterate that the number was based on a literature review of current practices in competent centers, but also let me emphasize that if you set a standard of 0.2, a center would need to achieve something lower than that in order to be able to repeatedly produce a statistical assessment showing it was no greater.

So, it, in fact, implies a more stringent actual performance.

DR. KUNERT: If I might ask a point of clarification. Are you going to be discussing later as far as when, at what time, either during storage or at out-date, that the products are going to be sampled, because I had a comment on that, as well, and I can wait on it if that is going to be discussed later.

DR. WILLIAMS: I think it will be probably addressed in some of the subsequent talks, but it is not a specific decisional issue for the meeting.

The devices that are cleared for quality control are cleared for as soon as 24 hours after collection. Clearly, if you are simply doing quality control, not using the product, the best time to sample it is probably after 48 hours or ideally at out-date.

Basically, we are looking for harmony between what the labeling permits and what would suffice as a quality control program.

DR. KUNERT: I was going to just make the comment, because it does relate to the statistical methodology, I wanted to clarify, on the BACON data, there was a reference in the Aubuchon paper that was based on an abstract, and I just wanted to clarify that those cases that were associated with serious clinical sepsis were associated actually not necessarily with long storage times, I mean they were associated at day 2, day 3,

infrequently day 4, overall, true, day 4 or day 5, but the ones that caused the greatest clinical impact were the ones that actually grew very quickly.

So, I would urge that there was a strategy or an option was to look at culturing at release, that that would be preferable to those done at out-date because you want to get as many units as possible because the incidence of these fatalities and these very serious events are very, very low, so it is important to get as many as possible at the time of release, I think. That was my third comment.

Thank you.

DR. FITZPATRICK: I am trying to put this in the perspective of how I manage from a practical standpoint when I see that I might have a trend or I have a couple positive units, I am moving toward or above the 0.2 percent range.

I have data, but now I have to go back and figure out the root cause in order to make an intervention. So, now I have to from what I have heard, I am going to have to culture my welds, I am going to have to culture my arm preps, I am going to have to look at the training and methods used by my phlebotomists and my technologists in that.

I also have to look at the nursing staff and administration. That also is going to take time and effort

and a lot of work, and I am not sure that you are going to find a root cause to intervene and make an improvement on.

The end outcome that we want here is to try to reduce that 5 to 9 fatalities per year. I am worried about the focus of the data collection. I think the data collection should be focused on an attempt to find the root cause of the problem and I am not sure we are doing that.

I don't have an answer for that, but I think we need to look at the work and effort involved and is there a way to focus the data collection on attempting to identify the root cause as to just confirming what we know, which is that we have a problem with platelet contamination and that there needs to be a way to intervene. That is my concern overall.

The other question is if you look at applying the QC effort to current practices, and if you evaluate the fatalities that have occurred over the past few years, one, have you looked at that, and, two, do you think that there is an impact that would be made on those fatalities by applying the QC method?

DR. WILLIAMS: I think it is a good point. It would be an extensive undertaking to look at each of those cases in that context, so it is a fair question, but, no, it hasn't been looked at specifically.

DR. SIMON: Maybe following up on that, asking that a different way, let us assume you did this, every blood center in the country met this requirement, is it more likely than not that the 5 to 9 fatalities would continue.

DR. WILLIAMS: Well, I guess I would again go back to the differing prevalence of contamination between sites. I mean what is being argued is there is a certain low level of contamination that you can't identify a cause, and is constant, and you simply need to culture to identify those units.

I think where the quality control gets you is where there are variations between prevalence of contamination between sites and there are extrinsic factors, that you allow some control over those factors, so that you can identify them, eliminate them, and reapproach that baseline level.

DR. NELSON: My guess is that if we had data on all blood collection centers, that they wouldn't be totally homogeneous, that there might be outliers, and that might be useful.

DR. SIMON: Historically, the discovery of this problem came from well-known academic centers, Johns Hopkins, Cleveland--

DR. NELSON: We are probably an outlier.

DR. SIMON: Yes, which presumably had no history of poor technique problems like this. It appears to me that this problem as it has appeared around the country is not related to the kinds of root causes that Dr. Fitzpatrick would be looking for.

DR. KLEIN: Since we know that up to half of these are actually from the donor, circulating in the blood, are not going to be corrected by correcting the arm prep and probably not effectively by diverting blood either.

This is an approach that I believe we are trying to take to do something, and I am not against it. What we would really like is a release criterion. The more we culture, the more that we will eliminate because they are positive, but what we are left with is an in-process test which is not ideal, and I think we simply have to recognize that and move on.

DR. EPSTEIN: I think a distinction has to be made here. The proposal for a quality control strategy is not a proposed method for eliminating the residual risk. It is a strategy designed to ensure that all centers are operating in compliance with current standard procedures.

What we are reacting to is the finding that if you start culturing, there have been reports in the literature of as much as 2 and 3 percent positive cultures,

and we think that if all appropriate procedures are followed, that shouldn't be happening.

So, we are really not suggesting that this is the cure for the current, you know, residual rate of sepsis and fatality, but we want to at least assure that all centers are able to demonstrate that they are operating to current standards. So, they are separable issues is what I am trying to argue.

DR. NELSON: Thank you.

Next, is Dr. Aubuchon, Experience with Plastic Tubing and Universal Bacterial Culturing.

E. Experience with Plastic Tubing and Universal Bacterial Culturing

James Aubuchon, M.D.

DR. AUBUCHON: Thank you very much and I appreciate the opportunity to address the committee again on this subject. This is an area that we have been involved with, with various research projects over a number of years.

[Slide.]

Clearly, as you have heard this morning, there are many uses for sterile connecting devices in conjunction with platelet units, particularly for QC sampling, to dock on filters in order to leukoreduce the unit, to pool either before storage, as is done in Europe, or after storage, as

is done in this country, to sample for bacterial detection, and to remove an aliquot for transfusion to a neonate, for example.

[Slide.]

Units can become contaminated in a number of ways and certainly the welding or the sterile connections that are conducted on the unit is a potential site for contamination.

[Slide.]

For those of you on the committee who have not ever used one of these devices, let me just walk you through briefly how they operate. This is my attempt to explain how it operates, and I don't understand all the inner workings. Possibly someone from Terumo can give you the details.

But the two pieces of tubing that are to be welded are placed in a metal chuck adjacent to each other. Beneath that chuck is a copper wafer. It looks like just a piece of copper, but there is actually an integrated circuit inside that piece of copper.

Before the instrument can be used, the prior wafer has to be ejected, so you are using a new wafer each time. The wafer then heats and comes up and slices through by melting the tubing. As the two pieces of tubing have been melted, seen here from on top, then, the chuck moves.

The chuck is actually in two halves, and this part of the chuck moves backwards, so it drags this piece of tubing and aligns it with this piece of tubing.

The outcome then is a new piece of tubing that is connected together in two pieces which are discarded. The weld then has to be opened by squeezing it with your finger after you remove it from the chuck.

[Slide.]

There is another device on the market by Haemonetics. I have not used it, I am not familiar with how it works. I presume it is something similar, but I don't know the details of that.

The device which we have been using most widely in this country and our laboratory has experience with was initially marketed by duPont and is now marketed by Terumo.

[Slide.]

To show you some pictures of how this works, you see the two-piece chuck opened here with the two pieces of tubing. Here is a platelet unit with tubing coming across the chuck, an aliquot bag over here that we are going to weld sitting in the other set of slots.

[Slide.]

First, the wafer from the previous weld is ejected by moving this handle forward. Here, it is coming out. You remove that, and a new wafer automatically comes

into position at that point from the cartridge of wafers. The wafers are designed to be used only once.

[Slide.]

The wafer then heats, comes up, cuts the tubing. You see here that this part of the chuck has moved backward, now aligning this platelet unit tubing with the aliquot tubing and opening it up. You see the two are now connected.

[Slide.]

We became interested in this several years ago while doing some research in bacterial contamination. In the spirit of good manufacturing practices, good laboratory practices, we sought information to validate that the sterile connecting device did what it was supposed to do sterilely.

We did find one piece of information in the literature using spore contamination. We proceeded then to do some testing with some real life stressors, and I will also comment on the European study that was mentioned in comparing the various culture results.

[Slide.]

What we found in the literature was presented at the American Society of Microbiology in 1983, and it took a fair amount of hunting to find this. What these investigators did was to contaminate a segment of tubing

with spores of Bacillus circulans and then connect that piece of tubing with another segment of tubing that had been filled with trypticase soy broth.

The weld was opened and the broth was allowed to cover the area of the weld, and it was maintained at 35 degrees for four days and then cultured in order to see if any of the spores had gotten into the interior of the tubing.

They conducted 758 welds on 17 different instruments and all of these experiments showed the contents of the tubing after welding to be sterile.

[Slide.]

We conducted a study in three different phases. I should note that the study was not funded by the sponsor. We did this in our own laboratory just to show that the technique did indeed work.

In the first phase, we used a leukocyte-reduced single donor platelet product aliquotted 4 ml each into 64 small bags. In the second phase, we used trypticase soy broth aliquotted at 5 ml into 80 small bags.

These bags were then joined with other empty bags after having dipped the tubing for both halves of the welding sides in a liquid suspension of either Staph epi, Flavobacterium odoratum, or E. coli, and note that the concentration of bacteria in this aqueous suspension was

40,000 to 3 million bacteria per ml. This wasn't just a small amount of contamination, this was heavy contamination.

A total of 10 ml between the two bags was then created. The weld was opened and the contents were moved back and forth several times in an attempt to pick up any bacteria that may have gotten into the weld. A culture was conducted immediately and also after seven days.

[Slide.]

The tubing itself was not always dry as the manufacturer would expect the instrument to be used. In some cases, the tubing was allowed to be wet and in other cases the contamination was allowed to dry before the dock was conducted.

In some cases, the tubing was filled with the trypticase soy broth or the platelet unit, in other cases it was empty, so we had multiple combinations of approaches here in these different phases.

[Slide.]

In the third phase of the study, we used a trypticase soy broth bag that we docked repetitively to a series of empty bags, 100 times in all using I believe 10 different initial bags here.

Each time we docked on another small bag, we were lengthening this tubing and the broth was moving through

successive weld sites in order to again stress the system and to pick up any contamination that may have occurred.

Here, we used the Staph epi or enterobacter solution of bacterium at 100,000 again to 3 million per ml as the contaminant and using either wet or dry tubing. So, we felt that this was really a stress of the system far beyond what would be seen in normal practice.

[Slide.]

The results are shown here. In the first phase, we performed 64 welds, 63 of them were evaluable. We found that we had actually contaminated one of the bags with a different organism. This organism did not come from the weld, so we had 63 units that could be evaluated. All were sterile.

In Phase 2 of the trypticase soy broth, two of the welds were incomplete. That is, when we took it took out of the chuck and went to open it, we could clearly see that the weld was defective and was not complete. That is not surprising when you are trying to weld wet tubing. It doesn't always melt and reseal properly.

So, of the 78 evaluable, complete welds, all 78 were sterile. In Phase 3 with the multiple lengthening of the tubing, trypticase soy broth, all 100 welds were complete, evaluable, and were sterile.

So, we had a total of 241 evaluable welds in all were sterile.

[Slide.]

What does this really mean in terms of safety? We would have loved to have done 10,000 welds, but my techs were about ready to hang me after doing 240.

Looking at this statistically, with 241 negative welds, we can say that this implies that the rate of positivity is not greater than 0.004, or if you combine these 241 observations with the 758 published previously, it means that the rate of the weld not being sterile is not greater than 1 in 1,000. So, we are able to document then that the rate, if you have a successful weld, the rate of contamination does not exceed 1 in 1,000.

[Slide.]

Just to tell you some experience about how frequently welds may not be complete, I pulled data from the first 10 months in our Transfusion Service of this year. We performed 5,636 welds. Each one of these is documented by unit number and documented that the tech has looked to see that the weld is indeed complete and not leaking.

There were 4 failures in those 5,600 welds or about 1 failure every 1,400 welds, so this has not occurred very frequently, but it does occur often enough that we do

indeed need to look at it, as the FDA guideline indicates that we should.

In a Belgian study we will be talking about in a minute, they noted that the failure rate of welds was about 1 in 3,000, so it is not a common problem and it is important then to look at the weld carefully when you go to open it and to check for leaks.

[Slide.]

Now, we have been using this welding technique in many ways, but certainly as part of our ongoing study of using bacterial culturing routinely on all of our units of platelets.

We use apheresis products at our center and on day 2 we perform a sterile weld with a small aliquot bag and move some of the platelet unit into this bag, which is then removed by heat sealing and entered by syringe and needle, transferring 5 ml into an aerobic culture bottle of the bacT/ALERT system, and placed in the bacT/ALERT cabinet.

The units are available for release at any time that they are needed for transfusion unless or until we receive a report from the microbiology laboratory that indicates that there is something growing in that unit, and then obviously we quarantine it.

[Slide.]

In the first three years of doing this, we are now at about 3 1/2 years, but in the first three years we cultured almost 4,000 units in this manner. We found 23 that were initially positive, 14 could not be confirmed on repeat culture, and 5, we didn't have anything retained to culture. That was early on in the protocol.

It is important to note that all of these which we believe are false positive occurred shortly after a new tech learned the procedure and began doing it.

[Slide.]

This procedure in our laboratory is performed in the open Transfusion Service laboratory by all techs in rotation, and there clearly is a training curve even beyond initially showing that the technologist knows what needs to be done, and you can see the falling rate of false positivity over time.

Dr. Mark Brecher at the University of North Carolina has been using this technique in his laboratory since late February of this year. He is performing it more in a research setting using a biological safety cabinet that is a laminar flow hood, and he tells me that in at least 2,000 units that he cultured, he did not have any false positives.

So, it would appear that if you take additional efforts to prevent contamination at the time of inoculating

the individual bottles, you may reduce the false positive rate.

We did have four confirmed positives in the first three years or a rate of positivity at about 1 in 1,000, or in this era of low viral risk where we are expressing risk now as occurrences per million, I would just note that that is 1,000 per million while we are talking about HIV and HCV risk where we use fractions per million, both a much larger risk.

[Slide.]

Now, how did we actually determine that some of these were false positives rather than true positives? This was done through repeat culture of the unit or a retained aliquot from that unit. So, of the 23 units that have initial growth, we did have something that we could reculture in 18 of those.

In 14 of those 18 recultures, the units had no growth on repeat culture. Four units, we were able to detect the same organism a second time, and we assume those were the true positives while we called the other 14 false positives. One could argue with the attribution, but we feel this is approximately correct.

It is important to note also that the time to a positive culture being reported was very different between these two groups.

If we could find the same organism again in that unit or an aliquot from that unit, the initial report was received by our laboratory in under 14 hours, where in those cases that we feel were false positive, where we could not identify the organism on repeat culture from that same unit, we were receiving a report at greater than 24 hours and often greater than 30 hours.

So, that would imply again that we are dealing with very different situations biologically.

[Slide.]

Where is this false positive contamination coming from? We feel it is most likely coming from either taking the sample from the small aliquot bag by needle or placing the 5 ml actually in the culture bottle. Of course, this is despite cleansing the septum before placing the needle through it.

Again, if this were done in a laminar flow hood, we might reduce the probability of this happening.

[Slide.]

Now, it was mentioned earlier that there is a report from the late 1990s, from Europe, suggesting that welding potentially caused bacterial contamination. In this study, they looked at 1,100 buffy coat pools, which were created from 6,100 welds of individual units.

They found 15 positive cultures from those pooled 1,100 buffy coat pools, and they went back to the individual units that were involved in each one of those pools and cultured them.

In 10 of those 15 occurrences, they identified the same organism in one of the units, and they concluded that in those 10 circumstances, the pool was indeed contaminated, they have a contaminated unit as part of the pool.

On 5 occasions, they were not able to grow the organism on reculturing each one of the individual units. Now, where could those 5 come from? It is an important number because that is 1 in 1,200, and this is approximately the same rate of positivity that we are seeing overall, and are we indeed contaminating as frequently as we are detecting true positives.

Well, I would question where these 5 incidences of growth came from. They could have come from a contaminated weld as these authors contend. It could also have come from a contaminated culture, a possibility they did not consider. It could be that on repeat culture of the bag when they went back to the initial units, they may have missed the organism.

[Slide.]

You might say, well, that is not likely, but let me share a case with you that occurred several months ago in our laboratory. We cultured a unit on day 2, as we usually did, and in 9 hours, we had reported to us growth in that bottle. The short time to detection implied to us that this was a true positive.

However, we went back to the same unit, which was still in inventory the next day, and on day 3, we cultured it again, and that culture remained sterile out to a week after beginning the culture. So, we were not able to find any organism on growing it and culturing it again on day 3.

This raised a question, was this day 2 culture then a false positive. We cultured the unit again on day 6 and we got growth, and importantly, we found the identical organism. It was a Staph epi which happened to have an unusual antibiotic sensitivity pattern, therefore, we were comfortable in identifying the two organisms found at day 2 and day 6 were indeed the same organism.

So, with the European study not finding an organism on going back to the bags, it may have been that they just missed it, and they didn't happen to take the right milliliters that happened to have the bacterium present.

[Slide.]

I think it is more important that we and the authors of this paper focus on the 10 pools that had contamination that were noted. One out of 110 transfusions that would otherwise have been given were cultured positive and contaminated with bacteria. That is a very high number that even exceeds the statistical rate that Dr. Williams was mentioning previously.

[Slide.]

So, is it safer to weld in culture, which I feel is the question that is being proposed here.

The current standard in the U.S. is not to do any welding to do any culturing because we don't routinely do cultures. Only a few centers are beginning that or considering it.

So, if you were to transfuse, for example, a million units of platelets or performing a million platelet transfusions, 1,000 units of those million would carry along bacterial contamination. That is the current state of practice in the United States today.

If culturing were performed with perfect welds, with welds that never contaminated either the culture or contaminated the unit, and if that culturing were 90 percent sensitive, which I feel culturing is probably greater than 90 percent sensitive, but even if you only assume 90 percent sensitivity, the million units with 1,000

of them being contaminated, the contamination would be detected in 900 of them, and 100 units only would be transfused with the contaminating bacteria.

In order for the sterile connecting process to decrease safety, if we were to go ahead and weld and culture, the sterile connecting process would have to cause contamination at a rate of 900 per million or 1 in 1,100, and we already have data that shows that the rate of contamination in welding, even in very stressful circumstances, is less than 1 in 1,000.

[Slide.]

So, I think the answer to the question is yes, it is safer to weld and culture than not to weld at all, and I will not quote Shakespeare.

[Slide.]

So, there are several alternatives that I think could be considered in approaching this problem. The European practice is to pool, what they use usually is buffy coat platelets, but to pool the platelets on day 1 to leukoreduce them at that time by attaching a filter, and to draw a culture at that point, and to put the units into inventory.

[Slide.]

Another approach would be to culture on day 1 or day 2, sometime after an initial period to allow the small

inoculum to grow up to be detectable. We are now talking about the common American practice of using individual platelet units from whole blood units, thinking of 6 units that would be transfused to a patient, we would have to aliquot 6 individual units and create 6 individual cultures, and to store those units individually because the FDA does not allow us to pool and then store the units for a prolonged period of time.

This would be very expensive, because the culturing cost would be multiplied by 6 and you would have to keep those 6 units together to make sure that they were going to the same pool ultimately, I would think, as well.

Another approach would be to take aliquots from 6 units and put them in one culture and then store them as separate units, another possibility.

In any of these cases, you are going to be taking a substantial volume from the individual platelet concentrate units. If one needs to take a volume to culture, it needs to be an appropriate volume to detect the bacteria, so we are probably looking at, at least 2 ml, if not 5 ml from each one of the bags. These bags are, in general, about 50 ml, so that is 10 percent reduction in efficacy of the platelet transfusions.

Of course, you could perform these cultures using sterile connecting devices or have a pre-attached sampling

bag on a platelet pooling bag, and most blood bankers I think in this country would be very happy to be able to pool and then store.

It would take the pooling out of the hands of the hospital, allow it to be conducted in a standardized fashion, matching essentially the European practice, but possibly the idea of using an additional pre-attached sampling bag might be another approach that manufacturers might want to consider.

[Slide.]

So, in my way of looking at the world, I think this problem indeed warrants intervention although it is relatively infrequent, say, 1 in 1,000, it really is too infrequent to be appropriately addressed by a statistical quality control approach.

It is certainly large enough to warrant us doing something about it, and I believe that bacterial detection can be accomplished with an overall reduction of the risk of platelet transfusion.

Thank you very much.

DR. NELSON: Thanks, Dr. Aubuchon.

Toby.

DR. SIMON: I assume with the culture on day 2, so that is at 48 hours, is that right? You can assume the day of draw day zero?

DR. AUBUCHON: The day of draw is day zero. We usually culture mid-morning, so I would say that the shortest time period is probably about 40 hours, and some units may be out to 50 hours by that point.

DR. SIMON: I wanted to just make sure I understand the data. It is still true that you have a higher rate of false positives than you do true positives, and those units would be interdicted in your system and not transfused.

DR. AUBUCHON: That is correct.

DR. SIMON: And you also have instances where you examine the welds and find them to be defective, and those units would not be transfused.

DR. AUBUCHON: I don't know if you saw the technique that we use at our institution where we clamp off the tubing, and we do not release the clamps on either side of the new weld until we document that the weld is a good weld.

DR. SIMON: Okay. So, if the weld is defective, you do not lose the units.

DR. AUBUCHON: That is correct. You seal it off and do another weld.

DR. SIMON: So, you just have to have a good examination procedure. Have you calculated the loss to the country in units from the false positivity? It would be

greater than the ones we are interdicting for true positivity, right?

DR. AUBUCHON: Yes. The predictive value of a positive is not very high because we do have a number of false positives. We are running now a false positive rate of about 1 in 500, and the true positive rate of about 1 in 1,000.

DR. SIMON: So, for every true positive, you would have two--

DR. AUBUCHON: I have two false positives, that is correct.

DR. SIMON: Thank you.

DR. FITZPATRICK: Testing for pre-release is, of course, what we want to do, and that is what you are doing. The question I have is, has anybody looked at the impact on the whole of the inventory in the country on wastage if we are holding products until the third or fourth day to transfuse?

DR. AUBUCHON: Certainly, the longer that you hold the platelet before distributing it to the hospital, the shorter its useful life span and the potential increases for outdating, that is certainly true.

I believe that most facilities are not labeling until sometime late on day 1 anyway because it takes that long to get the nucleic acid testing results.

So, with the current approach as approved by the FDA for use of the bacT/ALERT or the Pall BDS, where 24 hours after collection has to elapse before drawing the sample, that could probably be obtained without any delay to preclude release.

Now, a unit could be released before a result was obtained in the Pall BDS system 30 hours later or certainly would have to occur before the final culture was reported out five or seven days later from the microbiology laboratory as being negative.

Blood centers develop systems for notifying hospitals quickly in case of NAT positivity in Phase I of the NAT IND clinical trial, and that is the common practice in Europe, as well, where as soon as a positive is found, the hospital is contacted.

It doesn't happen very often obviously even at a false positive rate of 1 in 500, so it is not like the blood center is going to be calling up two dozen hospitals every day to recall units of platelets, but a retrieval mechanism probably would have to be instituted in order to allow platelets to be distributed at the normal time in order to prevent an increase in the outdating.

Of course, if we are able to convince the agency of the wisdom of culturing and then extending the storage period to seven days, something this committee considered

at a previous meeting, then, if we were to use one of those two additional days by holding the unit in the blood center until we got the final result, it would simplify the system without causing an increase in outdating. Sorry to editorialize.

DR. CHAMBERLAND: In the Merten's paper, looking at their methodology, they apparently used both new and reused welding wafers, which is a difference compared to the methodology that you used.

Now, this was published in 1997, so maybe over time these wafers, it has been determined that they should be single use, and they indicated that of the 15 contaminated pools, six were made with new and nine were made with reused welding wafers, and this was not a statistically significant difference.

I am quickly skimming, but they don't indicate in the five contaminated units if a reused wafer was used for those five units, and I was curious as to your thoughts about the role that reuse of wafers might potentially have played here.

DR. AUBUCHON: I don't have any data directly addressing that. I certainly do know that reuse of wafers is not according to manufacturers' directions, and the manufacturer has always stipulated that the wafers are to be used once and once only.

There are other blood centers outside the United States that do use them more than once. They clean them and reload the little cartridge packs, but that does not meet the manufacturers' requirements.

DR. NELSON: A brief comment because we are way behind.

DR. KUNERT: Okay. Matt Kunert, CDC.

You had some data here that wasn't in your excellent paper. I guess you went for two years and didn't have a true positive, and then in the third year, had four positives. I wondered if there was a difference between the organisms in the true positives and the false positives.

My other question is I didn't quite get whether all of these were stopped from being transfused or whether any were transfused, and if there were, sort of what the results were.

DR. AUBUCHON: All of the true positives are Staph epis. The first true positive unit was actually a split unit, which happened to be positive in the 25th month, right after the end of the second year.

I believe we have had two instances in which units have had the culture turn positive after the time of transfusion. One of those occurred very early on when we had not retained any aliquots for later culture, and that

prompted us to do exactly that, so we could resolve the question.

In that case, the patient was cultured extensively, nothing was ever grown from the patient's bloodstream, and the patient had no ill effects. On that basis, we concluded that it was a false positive.

The second occasion, we did have an aliquot. We recultured it and it was negative. We did culture the patient, as well, and as you would expect, the patient did not have any blood culture positivity.

DR. KUNERT: My final question is, of the four, the Staph epi cases when you did root cause analysis, did you have any revelations?

DR. AUBUCHON: No, we did not because we do keep track of our phlebotomists. We collect almost all of our own platelets, and we do keep track of our phlebotomists' technique, and periodically audit that, and we had not seen any deviation from the way that they were preparing the arms. We were using tincture of iodine and alcohol actually on the skin at that time in any case, and, of course, the welds were all complete and good welds, and we had the documentation for that.

So, I would agree with the comment before, that doing a root cause analysis is not likely to identify the source of the problem.

DR. VAUGHN: Evise Vaughn [ph].

Just one question. Seeing as the direction is to move towards testing for bacteria, is it not possible to use the pre-donation sampling bag to take the sample and grow from that instead of at the later stage?

DR. AUBUCHON: You certainly could. The difficulty is that there could be some concentration of the bacteria as the component is made. In addition, there is no guarantee that any particular aliquot is going to have the bacteria in it, and that is the reason, of course, that we wait for two days or at least one day to allow the culture to grow up to a point where we can take a small aliquot and culture it reliably.

I would be a little concerned about only culturing the small diversion segment. We would probably get many more positives and probably would end up throwing out some platelet units that we didn't need to throw out because the platelet unit itself was not contaminated.

Certainly, it appears that the rate of positivity is much higher in those diversion bags than in the culturing of the final product.

If we are going to culture it as a release criterion, I would rather actually culture what is being held and then going to be transfused.

The next speaker is Tracy Manlove from Terumo Corporation.

We are running very far behind. I notice you have got quite a few slides. I wonder if you could do it in 15 minutes?

MS. MANLOVE: I will do my best.

F. Data Presentation

Ms. Tracy Manlove

MS. MANLOVE: I guess I would like to begin by saying good afternoon since we have reached that point in the day and thank the FDA for the invitation and the opportunity to discuss this very important topic.

I do have a number of slides, but Dr. Aubuchon has provided a great introductory to this, so we may be able to speed through quite a lot of them.

[Slide.]

I am Tracy Manlove and I am speaking on behalf of Terumo Medical Corporation. We are the manufacturer of the sterile tubing welders.

[Slide.]

I would like to begin by reviewing some of the terminology that we have been using. The sterile tubing welders, STWs, are also known and commonly referred to in the literature as SCDs or sterile tubing connection

devices, and they are all referring to the same pieces of equipment.

The outline of my discussion was to go over a brief background and history, the cleared uses of the devices, and then to review the description of operation, weld integrity inspections, and general considerations in making welds, the device release testing criteria, some supporting data, which is I think what we are really interested in, and then to summarize, as well.

[Slide.]

The sterile tubing welders were originally developed by the duPont Company in the early 1980's. The device was conceived to join two pieces of polyvinyl chloride tubing while maintaining the sterile fluid pathway.

[Slide.]

The original SCD device was developed for use in the dialysis patients that were on home continuous ambulatory peritoneal dialysis or CAPD.

In the traditional CAPD procedure, the patient was required to aseptically connect an indwelling catheter to a bag of dialysis solution, and they had to do this four or five times daily. This contributed to an increased incidence of peritonitis in this patient population.

With the advent of the SCD, the risk of contamination was eliminated.

[Slide.]

Presently, the device product line consists of three devices - the SCD312, the TSCD, and the SCD IIB.

[Slide.]

The SCD312 that you saw pictures in Dr. Aubuchon's lab and the TSCD are utilized in the blood bank and transfusion medicine industries.

[Slide.]

While the SCD IIB is utilized in the biotechnology industry. Applications include cell culturing, fermentation systems, and bioreactors.

[Slide.]

The sterile tubing welders have been in use in these industries for over 15 years, and all devices within the product line function under the same principle of operation which Dr. Aubuchon has already described, and I will, as well, a little bit later in the presentation.

The field application differences of the devices are only due to the size of the tubing that the device can accommodate.

[Slide.]

Quickly, there are eight cleared uses for the sterile tubing welders, which are published in the FDA

guidance, which I have referenced here. This guidance was originally published in 1994 and was recently updated and reissued in November of 2000.

Uses include adding a new or smaller needle to a blood collection set, uses in component preparations, such as adding a third storage container to a plateletpheresis harness and connecting additive solutions to red blood cells, of special interest to today's conversation, the pooling of blood products, and I have included the verbiage in your handout that is directly from the guidance document.

[Slide.]

Also, to prepare aliquots for pediatric use and divided units, and this is particularly important in minimizing donor exposure in the pediatric population, as well as maintaining blood inventories.

Other uses and then, finally, with the removal of samples from blood product containers for testing, such as QC testing, and as we have been discussing, is currently done is Europe to remove a sample for the bacterial culture, and as is currently done in the U.S., to obtain platelet counts for the split apheresis products that Dr. Williams had mentioned and others earlier.

[Slide.]

Dr. Aubuchon already briefly described the device operation, but I would like to reiterate and emphasize what we feel, as the manufacturer, are some important operational points. So, I have included some diagrams, as well. They will hopefully assist in the visualization of the process.

It is a unique thermal process where the PVC tubings are set parallel to each other in what we refer to as holders, and Dr. Aubuchon referred to as chucks.

The welder wafer here, as he mentioned, is a copper wafer and it is positioned in a perpendicular plane to the tubing. The wafer is heated to a temperature of approximately 500 degrees Fahrenheit.

[Slide.]

When this temperature is achieved, the wafer is then raised and crosses the plane of the tubing. As it does this, the tubing is melted. The wafer remains stationary with the melted ends of the tubing adhering to the wafer.

[Slide.]

Then, also, as Dr. Aubuchon mentioned, the holders undergo some movement, so that the left hand tubing is moved to the rear and put into alignment with the right hand tubing, so these are the two pieces of tubing that we are connecting.

[Slide.]

When they are directly opposite each other, the wafer is then lowered. As the wafer recedes, the melted tubing is fused together and form a weld that has maintained the internal tubing sterility.

Once this cools, because it was heated to 500 degrees Fahrenheit, after the cooling process, the welded tubing can be removed from the device and handled.

[Slide.]

This is a very critical step in the process because it is as this point that the operator must conduct an inspection of the weld integrity.

Each weld must be visually inspected. This can be accomplished by once the tubing is removed from the device, rotation of the welded tubing in a 360 degree fashion and visually inspecting the weld.

If the weld is acceptable, it will appear as in Diagram A, where you can see that the two pieces of tubing have fused together and are in alignment. If it is unacceptable, it will be visually recognized as what appears in View B, where you can see that there is a gap in the alignment of the two tubing pieces.

Also, during this visual inspection, if any leaky welds are detected, they should be treated as air contaminated and handled accordingly, so that their out-

date should change or that there should be a discontinuation of processing of those units.

[Slide.]

As we have discussed previously, the weld integrity inspection is so critical that it is noted in both the FDA Guidance for Industry, and here are the specific wordings from that document, as well as the AABB's 21st edition of their standards.

Again, two standards addressing the need for completeness of the weld and appropriate actions to take if the weld is not intact.

[Slide.]

Once the operator verifies the weld integrity, the weld is opened, as Dr Aubuchon said, by simply rolling the tubing between your thumb and forefingers and the weld will open.

[Slide.]

This is a picture of an open and acceptable weld. Right here is the welded site. These were two separate pieces of tubing prior to the weld. You can see at the connection site that they are perfectly aligned and there are no leakages.

[Slide.]

I would like to discuss from the manufacturer's viewpoint and from an operator's viewpoint some general considerations when making a weld.

It is an automated process once the tubing is placed in and the new wafer is advanced, and we are going to talk a little bit later about the reuse of wafers and the single use, and hopefully will answer the question that the committee posed.

This entire process occurs in approximately 30 seconds once the tubing is placed and the Start button is initiated.

[Slide.]

A new wafer is used for each weld connection and this has always been the policy in the United States. Again, a picture of the cartridge of wafers and just for scale representation, an individual wafer in a hand.

[Slide.]

The sterility of the component and the system is maintained by key features of the welder.

Number 1 is that the heated wafer kills any bacteria or spores encountered on the outside of the tubing, and I will show you some studies to substantiate this claim.

Number 2 is that the melted tubing adheres to the wafer and forms a seal which prevents any atmospheric contamination from entering the system.

[Slide.]

Sterile tubing welders are semi-automated devices with built-in checks to monitor the proper welder function and user operation. These include clamp interlocks, wafer checks, audible alarms, and indicator lamps.

When there is a problem detected by the device, an audible alarm occurs and indicates the process failure to the operator.

[Slide.]

Preparing a good weld is operator-dependent in a number of areas. The devices are intended for use by trained individuals in settings, such as blood banks, hospitals, and laboratories, but the devices are easy to use and the operating instructions are very straightforward and simple.

[Slide.]

One of the operator-dependent instruction in areas is, as we described with the operation, is that the tubing clamps begin in an aligned position, but at the end of the welding cycle, there is a different positioning of the tubing clamps, so in order to initiate the welding

process, the operator must take an action to return that to an aligned position.

The operator must also verify proper placement of the tubing. It is indicated on each of the devices on the deck of the devices where the dry tubing goes, which would be such as to the leukoreduction filter, or the wet product, such as would be coming from the blood component.

This is dictated by the manufacturer through testing that we have done to demonstrate that this proper positioning verifies sufficient weld strength to guarantee the integrity of the weld. Only PVC tubing should be utilized.

[Slide.]

Other considerations the operator must take into consideration is that the tubing length must extend beyond the tubing holders. The tubing must be properly seated. You can imagine if you are trying to align two things, if you don't have them on the same plane, it is never going to happen, and that the clamp covers play an integral role in keeping that alignment, and that they must be properly locked into place before beginning the welding process.

Again, there are audible alarms that will alert the operator if this has not occurred.

[Slide.]

Hopefully, getting to the question here. Failure to advance a new wafer prevents the weld cycle. Again, an audible alarm and/or a visual indicator will alert the operator to this.

The wafers are single use only and reuse of wafers is in direct opposition to the operating instructions, and voids any and all device warranties.

[Slide.]

In 1993, there was an abstract presented at the AABB by Hawker and others from the UK, where they conducted a study with repeatedly used wafers. What they were able to demonstrate was that the wafers became contaminated with the solidified PVC from the tubing. The welds demonstrated low tensile strength, and we will talk about what that means later on.

The contamination resulted in misalignment of the welded tubing and ultimately, they had weld porosity, and that is to say that they had leaky welds.

[Slide.]

Other things that the operator needs to consider when they are making the weld to ensure the integrity is to not touch the clamps, not open the clamps, and to not pull on the tubing. These are all important in maintaining the integrity of the weld.

With each of the devices, we do have bag supports that are provided to help elevate and support the bags, so that everything can remain on the same plane and move freely.

[Slide.]

In speaking about the devices, they are manufactured, as I said earlier, by Terumo Medical Corporation. We are an ISO 9001 facility located in Elkton, Maryland.

Each device that is manufactured there is subjected to what we consider as rigorous release criteria, and this includes 10 dry to dry welds being made on every device, and 20 wet to dry welds.

[Slide.]

All of these welds, 30 welds in total, must meet the following criteria. Tensile strength or the force that can be exerted on the weld before it will break must be demonstrated to be equal to or greater than 15.3 pounds for wet to dry welds and greater than or equal to 15.9 pounds for dry to dry welds.

The minimum tensile strength of any of those 30 welds must be demonstrated to be above or equal to 11.2 pounds.

All of those welds must be aligned and easy to open, and they are subjected to an air pressure leak test with pounds per square inch of compressed air.

These five criteria combined assure the weld strength and the integrity of every weld made on that device before it is released.

[Slide.]

Turning to some data that supports the sterile connection abilities of the devices, I would like to look at our 510(k) submissions. This is the reference here to the submissions.

The performance testing that was supplied in these submissions included sterility testing and weld strength testing, as well as four other tests that demonstrated acceptable test parameters, and that is on file with the device applications, but won't be discussed in this presentation as it is not relevant to the discussion.

[Slide.]

For the TSCD, the study design for the sterility testing is what I believe Dr. Aubuchon modeled his test off of, so we are going to discuss a couple of tests, and they are all very similar in design.

In this case, the exterior of the tubing was coated with Bacillus subtilis. This was chosen because

these spores demonstrate a high resistance to dry heat. There were 1,215 total welds prepared; 405 were test welds with the coated tubing.

But then there were two additional welds, that is, 810 welds that were made to each of these test welds, and that was to dock on the bag with the growth media on one side of the weld and a transfer bag on the other side of the weld, and then the fluid traversed the weld site.

There were three devices tested. There were multiple manufacturers tubing encompassed, both dry to dry and wet to dry welds were utilized, and when wet tubing was used, it was filled with 5 percent human serum albumin.

[Slide.]

The conclusion of this study demonstrated that there was no growth in any of the 405 cultures after 14 days and that the interior tubing sterility of both the dry to dry and the wet to dry combinations was not compromised by the welding process.

There was positive growth exhibited in the control tubing which verified the viability of the organism chosen for the test system.

[Slide.]

The SCD312 underwent similar sterility studies. In this case, the exterior of the tubing was coated with either Bacillus circulans spores or Staph epidermidis, so

again a heat resistant spore and a commonly found skin contaminant that might be found in a real-life application of this device.

Six hundred welds were made with the B. circulans tubing, 50 with the Staph epi, and 6 devices were utilized.

The conclusion in this test was also that the interior tubing sterility of the welds was not compromised by the welding process.

[Slide.]

Also published in an article by Nicholas in the American Biotechnology Laboratory in July and August of 1987, is a study entitled, "A Sterile Connection Device for Cell Culture and Fermentation Systems."

In this study, Nicholas had two aspects to the study. She looked at sterility studies, as well as airborne contamination studies.

The lengths of tubing were sterilized by ethylene oxide gas prior to any welding or manipulation. Then, the tubing exteriors were coated again with the B. circulans. A microbiological growth medium was present in the tubing, this was the medium, and there was also a bacterial growth indicator. 758 welds were made.

[Slide.]

At the conclusion of the sterility studies, it was ascertained that there was no microbiological growth

after 96 hours in the test system, while the control tubing exhibited growth at 48 hours.

They made the conclusion that under the correct operating procedures, all welds were shown to be sterile.

[Slide.]

As I mentioned, they also looked at the airborne contamination studies. So, they designed this study similarly to the previous protocol described except that they did not coat the tubing with spores at this point. They placed the device into a sport-laden atmosphere with an average spore density of 260 spores per liter of air, and they performed 114 welds.

At the conclusion, they found that all of these 114 welds were sterile and the sterility of the system was maintained.

[Slide.]

So, the Nicholas study does offer us some practical evidence that the impact a sterile tubing welder can have in a fermentation of cell culture lab. When the study was published in 1987, the sterile tubing welder had been implemented in their laboratory and at that time they had performed 400 welds and 5,000 connections were made with no loss due to system contamination.

Prior to the implementation of the device, they were losing approximately 10 percent of the runs due to contamination.

[Slide.]

They also did greater than 1,500 connections to bioreactor systems, and they did not have to abort any runs because of the contamination when using the device. Again, prior to implementation of the device, they were losing approximately 10 percent due to contamination.

[Slide.]

I think I can go through this without anything. I think Dr. Aubuchon has provided us a very good overview of his study. The only point that I would like to make is, as I said, the tubing is still coated with organisms and as he had alluded to, in a very, very high concentration, it is a very, very vigorous test for the device to be challenged with.

[Slide.]

Again, as he had described, he did three phases of the study, passing the liquid across the weld, incubated at room temperature, and showed that all cultures were sterile at the end of the time.

[Slide.]

I would like to emphasize, as Dr. Aubuchon did, as well, that they had two incomplete and leaky welds, but

they were doing some innovative procedures there where they were leaving the tubing wet and making welds to provide an additional stress and challenge to the system.

So, it would be interesting to know if that wasn't done, if any of those two incomplete or leaky welds would have occurred.

His conclusions, as he already described, but again to emphasize, the fact that he is advocating visual inspection is in agreement with the manufacturer's instructions, the FDA, and AABB guidance documents.

[Slide.]

At the AABB in 2001, we presented a study that we had done at Terumo Medical Corporation, myself and some associates had looked at the weld quality with various tubing combinations from multiple manufacturers.

We utilized two TSCD's and two SCD312's. We were looking at wet to dry welds, and we made a total of 320 welds.

[Slide.]

What we saw is summarized here. This is for the TSCD. Again, these were the tubing combinations that we were looking at, the wet tubing noted first, followed by the dry tubing, the average tensile strength release criteria, which I mentioned earlier, and the minimum tensile strength, and you can see that all the values are

well above both of those minimal requirements, and we had no air pressure leaks.

[Slide.]

The results for the SCD312 are very comparable. Again, no air pressure leaks, no leaky welds.

[Slide.]

So, the overall results of our study show that all the welds were aligned, there were no leaks. The weld strength exceeded the minimum strength requirements, and we achieved acceptable weld integrity with each of our 320 welds.

[Slide.]

Recently, Terumo Medical Corporation has undertaken another internal study where we are looking at an expanded number of tubing types and manufacturers in conjunction with sterile tubing device.

Again, we are looking at two TSCD's, two SCD312's. Here, we looked at dry to dry and wet to dry welds, and a total of 2,400 welds were made.

[Slide.]

Here are the tubing combinations as expressed only as dry to dry or wet to dry, but you can see again the average tensile strength is well above the minimums, and the minimum tensile strength for the dry to dry welds, the minimum that we encountered was a weld strength of 15.3

pounds, and for the wet to dry, a minimum of 11.7. This is out of 1,200 welds. Again, no air pressure leaks in 2,400 welds.

DR. NELSON: I wonder if you could summarize because we are way behind and we need to have time for the questions for the committee. If we don't do this, we are not going to have time.

MS. MANLOVE: Absolutely. Okay.

[Slide.]

This is just a graphical representation again to see that everything is well above the minimum, which is demonstrated by the red line.

[Slide.]

So, we feel that these two studies show that the sterile tubing welders consistently prepared welds that exceeded the minimum tensile strength regardless of the manufacturers type and combination of tubing used.

[Slide.]

I wanted to briefly show you some data from our QA Department. They are responsible for tracking and trending our Quality Assurance Department.

Since January of 2000, these reports have described unacceptable welds, which are misaligned, leaky, or hard to open welds occurring at a rate of 3 for every 200,000 welds or 0.0015 percent. This number is derived

based upon these reports as the numerator and the number of wafer sales in that same time period as the denominator.

The low incidence of unacceptable welds, we believe further supports the performance and reliability of the device.

[Slide.]

Dr. Aubuchon has discussed the Merten's paper. I think the only thing that we feel incumbent upon us to comment is that there were two blatant author recognized areas where they were not in compliance with the manufacturer's instructions.

They were reusing wafers and, as I mentioned earlier in the discussion, the Hawker group was able to accurately identify what that did to welds. Despite the visualization of the one leaky weld that they saw, they continued utilizing that unit in the pooling and storage process. Our guidance documents in the U.S. would not have permitted that.

DR. NELSON: I wonder if you could just conclude or summarize.

MS. MANLOVE: Summary.

DR. NELSON: There, you are. Okay.

[Slide.]

So, in summary, I would like to remind the committee that the Terumo sterile tubing welders have been

in use for over 15 years. In that time period, there has been no reports of transfusion reactions or contaminated units.

The rigorous sterility testing studies that I have put forth here and that Dr. Aubuchon has put forth approximate 3,000 welds that were made that demonstrate consistency and reliability of the devices and indicate that there were no incidents of contamination in any of the successful welds.

We consider that these studies are scientifically sound and controlled studies, and that they, coupled with the years of use and the quality assurance data that I have presented, offer confirmation of the ability of the sterile tubing welder to safely prepare the sterile welds for products stored at room temperature.

[Slide.]

Furthermore, we feel that the use of the sterile tubing welders to pool and store platelets for greater than four hours, when combined with a bacterial detection system, is appropriate.

We believe that the available data on the sterility of the sterile connection device procedure supports the use of this procedures to collect the samples under debate for bacterial detection from in-date platelet products.

[Slide.]

We are confident that the sterile tubing welders maintain the integrity of closed systems when used according to the manufacturer's instructions and in accordance with FDA and AABB guidance and standards.

Thank you.

DR. NELSON: Thank you.

Questions?

Okay. The next speaker is Dr. Steven Wagner from American Red Cross.

G. Design of Clinical Trials for Clearance of Devices Intended for Screening of Platelet Products Prior to Transfusion

Steven Wagner, Ph.D.

Background

DR. WAGNER: Hi. My name is Steve Wagner. I am with the American Red Cross. My stomach is grumbling, so I am going to try to go as quickly as I can.

[Slide.]

I am going to talk today about blood culture methods for screening platelet components. I am going to provide a background for Jaro Vostal's talk on potential designs for clinical trials for release of platelets as a function of culturing.

[Slide.]

Just a very quick comment. Sepsis is probably the first recognized infectious disease risk of transfusion that has clearly been indicated in the times around World War II. The frequency of transfusion-associated bacterial sepsis was greatly reduced with the advent of closed systems for collection and storage for blood and with the dramatic improvements in safety realized by viral testing, bacterial sepsis remains as the most frequent infectious disease adverse event in transfusion medicine.

[Slide.]

We have seen these numbers before. I don't really need to go over them. I do want to make a point in terms of fatalities that are reported to the FDA, that between 1990 and 1998, 16.7 percent--sometimes that is misquoted as 10 percent--of the reported fatalities to FDA were due to sepsis.

[Slide.]

From the BACON study, we know that in platelet components, sepsis or fatalities from sepsis is measured in about 1 in 450,000 units. In red cells, it is much less infrequent because of their cold storage, about 1 in 7,700,000 units, and because of that, most people are focusing on trying to intervene with culturing platelets.

[Slide.]

In plasma, to my knowledge, no observed fatalities from sepsis have yet been observed.

[Slide.]

There are two systems that have been cleared by the FDA for screening of platelets for bacterial contamination. One uses a color change or a rate of a color change in a pH-sensitive disk or sensor area, and it is presumably by bacterial-generated carbon dioxide evolution, and the other, from another manufacturer, involves the detection of a reduction of blood gas oxygen caused by bio-oxygen consumption.

[Slide.]

This is just a comparison of the two systems that I alluded to. One system is the bacT/ALERT. The cleared component is for apheresis platelets. It involves 4 ml that is cultured in aerobic bottle and 4 ml that is cultured in anaerobic bottle.

The sampling time that is permitted is greater than 24 hours. This allows the bacteria to grow to a level where, when you take a sample that there is a more likely event that bacteria will be present.

The incubation time after inoculation into the culture bottles should be greater than 24 hours. The number of evaluations of the culture is continuous.

Another system that has been cleared, that is marketed by Pall, has been cleared for both leukoreduced random donor platelets, as well as apheresis platelets. The volume required in the pouch where the oxygen is sensed is 2 ml, but in actuality, it uses 6 to 7 ml of a platelet concentrate simply because filling the tubing, going through a filter requires some volume of platelets.

The sampling time that is recommended is 48 hours, but it is permitted for sampling to occur after 24 hours. The incubation time is recommended to be 30 hours in this system, but again is permitted to be after 24 hours, and the number of evaluations for a platelet component is once.

[Slide.]

Culture systems are quite sensitive and by definition they are able to detect one viable organism that is capable of growth if that sample is inoculated into a culture medium. That requirement is dependent on, of course, first, the initial bacterial load in the component.

Most people who work in this area believe that the initial bacterial load is quite low. From essentially one organism in an entire platelet component to 10 organisms per ml. The rate of growth in the platelet component also determines whether you get a sample in your

syringe for inoculation into a blood culture instrument and also the volume of the sample.

[Slide.]

For fast-growing organisms, it is pretty clear that if you wait greater than 24 hours to take your sample and you wait longer than 24 hours to incubate your sample, that you are going to have a very, very high level of detection.

In the two studies cited here, one through my lab, which was, by the way, sponsored by Organon Technika, which is the manufacturer of one of the devices, and also through another lab, which is an industrial lab in Gambro BCT, it showed 100 percent detection of fast-growing organisms.

[Slide.]

But slow-growing organisms and low bacterial loads represent the most stringent conditions for evaluating culture conditions. In these sorts of systems, Staph epidermidis is probably the most frequently implicated slog-growing organisms identified in clinical cases of transfusion-associated sepsis.

[Slide.]

From our laboratory, we were able to show if you sample immediately after culture, using a very low inoculum, a tenth of an organism per ml, you don't detect

anything, and after around 24 hours, you can detect around 67 or so percent of the cultures as culture positive.

If you are less stringent and inoculate with 1 organism per ml or 10 organisms per ml, the 67 percent detection actually goes up to 100 percent detection. If you wait longer than 24 hours and sample at 48 hours, you essentially detect everything.

[Slide.]

So, how large should the sample volumes be? The answer depends on when you sample. If you sample at day zero or an early time, before 24 hours, it turns out that the larger the sample volume, the better the frequency of detection.

If you wait for one or two days before you take a sample, and during that time, of course, the bacteria will be proliferating in the platelets components, we were able to find that both a half a ml sample, as well as a 2 ml sample yielded identical frequencies of bacterial detection.

[Slide.]

I also wanted to address a question of whether anaerobic culture really is needed. The partial pressure of oxygen and platelet components is between 40 and 100 ml of mercury.

There have been two cases where strict anaerobes have been associated with clinical cases of sepsis, and the two cases both involved Clostridium perfringens. In one case there was a fatality, and in another case there was morbidity. One case was in a red cell unit, another case from a pooled platelet unit.

The microbiological textbooks indicate that Clostridia cover an entire range and the need for anaerobicist, and many are not fastidious, so many of them you would pick up in an aerobic culture bottle anyway.

This compares to many scores more bacteria that have been implicated in transfusion-associated bacterial sepsis that have been able to grow up in non-anaerobic conditions.

[Slide.]

How long to incubate? In these very stringent conditions, we found that the incubation time was inversely related to the time when you initially sampled, so if you waited a day for sampling, it could take you a little bit over a day for detection with this sample volume and with 2 ml, that didn't change. If you wait 48 hours, it takes about a half a day.

[Slide.]

There has been some talk about 100 percent QC of platelet components. This would be done on day 1 or 2

sampling, and after sampling, sometime soon after sampling, the platelets would be released.

There would be adequate platelet availability through the week as long as the shipping was less than one day and in most cases, we can get our platelets to hospitals within a day, but it does require a failsafe, real-time communication between the blood collection center and the hospital.

This has been done before as has been indicated or mentioned for NAT testing. What are the ramifications when a contaminated product is infused, that is later to be determined to be culture-positive?

I really can't answer that question, but I imagine that would be of great importance to both the blood providers, as well as the recipients.

[Slide.]

The implications of using culture in terms of platelet release are a bit different. My analysis is that hospitals probably wouldn't receive platelets until day 3 because it takes some shipping time, there is some time until sampling, and there is some incubation time.

This has been studied by Chang Phang at the American Red Cross. Assuming that all centers do not collect on weekends, what that would mean is that there would be no platelets available on Thursdays. With no

collection on a Friday, for example, there was a long weekend, that would mean that there would be no platelets available on Wednesdays.

On a long weekend with a Monday holiday, that would mean that there would be no platelets available on Fridays. So, I guess what I am trying to address is there are some availability issues involved with a culture release model where the hospitals don't get the platelets until day 3.

There conditions would require either uniform weekend collections, which is possible, but quite a change for the blood providers, or an extension of platelet storage time.

[Slide.]

In terms of the extension of platelet storage time, Jim Aubuchon hasn't presented his data, but there is an abstract out indicating that platelet properties and survival look initially good after seven days of storage, the data are encouraging.

An extension of storage might offset the cost of testing by reducing the percentage of outdated platelet components, so that is good for the blood providers, but microbiological data needs to be collected to support extension of the platelet storage time with the introduction of a particular bacterial test.

[Slide.]

So, after introducing bacterial culture, the development of a seven-day platelet component would be facilitated by demonstrating that the frequency of repeat culture-positive units is similar after five and seven days, and I think that would probably form the basis for determining whether a seven-day product is safe or not.

[Slide.]

In conclusion, bacterial culture is a sensitive method for detecting bacteria in blood components, aerobic cultures should detect a great majority of clinically important organisms.

The choice of sampling and incubation times are an important determinant of detection frequency with sampling and incubation times chosen for acceptable detection frequencies. A 100 percent QC culture release notification model should be compatible with adequate platelet availability.

A quarantine release model for bacterial culture would require weekend platelet collection or an extension of the platelet storage time. Studies suggest that seven-day-old platelets maintain their in vitro and in vivo properties and data need to be collected on the microbiological risk of storing platelets for five compared

to seven days following the introduction of bacterial culture.

Thank you very much.

DR. NELSON: Thanks very much.

Questions?

It seems like, as opposed to two days after collection, one day after collection, the problem is I guess you would have to have longer incubation times to make up for the earlier collection, so the time at which the platelets were released would not be shortened by earlier culturing.

DR. WAGNER: That's right. I think the reason for that is bacteria grow in the culture about as well as they do in the bottle, so you still need the same amount of time whether you slice it one way or the other.

DR. KLEIN: But in point of fact, the agents that are the ones we were really most worried about are the ones that grow faster, so clearly, what you did was the way to do the experiment with those that grow most slowly in the lowest concentrations.

Maybe we could calculate in terms of reactions and deaths what the interdiction would be if we sampled, for example, at 24 hours and then released at 24 hours after culture.

DR. WAGNER: I agree. I think that is worthy of study. I think that the bad actors are the gram-negatives that are fast growers.

DR. ALLEN: Two questions. Let me ask the first to you and perhaps Dr. Klein could comment also.

Given the information available now, would you recommend the culture release notification model or a quarantine release model, or do you think we need more study?

DR. WAGNER: I am with the Red Cross, so I am biased in this a little bit. I believe that logistically, right now, what we can handle is a culture release model and I think that we would need a longer platelet storage time greater than five days to be able to handle a quarantine release model.

DR. KLEIN: I would just comment that I think you can make the culture release model work. It is not going to be perfect, but it is going to be much better than what we have now without worrying about having a lack of availability of platelets.

DR. ALLEN: The second question. You commented on the paucity of any data suggesting that anaerobic bacteria, by and large, are a significant problem in terms of platelet contamination.

Can you do an aerobic culture only, would you recommend that, or do you think you still need to follow the recommended model of the aerobic and anaerobic bottles?

DR. WAGNER: My answer is I believe anaerobic culture would detect the great majority, a vast majority of clinically relevant cases of sepsis.

However, in the product insert for the bacT/ALERT, it said it was recommended that both aerobic and anaerobic cultures be performed. I wanted to bring this up because personally, I disagree with that.

DR. SIMON: I know the FDA has not put before us the question of a culture release model for discussion, but I think you raise the issue tangentially, but certainly the liability issue is going to be on the minds of any blood center that adopts such a bottle or considers adoption of such a model whereby they would release the unit once they have taken the culture and not wait at least for a 24-hour result.

The Blood Centers of America are very risk averse for obvious reasons. I think that could result in a significant impact on availability of platelets for patients in need. So, I just bring that up as something that is in the background.

DR. WAGNER: There are alternative ways of looking at it that are, as I think of it, shades of gray

where you took a sample at 24 hours, kept it, and did not send it out of your facility for 10 or 12 hours, but you are not really doing release from a quarantine and then let the units out.

That would interdict most of the fast growing organisms and then the slow growers, you would have to call on later.

So, I think that it is difficult to look at something as dynamic as culturing in kind of a digital system. It is more of an analogue type of system.

DR. NELSON: In order to have time for lunch, I wanted to have Dr. Vostal talk about a proposed study design for evaluation.

H. Proposed Study Design

Jaro Vostal, M.D., Ph.D.

DR. VOSTAL: Thank you very much.

I will try to sprint to the finish and get us to lunch before the lunchroom closes.

What I would like to start off with by saying that this is our current thinking about clinical trial design and we are really open to suggestions and discussion about how this should be designed.

Dr. Wagner has done a very nice introduction for me, so I will actually be able to skip some slides in the beginning.

[Slide.]

The issue of 100 percent QC of platelet products was raised. We think that we still need a clinical trial of automatic bacterial culture devices or ABC devices even though there will be 100 percent QC of platelet products because the QC monitoring will not assure that products are culture negative at the time of transfusion either day 5 or day 7 because the devices have not been validated for this issue.

So far no clinical data is available on whether a negative culture early in the storage period is predictive of a negative culture at day 5 or at day 7.

[Slide.]

So, the intended use of these devices is to screen bacterial contaminated platelet products prior to transfusion. The evaluation process that we will be looking at will be laboratory testing, as Dr. Wagner covered, and we think we require a clinical trial.

[Slide.]

Now, if you do go through a clinical trial or if the device goes through a clinical trial, what kind of label can you put on your product if you have been screened by a device such as that.

We think the appropriate label would be bacterial culture negative for up to five days of storage for five-

day-old platelets or a bacterial culture negative for up to seven days of storage, and the asterisk here is this requires that the storage must be under conditions validated to adequately store platelets up to seven days. Actually, that is a separate issue from the contamination rate.

[Slide.]

In the laboratory testing of these devices, as has been already described, you spike in bacteria at a certain concentration and you can then follow the growth of bacteria in the platelet product over the storage period.

With your device, you can sample at different time points and culture to get a result either 24 or 48 hours later, and with this design, you can also determine the sensitivity at the point of collection and CFUs per ml at the time of sampling. So, this would be a design of the laboratory type studies.

[Slide.]

Actually, this slide just briefly talks about the different organisms that we recommend that are tested during the laboratory studies, and these are described by Mark Brecher's paper in Transfusion in 2001.

[Slide.]

The information you get from laboratory studies is the approximate level of sensitivity and this is a

moving target. It is based on when you sample and it is based on the device.

We think for day 1 sampling, sensitivity should be on the order of 10 to 100 CFU per ml. The other things you get out of the laboratory study is the optimal sampling time, the length that you keep it in culture, and the optimal sampling volume.

[Slide.]

So, moving on to the clinical trial, we think that the trial should demonstrate that a second culture taken at the end of the storage period confirms the results obtained from a culture taken early in the storage period.

So, a comparison study where you have a culture early on in the culture, later in storage, to see if the results agree. This is just a graphic demonstration of what a study could look like.

This would be an ideal study where you actually take your sample early on and then you wait until the full length of the storage, right now it would be day 5, and then take your second sample and see if you get agreement.

The reason it is ideal is because this would be a high-risk day for platelet contamination. The problem with the study is you actually have to wait to out-date and you lose the ability to transfuse these platelet products, which is probably not good for the clinical community.

[Slide.]

This just runs through the ideal study. Basically, you collect your first sample time point at a time point that is identified by laboratory studies and which has the optimal chance of assuring that the product is culture negative at day 5.

The second culture is collected at out-date. The primary endpoint of these studies would be agreement between the first and second culture, and we can discuss the level of confidence that we want for this type of agreement.

As I mentioned, the design is not practical because you lose someone's transfusion products, however, this design could be modified to look at platelets that are going to be outdated anyway.

Let's say if you screen all of your platelets with the first culture, and then only culture the platelets that are going to be outdated at day 5, and even you could hold those up to day 7, so you could do a study like that if you only looked at the outdated platelet products.

[Slide.]

Another way to do this would be to actually transfuse the products during the study, and you can transfuse them up to day 5, and collect your second culture at the point of transfusion.

Because the risk would be with longer storage, it would be better to have sort of a waiting of the data towards the later end of the storage, so we have suggested here that day 5 makes at least 25 percent of the total samples, but at least in this type of design, you would be able to transfuse your products, which would make it lot more cost effective than the other study.

[Slide.]

We are calling this a realistic study. You have the confirmatory sample at a time point day 2 to day 5, and day 5 samples should represent a high percentage of the collected data. Again, you are looking for agreement between the first and the second culture.

Now, as has been pointed out, if you could extend the storage out to 7 days, you would actually have an added benefit from these transfusion products, so you could actually offset the cost of doing these studies.

So, we are considering that such a study would be possible, and we think it should also be designed in a similar way that you have a first sample early on and then the second sample would be at the point of transfusion, just like it was in the day 5 study, and then you would do this at day 6 and day 7, as well.

Since these products are the ones that have the highest risks, since that was the reason, bacterial

contamination was the reason they were taken off the market, we would like to see a high percentage of the second culture be done on day 6 and day 7 platelets.

[Slide.]

Now, how to get around the question of transfusing these products at day 6 and day 7, since they are at high risk for bacterial contamination, we thought that maybe it could be screened by yet a third culture of a third bacterial detection method, for example, after day 5, could transfuse products if a bacterial detection screen is done before transfusion, just to make sure that you don't have a highly contaminated unit that you are going to transfuse because you second culture done on this product would come back 24 hours later.

So, it is screened by bacterial culture, then sampled at day 5. If you decide to use a culture as the third detection mechanism, if you sample at day 5, then, you can transfuse that if it's negative by 24 hours.

If you use a non-culture detection method, such as Gram stain or dipstick or something else that is less sensitive, but may be appropriate for units that would be highly contaminated with the bacteria, you could transfuse as soon as these tests come back negative.

Again, the confirmatory second culture needs to be taken at the point of transfusion for comparison with the first culture.

[Slide.]

This is again a graphic demonstration, so you would be taking your first sample, your second sample at the time of transfusion, and you would guarantee the safety or you would attempt to guarantee the safety of these day 6 and day 7 units by a bacterial screen either by culture method or by some other bacterial detection method.

[Slide.]

So, what would be the size of this clinical study? Well, it is actually very difficult to estimate this because it depends on the expected contamination rate of the platelet products.

We have heard several numbers mentioned today. It could be 1 in 1,000, 1 in 2,000, 1 in 3,000, and also the size of the study depends on the level of certainty that the first culture would be predictive of a culture-negative platelet product at the end of the storage. You can choose your level of comfort at 99, 95 percent or less.

[Slide.]

So, I have had some help with my biostatistician colleagues. They actually pointed out that this should be

more in agreement between sensitivities, similar sensitivities at the 99 or 95 or lower level.

If you choose this type of agreement, you would need to screen or at least collect 300 contaminated units, and your expected contamination rate is 1 per 1,000, you have to screen about 300,000 units.

If you decrease your agreement level, this number goes down, and we feel actually that probably 95 percent agreement would be appropriate, so it may be somewhere in the order of screening 60,000 units, but again this depends on what the expected contamination rate is.

So, this is sort of a rough draft of a clinical study proposal. We welcome any comments or discussion that you would have.

Thank you.

DR. NELSON: Thank you, Dr. Vostal.

Questions, comments? It sounds like a big study.

Yes, Mary.

DR. CHAMBERLAND: Given the difficulty that you alluded to, the ideal example of actually being able to culture units that truly were on the shelf for five days or seven days, would another possible variation be the day that they are actually going to be transfused?

Let's say it's day 3 that they are selected to be transfused, and you take the sample, could you just

incubate, you know, maintain that sample out for a total of five or seven days and then culture? You know, maintain the sample at similar conditions to which the platelets are normally maintained.

Obviously, there is big volume differences and whether that would preclude that as being a valid approach, but I was just curious about that.

DR. VOSTAL: That is an interesting suggestion. I guess the problem with that would be that the growth of the bacteria may be different in this new environment that you put them in, you know, the smaller volume, less gas permeability, then what actually would be going on in the bag itself. So, it might not represent the growth curve that you would see in the actual product.

DR. FITZPATRICK: I think one of the goals needs to be the earliest point of detection that correlates to the five and seven day level of contamination, so if you sample only at day 1 and then at the point of transfusion, you miss a block of time that may be important.

So, I think you would want to sample at a 24-hour interval up until the point of transfusion, so that you can determine if day 1 didn't work, and didn't correlate, now you have got to repeat the study and try it at day 2 or try it at day 3.

So, if you don't see a correlation between day 1 and day 5 or day 7, you haven't collected the data you need to determine when that correlation occurs. I just would support what Mary said.

I think if you worked with the manufacturers, while you couldn't find a perfect way to collect an aliquot at the time of transfusion, you could find a way to prepare a 10 ml pouch or a 15 ml pouch that approximates the conditions, that you could store until day 5 or day 7, that would help give you that information without wasting the products.

DR. NELSON: You might also have to vary the incubation times based upon when the culture was taken, so it is a bit of a complex experiment, but I can see that it would be useful.

How solid do you think the 1 to 1,000 estimate is, because if that is way off, then, all of a sudden you are talking about an astronomically larger--I mean if it is much lower than that, to get the results might be even more of a problem.

Is that pretty solid, the 1 in 1,000, do you think?

DR. VOSTAL: Actually, I don't that is very solid. I mean nobody really knows what the true contamination rate is. It will be pretty much a guess.

DR. SIMON: See if my interpretation is correct, but from what Dr. Williams said, I gather that if the industry wishes to exceed a quality control standard and actually test all units, do a culture on all units and use it as a release criteria, either culture release or wait for the results and release, then, the practical impact of your clinical trial would just to allow the company to make a claim.

We could already have actual culture of all units before the clinical trial was done.

DR. VOSTAL: Right. I guess it depends on when you take your culture. If you take your culture early on, we are not really sure right now whether that culture will be predictive of what will happen at the end of storage. I mean that is why we need the study.

If you take your QC like at day 3, and you are willing to wait for the results, so you transfuse at day 4, that probably would work, but I think you would lose three or four days of transfusion.

DR. SIMON: You are saying that you are dubious about the whole concept of the 24-hour culture as eliminating almost all of this problem?

DR. VOSTAL: Oh, you mean taking sampling at 24 hours. Well, I think as Steve pointed out, the longer you

wait, the higher your sensitivity gets because the bacteria grow to a higher level.

So, I think it's a tradeoff. If you sample early on, you might miss some, and the question is how many do you miss and will that be a risk.

DR. NELSON: From a practical standpoint, five days is the limit now, but how many platelets are actually released, you know, one, two, three, four days earlier than that?

Somebody has those data, I guess, but given "never on Thursday" scenario that Dr. Wagner presented, it seems a little bit complicated.

Do you have a comment?

DR. KUNERT: I just had a quick question. On your sample sizes, was that assuming the two cultures or was that assuming three cultures lengthening out to day 7?

DR. VOSTAL: It would be looking at the two cultures. The third culture is actually just to provide safety if you plan to transfuse the day 6 and day 7 product.

DR. KUNERT: What data are there to suggest that you wouldn't have cultured it out at, say--I am not sure what the assumption is on the second culture--but if it is day 3 or 4, that you would then culture it on day 5?

Staph epi would be the biggest example, but I don't know even know with Staph epi that--I mean you should be able to culture it at day 3 or 4, so is it the concern mainly fastidious organisms or is there any particular scenario you had in mind for that?

DR. VOSTAL: I guess if you are saying that if we culture at day 3, that should be sufficient to cover day 4, 5, and 6, out day 7, right?

DR. KUNERT: As Dr. Wagner pointed out, it depends on the time of sampling to the time of culture, but there could be some point where there should be a level of confidence where you might not need to culture at day 5 depending on those parameters.

DR. VOSTAL: You have to optimize it, I guess, because if you culture at day 3, are you going to not transfuse day 1, 2, and 3 platelets, or are you going to transfuse them or hold them.

I think you have to play around with the logistics of the study and logistics in the blood bank to try to optimize it.

DR. NELSON: Yes.

DR. SNYDER: Ed Snyder, New Haven.

Do you have a similar approach that might be useful for random donor platelets? I mean that could be used, but you would have to sample each bag. We use a

four-unit pool, so that would be a fair amount of sampling.

I assume you wouldn't let us pool and store the pool before release and testing at various times.

DR. VOSTAL: Well, I think we are actually having discussions about pooling upfront and storing pools, however, we need more data on that in terms of at least platelet efficacy and also in terms of whether these devices can--you know, if the growth of bacteria in the pools is different and whether the devices can pick up that contamination.

So, we would expect a separate study done on the pools themselves.

DR. STYLES: I was just going to suggest that if you are going to undertake such a large study, that you want to incorporate DNA-based screening techniques within that study instead of having to go back and repeat it with the advent of PCR and all. I mean you are going to avoid the whole need to wait after culture if those techniques come to fruition. Just a thought.

DR. VOSTAL: I mean these studies are designed to look at culture devices and, you know, the sensitivity and the time you have to wait to get a readout, but if there is a screening method that would be immediate, I think that would be a lot better.

DR. NELSON: Here is the dilemma. We have got four people that wanted to make statements in the open public hearing and then we have to consider the questions, and the lunchroom closes in about 15 minutes.

I propose that, of the three alternatives, lunch is a higher priority at this time. Why don't we break now. Let's come back at 2:30.

DR. UNDERWOOD: Those people that are speaking in the open public hearing after lunch, you know my rule is five to seven minutes. It is now five and half each, so please be prepared.

Thank you.

[Whereupon, at 1:35 p.m., the proceedings were recessed, to be resumed at 2:30 p.m.]

AFTERNOON PROCEEDINGS

[2:30 p.m.]

I. Open Public Hearing

DR. UNDERWOOD: This is the open public hearing for the bacterial contamination. As I admonished those speakers prior to lunch, if you can make your presentation as brief as possible.

We have four scheduled speakers for the open public hearing on bacterial contamination: T.J. Smith from Medi-Flex Hospitals, Dr. Roger Dodd, Kay Gregory, Dr. Bianco. Are those people here in the room?

Those that will not need to use the slide projector, if you can proceed and perhaps use the mike in the center aisle, please.

Kay R. Gregory

MS. GREGORY: My name is Kay Gregory. At this time I am representing the American Association of Blood Banks.

The American Association of Blood Banks (AABB) is the professional society for over 8,000 individuals involved in blood banking and transfusion medicine and represents approximately 2,000 institutional members, including blood collection centers, hospital-based blood banks, and transfusion services as they collect, process,

distribute, and transfuse blood and blood components and hematopoietic stem cells.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's high priority has been to maintain and enhance the safety and availability of the nation's blood supply.

The AABB believes that bacterial contamination of platelets is the most significant current infectious threat from blood transfusion and appreciates the opportunity to comment on this issue. For decades, bacterial contamination has been recognized as a significant risk associated with room temperature storage of platelets. The AABB believes the time has now come to take action on this issue.

As other infectious risks of transfusion have been reduced, the magnitude and relative importance of bacterial contamination of platelets has become more pronounced. Various innovative strategies have been and are being developed to address this risk.

Although no single method or strategy provides a perfect solution, the AABB believes that multiple approaches may be appropriate for consideration. Methods to prevent and detect bacterial contamination in both

apheresis and pooled platelets made from whole blood have been implemented in other countries.

These methods have undergone clinical evaluation in this country, demonstrating the ability to detect some bacterially-contaminated units. The AABB notes that the FDA has recently approved two culture-based bacterial detection systems for quality control testing of leukocyte-reduced platelets.

At this critical juncture, the AABB sees a valuable opportunity for cooperation between the transfusion medicine community and FDA.

The AABB reviews its voluntary Standards for Blood Banks and Transfusion Services on a planned basis. The next edition of these Standards, the 22nd edition, has just been published for public comment and proposes two significant changes with regard to decreasing the risk of bacterial infection for recipients of platelet transfusions.

The first focuses on prevention of bacterial contamination of the donated unit, and involves changes to the skin preparation method. Based on the data reviewed, AABB has recommended that alcohol/tincture of iodine be the method of choice, with chlorhexidine being acceptable for individuals who are allergic to iodine. On the basis of

the data reviewed, the Standards Committee has concluded that green soap is not acceptable for skin preparation.

The second change the AABB has proposed is a draft standard requiring that facilities have methods to detect bacterial contamination in all platelet components. In light of the fact that no single system or method is effective in eliminating the risk of bacterial contamination in all components, the AABB has declined to be specific as to the method of bacterial detection required in this proposed standard.

There are a number of logistical and scientific issues to be resolved prior to implementation of any detection system, but the AABB believes it is critical to begin to address these issues now. The AABB recognizes that some facilities may opt to use a method that gives immediate results, while others may be able to adopt culture technologies.

It is also relevant to note that this proposed standard would require screening of all platelet components. If the goal is to reduce infections in recipients, it is essential that all platelet components be evaluated. A statistical sampling approach runs the risk of not effectively decreasing the rate of bacterial infection.

It is much more feasible and practical from both a logistical and a product loss standpoint to perform bacterial detection, especially using culture methods, on apheresis platelets. However, the entire need for platelet transfusion is not currently, nor will it be in the foreseeable future, met by single donor apheresis platelets.

Whole blood derived platelets are necessary to ensure an adequate supply of platelets. The potential application of culture methods to detect bacterial contamination in apheresis platelets cannot be allowed to render platelets from whole blood an undesirable component.

To this end, the AABB recognizes that detection techniques such as Gram's or Wright's stain, or dipstick monitoring may initially need to be used for whole blood derived platelets.

The AABB believes that the FDA can facilitate bacterial detection of whole blood derived platelets by reexamining its current thinking under which platelets pooled in either the blood collection facility or the transfusing facility, regardless of the use of sterile methods, cannot be used beyond four hours after pooling.

The FDA's current thinking makes the culture of pooled platelets impossible. In the interim, alternative, albeit less ideal, methods, including microscopy with

acridine orange, Wright's or Gram's stains, or dipstick monitoring of glucose and/or pH with appropriate thresholds are available for use at the time pooled platelets are released.

The FDA appears to have indicated that it would require in vivo studies of platelet effectiveness before considering extending the storage of platelets pooled using sterile methods to five days, as is currently allowed for non-pooled product.

However, such in-vivo studies are difficult to perform, expensive, require the enrollment of large numbers of patients from multiple institutions, and are difficult to analyze due to multiple, unavoidable confounding factors.

In light of existing in vivo data from Europe concerning the five-day storage of pooled platelets derived by the buffy coat method and in vitro data showing the similarity between platelet-rich plasma derived platelets and buffy coat platelets, the AABB urges the FDA to examine ways in which it could expedite approval of the extended storage of a pooled platelet product.

The AABB urges the FDA to act quickly to consider what data will be required to extend platelet storage to seven days, provided that an acceptable bacterial detection system is used.

In light of the challenges and tremendous opportunity for improving the safety of the blood supply through the implementation of the bacterial contamination methods described above, the AABB requests the following assistance from FDA:

1. Regulatory support towards accomplishing AABB's current goal of requiring bacterial detection and interdiction of contaminated products.

2. Regulatory support in developing consensus on arm preparation solutions and techniques, with a specific emphasis on prohibiting the use of green soap.

3. Discussion of data required to increase the storage time for random pooled platelets with a particular focus on whether in vitro data on platelet bacterial growth rates is acceptable.

4. Discussion of the data needed to extend the out-date of platelets to seven days.

As has been the case relating to the development of new tests for emerging infectious diseases, the blood banking and transfusion medicine community and the FDA must understand the need to implement less than perfect solutions, while we work to improve the available methodology and technology, recognizing that such incremental steps will improve the safety of the blood supply.

Thank you.

DR. NELSON: Thanks very much.

Roger.

Roger Y. Dodd, Ph.D.

DR. DODD: Thank you very much, Ken.

My name is Roger Dodd. I am the Executive Director, Biomedical Safety at the American Red Cross. At the moment I am representing the American Red Cross, which collects about half of the blood components used for transfusion in the United States.

One of our strategic priorities is: "To provide high quality, safe products." The American Red Cross thanks the Food and Drug Administration and the Blood Products Advisory Committee for this opportunity to address a topic of great importance to platelet recipients in the United States. We applaud the FDA for its attention to the issue of bacterial contamination of platelet components.

The Red Cross agrees with the AABB statement relating to the serious nature of bacterial contamination and recognizes that measures should be taken to reduce or eliminate the occurrence of transfusion-related sepsis.

We recognize that an immediate, single solution is not currently available and acknowledge that attention to aseptic practice and to appropriate skin preparation

continue to be a critical foundation for maintenance of bacterial safety.

We further agree that it is highly desirable to implement means to detect bacterially contaminated platelet units and recognize that some approach to diversion of the initial collection volume may complement such detection.

We challenge researchers and manufacturers to develop rapid, highly sensitive tests that may be used to assure their platelets are bacterially safe; ideally, such methods could be used prior to release of products. In the meantime, we recognize that FDA's approval of two culture-based methods for platelet quality control is a step in the right direction.

The Red Cross is in the process of determining the feasibility of implementing procedures to assure quality control for bacterial contamination of all apheresis platelets and will discuss with the FDA available options to assist hospital customers in reducing the risk of transfusing any components that fail to meet bacterial QC requirements.

In common with the AABB, the Red Cross is concerned about the ability to complete such QC on random donor platelets without compromising their availability and efficacy.

We hope that the FDA will be willing to consider the concerns expressed by the AABB and thus to assist the Red Cross in fulfilling its mission.

Thank you for your attention.

DR. NELSON: Thank you.

Celso.

Celso Bianco, M.D.

DR. BIANCO: I am Celso Bianco. I am speaking for America's Blood Centers.

America's Blood Centers (ABC) is a national network of locally-controlled, not-for-profit community blood centers that provide nearly half of the U.S. blood supply from volunteer donors.

Collectively, America's Blood Centers' total blood collections exceeded 7 million donations in 2001. ABC members operate in 45 states and in Quebec, Canada, and serve more than half of the 6,000 hospitals in the U.S.

Members of America's Blood Centers thank the FDA for the opportunity to participate in this public discussion about the reduction of the incidence of bacterial contamination of blood components. Bacterial contamination is the second cause of transfusion-related fatalities reported to FDA, representing 10 percent of the cases with an average of five reports a year.

Only hemolytic reactions due to errors cause more fatalities--an average of 18 a year and half of the reported transfusion-associated fatalities (Jong-Hoon Lee, M.D., CBER, FDA September 1999).

ABC members also agree that measures to reduce the incidence of bacterial contamination of blood components should be implemented. However, they believe that a number of unresolved issues must be considered by this committee and by FDA before the agency issues any specific requirements.

Bacterial contamination of blood components is a far more complex problem than viral contamination. Substantial reduction of transmission of HBV, HCV, and HIV by transfusion has been achieved by screening assays that are specific for each virus, as well s by donor history questions and donor deferrals.

Viruses do not replicate during component storage; what is in the donor is in the blood sample collected for testing and is in the blood bag.

Bacteria, on the other hand, are everywhere. There are thousands of species that may contaminate blood products, and they replicate during storage. They may be present in minuscule amounts in the donor's circulation, they may survive skin disinfection, and there are no specific tests.

The sensitivity of disinfection and detection systems varies according to the type of bacterium. Thus, while everyone agrees that something should be done, there is no clear agreement about what should be done.

The American Association of Blood Banks' Standards Committee is proposing new standards for skin disinfection in the next edition of AABB's Standards. The Standards Committee has also proposed the implementation of bacterial detection systems (without specifying how this should be done).

We all agree that disinfection of the venipuncture site should be performed using the most effective method possible. Recent studies suggest that tincture of iodine would be better than current methods.

A second approach to reducing the incidence of bacterial contamination adopted in some European countries, e.g., The Netherlands, is attaching a diversion pouch to the collection bag. The first several ml of collected blood are diverted to the pouch and used for testing.

This prevents skin contaminants and the skin plug often generated by penetration of the needle from entering the collection bag. These diversion pouches are available in some apheresis sets, but are not yet approved for whole blood collection systems.

Unfortunately, skin disinfection and diversion pouches only reduce skin and environmental contaminants. Several bacteria of importance are in the donor's circulation and are not affected by these measures. Detection systems appear, at first sight, to be the solution.

In theory, bacterial culture and detection of bacterial growth could resolve the problem of bacterial contamination of blood components, and FDA has approved two such systems in recent months. However, the approval is specific for quality control, not for release of blood components as free of bacterial contamination.

Concerned about bacterial contamination, European blood agencies have decided to adapt clinical laboratory culture systems to their operations. In The Netherlands, platelets from whole blood are prepared by the buffy coat method, pooled, and a sample from the pool is placed in a culture system with automated detection of bacterial growth.

After 24 hours, if the culture is negative, the platelets are released to hospitals. If growth is observed in subsequent days, the hospital and physicians are notified. This method for the preparation of pools of platelets from whole blood is not approved in the U.S.

Hema-Quebec, our Canadian member, has implemented bacterial detection systems for platelets collected by apheresis and is studying the adoption of the buffy coat method for preparation of platelets from whole blood.

Among the 75 ABC member centers, 8 have decided to implement bacterial detection systems in the near future. They plan to use he ones currently approved for QC of apheresis platelets, in a way similar to that used by the Dutch. These systems are complex and expensive; moreover, they cannot be applied in a practical manner to platelets derived from whole blood.

Current FDA regulations prevent us from pre-pooling platelets from whole blood. When pooled, they must be transfused within four hours, even if the pooling is performed in a closed system, using sterile connecting devices.

For this reason, the implementation of bacterial detection systems threatens the survival of platelets from whole blood. Members of this committee should be aware that there aren't enough platelets collected by apheresis to supply the needs of the U.S. healthcare system.

Last year, ABC members distributed about 550,000 platelets by apheresis and 1.5 million units of platelets derived from whole blood, and it would take several years

to reach sufficiency if we were to convert entirely to platelets by apheresis.

In addition, many hospitals are resistant to the conversion, because of the substantial cost differential between the two components.

Some less cumbersome and less expensive approaches have been proposed for the screening of random donor platelets for bacterial contamination. One is the use of a reagent dipstick for pH and glucose; a pH lower than 7 and/or a glucose level of less than 250 mg/dl would be considered indicators of bacterial contamination.

The sensitivity and specificity of dipsticks is not yet fully assessed. In the past, some centers have screened platelets with a Gram stain immediately before transfusion. However, we know that these two methods are much less sensitive than systems based on bacterial culture.

In our opinion, a number of practical issues need to be dealt with before restrictive standards or regulatory mandates are issued for interventions designed to reduce the incidence of bacterial contamination.

The mode of application of the systems approved for quality control is still unclear for us. What would be the corrective actions triggered by the finding of an occasional component with bacterial growth? We can think

of personnel retraining and very little else. How should we interpret these findings from the QC point of view?

Where should bacterial detection be performed? At the blood center where the components are prepared, or at the hospital, closer to the transfusion event? The requirements for the two approaches are quite different.

Detection at the collection facility requires high sensitivity, and results obtained at the time of release of the platelets (consider the five-day out-date) may not be predictive of the bacterial load at expiration. On the other hand, there are no reliable systems for testing close to the transfusion event, when platelet concentrates are pooled.

One of the approved systems (Pall) focuses mainly on aerobes; the manufacturer of the other is recommending cultures for aerobes and anaerobes (BioMerieux). Are cultures for anaerobes warranted, considering that platelets are stored in gas permeable bags in an oxygen-containing atmosphere?

Recognizing that anaerobes are rare causes of clinical bacterial contamination, and sometimes not detected in vitro until beyond the expiration of the product, we do not think that use of anaerobic media is a key initial part of this initiative.

What inoculation systems should we use to prevent false positive results? Do we need to use laminar flow hoods? How do we deal with false positives?

The Pall BDS is an endpoint system. Specimens are inoculated 24 hours after collection and the cultures read at least 24 hours later. In contrast, the BioMerieux bacT/ALERT is a continuous system, raising the question of when cultures should be considered negative.

Then the BioMerieux system is used and the cultures continue to be followed after release of the platelets to a hospital, if subsequently positive, what should physicians be told (since in many cases the platelets will have been transfused)?

To what level should centers or contract microbiology services identify positives? Is there a need for performance of antimicrobial susceptibility assays? Probably yes.

Could cultures be inoculated at the collection facility and read at the hospital that received the component? If so, how would specimens be identified? What software modifications are needed to assure correlation between components and culture results? In this case, how should reports of positive results be handled?

How do we validate these systems? What are the positive controls? How can we measure the efficacy of the

detection procedures in light of the low frequency of events?

Finally, should a recommendation be made for implementing these very expensive new procedures, there should be a consistent message to hospitals and insurers explaining that their benefit far exceeds their cost.

Considering these and many other issues that need to be reviewed, we respectfully request that this committee and FDA consider the following:

Support collection facilities that implement methods to reduce the risk of bacterial contamination by skin contaminants in blood and blood components.

Facilitate the licensure of bacterial detection systems for component release, allowing claims such as "negative for bacteria at time of release."

Support collection facilities that decide to implement 100 percent Quality Control for their apheresis platelets. Their experience will be invaluable for progress in this area. Regulatory actions could have serious inhibitory effects and delay the implementation of procedures that will certainly increase the safety of transfusion.

Encourage the development of alternative technologies for bacterial detection that are less laborious, less expensive, and can be applied at the

hospital level, closer to the transfusion event. This is essential for the survival of whole blood derived platelets and for the fulfillment of patient needs.

Speed the regulatory process for the extension of the expiration date of platelets to seven days if negative for contamination.

Allow pre-pooling of platelets from whole blood using approved sterile connecting devices, based on the long and successful European experience with buffy coat platelets.

We strongly believe that these actions will encourage the implementation of means to reduce bacterial contamination of platelets and hence increase the availability of safer platelets for transfusion. When we reach this stage of development, we will welcome FDA regulation.

Thank you very much for the opportunity to present our point of view.

DR. NELSON: Thanks, Celso.

T.J. Smith?

MS. CROSBY: T.J. Smith has asked me to give the presentation.

Cynthia Crosby

MS. CROSBY: I am Cynthia Crosby.

As we go forward, I am going to skip through these slides really fast, but I want to challenge the FDA Advisory Committee to understand the modes and mechanisms of antimicrobial solutions in choosing what I am hearing a plea from your Red Cross, the ABC to adequately assess skin preparation prior to the venipuncture.

[Slide.]

Understanding antiseptic agents is very easy and readily available in the texts that are out there. I am with Medi-Flex. We have been in the business for 17 years of providing aseptic tools to deliver antiseptic products to the donor site.

Our bread and butter is in the donor prep market outside the United States by them using alcohol followed by tincture of iodine. Our bread and butter in the United States is blood culture kits that provide alcohol followed by tincture of iodine.

[Slide.]

Why is tincture of iodine superior to your current AABB recommendation of povidone-iodine? Povidone-iodine is complex with an inert polymer that must dry for the polymer, must dry for the iodine to decomplex, to have a kill mode.

[Slide.]

With tincture of iodine, you have readily available iodine. It is there in the position to have an immediate effect prior to your venipuncture.

[Slide.]

We have had great demand from the blood donation facilities for a chlorhexidine type based product whether it be tincture or aqueous. We are hearing that every day if this product has been approved by the FDA to be used for blood donation.

Right now we have several facilities that are running validations. The National Blood Authority in the UK is in the mode right at this time of implementing a chlorhexidine/alcohol/tincture for blood donation.

Carl McDonald presented at the International Blood Banking Conference in Canada that stated that there was an equivalence to the tincture of iodine two-step procedure, alcohol followed by tincture of iodine.

In this, there was 2.76 log reduction with tincture of iodine versus a 2.6 log reduction with the chlorhexidine/tincture. Over 99 percent of the bacteria were killed at the time of the venipuncture.

[Slide.]

What makes chlorhexidine ideal is its affinity to bind to the skin surface. Ideal antiseptics should be broad spectrum, they have to be rapid.

[Slide.]

They have to be rapid because of one key component, and that is convenience and compliance to protocol. As our staffing nurses are reduced, our average age nurse is now 47 years old in our facilities, and as phlebotomy teams are reduced, compliance and convenience to protocol is necessary.

Industry has met that demand by combining products that will have a quick dry time, a quick kill.

[Slide.]

As of July 2000, there was an NDA approval for a new chlorhexidine/tincture product, 2 percent chlorhexidine and 70 percent isopropyl. It has been demanded from the health care worker or clinician for the care of catheter insertion and catheter lines.

In 10 years, we have heard the data over and over again in the 50 percent reduction to catheter-related bloodstream infections. We see it now in the studies that are followed in the data that I gave you as a package that shows the 50 percent reduction by going to use a chlorhexidine/tincture prior to a vascular procedure.

[Slide.]

Povidone-iodine is your current prep. It's a two-step procedure. Tincture of iodine and CHD are far superior in the clinical and in the in vitro data to

povidone-iodine. Tincture of iodine is a two-step procedure. It is proposed for the standards of blood banking and transfusion.

Two percent chlorhexidine based products that are currently available, which only happens to be one, is a one-step procedure. It is equivalent to the two-step tincture of iodine. It is proposed as an alternate prep.

One thing I can state is that we see huge compliance to protocol in the hospital community. New CDC guidelines for the prevention speaks I think, and I am going to go out on a limb here, to your donation facilities, that is, educated and dedicated resources are necessary to reduce your contaminations.

Maximal barriers and the understanding of maximal barriers are necessary in reducing contamination, and 2 percent chlorhexidine-based antiseptics are preferred, they are the preferred antiseptic of choice by the CDC, and they have superior efficacy compared to povidone-iodine.

[Slide.]

Preventative measures are the highest quality in medical treatment and the most cost efficient. They are simple. We just have to make the decision to use those preventative measures.

Thank you.

DR. NELSON: Thank you very much.

Pall Corporation also had a statement to make, but they have decided to submit it for the record rather than to read it or present it at the meeting at this time.

We are no longer in the open public hearing.

Maybe we can go to the questions. John.

Questions for the Committee

DR. LEE: I guess I will just read the question one more time regarding donor arm prep.

Do available scientific data support preferential use of an isopropanol/tincture of iodine procedure for preparation of the donor's phlebotomy site?

I guess I would just comment that some of the comments we heard during open public hearing session just now didn't really refer back to some of the material that I presented in the morning. The fact that isopropanol/tincture of iodine is proven to be superior in the donor setting seems a bit of an overclaim in view of what I presented.

DR. SIMON: Is it appropriate to start the discussion? I guess it is an interesting topic because I have a long-standing interest in it, and actually, data that were not presented here, but there was a study done, the United Blood Services in 1993-94. It was only presented in abstract form and it is referred to in the

Goldman paper, and it showed that tincture of iodine was superior in eradicating organisms from the skin.

I actually wrote the AABB at that time and proposed that we make the change then, and that obviously did not occur. So, I think that there is data and I think there is data in the blood culture literature, as well, to indicate that looking strictly at data, it would appear that tincture of iodine is superior to the povidone and that, in addition, chlorhexidine is also superior.

Actually, we use chlorhexidine in our laboratory for our blood cultures, but when I questioned our microbiologist on why we made that choice instead of tincture of iodine, it was because we have a lot of these cultures drawn by non-dedicated personnel, not personnel that we control, intensive care, emergency room nurses, and so one-step procedure, which the chlorhexidine is, is superior or we feel we get superior compliance and went with that instead.

I think there is data to support the change as AABB plans. I must say that I was impressed with your presentation and I think from the common sense point of view, one could well raise the question, does it really make a difference in the donor setting where you have so many other things going on, and you have sort of a multifactorial situation.

But I would guess if we are this concerned about this subject to be willing to move to some of these other steps that we are going to discuss, I would think, as a first step, that we would want to have the most effective removal of organisms from the arm to begin with when the unit is drawn.

I think that the tincture of iodine, as AABB has proposed, with the chlorhexidine as the backup for iodine-sensitive individual, that would be the step to go, so I would support this.

I would put into that statement, however, that I don't think the plasma industry should be required to go this direction because none of their products are stored are either refrigeration or room temperature. They are frozen, and they have not had a problem with bacterial infection in that industry.

So, I would think that they should be okay to go with either one, but I would support the AABB position at this time.

DR. ALLEN: Thank you, Toby. I think that is a good introduction to the discussion. I have been mulling over, given the way in which the question is worded, whether I would vote yes or abstain.

My feeling is that there is some evidence that tends to lean towards tincture of iodine in isopropanol, or

the combination, the two step, as clearly the preferred way to go although I would have real trouble given the broader view of 2 percent chlorhexidine in isopropanol as an equal alternative.

I guess my question is what is the implication of voting yes for this in terms of action that the FDA might take given that the AABB already has revised proposed standards out that use this with the chlorhexidine as an alternative.

So, if we vote yes for this, what are the implications in terms of how the FDA is going to use this information?

DR. LEE: That's a million dollar question. Dr. Epstein, would you like to field that question?

DR. EPSTEIN: The question before the agency is whether we should issue a regulatory guidance recommending preferred use of isopropanol/tincture of iodine. It has occurred from time to time that we disagree with an industry voluntary standard, and then we may take a regulatory position to override it.

So, in this case, our options would be to remain neutral and let the preference be voluntary or to endorse it through a regulatory recommendation.

DR. ALLEN: I would certainly feel comfortable and I would vote yes if it is to be a voluntary recommended

standard. I am much less comfortable I think to take it to the regulatory level.

DR. EPSTEIN: Well--okay.

[Laughter.]

DR. NELSON: Actually, this committee doesn't exactly make regulations. We are supposed to help the FDA evaluate data and evaluate what is there and what is missing. So, I don't think you need to consider yourself a judge or a congressman at this point, I guess.

DR. KLEIN: I appreciated Dr. Lee's very thorough review, but I must say I sort of discounted the studies that simply showed that you can't culture something or you culture something less frequently from the site, because that really isn't a good demonstration of what might be the risk in the bag.

Actually, I think you could be fairly badly misled by those studies. What you really want to know is what the risk is of contaminating the component. We don't have those studies unfortunately, and I think the best that we have are the blood culture studies which by and large show that all of these preps are just about the same, I guess, with the exception of soap, which I don't think anyone supports.

The problem with those studies, of course, is that the background level is so high that it could mask slight differences between different arm preps.

So, I don't have any problem with saying that this is a good preparation, I guess as the AABB is suggesting in its standard. I would hate to see anything regulated based on that, however. I don't think the data support it.

DR. NELSON: In these studies, apparently what happened, the way they did it is they cultured before the preparation and then they applied the material and then recultured. It was stated as a percent reduction of flora.

DR. LEE: Well, many of the blood culture studies were comparisons.

DR. NELSON: Not the blood cultures, the McDonald.

DR. LEE: The blood collection studies, yes, it was cultured before and after. Again, when represented as percent reduction, the values don't strike out at you as much, the difference between 99 and 98, I don't know what that really means.

DR. NELSON: Mary.

DR. CHAMBERLAND: I guess I am puzzling over this, too, because I guess what are the criteria, what is

the level or rigor that is going to demonstrate that one of these preparations is "preferential."

I agree with Dr. Klein's comments that log reduction of bacteria skin contaminants is not necessarily at all the whole story. I just wanted to make sure because it was a quite a load of literature that the committee was given to review in advance, in a relatively short period of time, so I think it is really hard for us to basically digest all of this.

I do want to commend you because I think you did really put together a really nice, critical review. As I understand it, there are no data for this proposed prep that look at contamination rates in bags of platelets, that is correct, it is just all skin studies.

DR. LEE: That is my understanding. The thing that comes closest is the third study that I described, within which cultures of actual platelet units were done, but that study did not include the tincture of iodine/isopropanol method.

DR. CHAMBERLAND: So, as a surrogate, then, you brought up in some of your slides some reviews of literature that is available on looking at blood culture data.

DR. LEE: Right.

DR. CHAMBERLAND: And the various preps. Again, I want to make sure I have got the bottom line here straight, but in looking at the blood culture data, were there any clear winners here? This isopropanol/tincture of iodine did not emerge in the blood culture studies as showing a preferential--

DR. LEE: No, it did not. There are some conflicting results. Some showed marginally better performance, but there were many others, equally as many, that showed no difference.

DR. CHAMBERLAND: I think it comes down to--again, this is what I am struggling with--if FDA is signaling that they are potentially considering guidance, then, you usually have to put forward what your criteria are that you are going to evaluate.

I guess a fair question is if the only data for this new prep are skin culture data, is that adequate, is that the whole story, would you require more rigorous data.

In the end, at the end of the day, how much of a difference is it going to make.

DR. LEE: I see Dr. Epstein at the mike.

DR. EPSTEIN: Maybe I can shed some light. I think Dr. Lee said this earlier. What has happened here is we have had a series of workshops over a period of years. At every single workshop or symposium, someone shows the

studies on the isopropanol alcohol/tincture of iodine prep and says, look, this reduces bacterial contamination of the skin.

We all agree that we don't have a good endpoint study in platelets, and the FDA has not come forward in the face of that with a recommendation for preferred use of that procedure because we keep taking a look at the larger literature and scratching our heads and saying we are not ready to do this.

On the other hand, the AABB has now, listening to the same workshops, the symposiums, reading the same literature, has decided to make this a voluntary standard.

Now, there are two positions that the FDA could take. One is we agree, so we will make it a regulatory standard, or we are not so sure, but we are not opposed to the industry voluntary standard.

Again, and I guess this comes back to you, Jim, we are not asking you to decide the regulatory position. We are just asking you whether you are, in effect, in agreement with the FDA that the science is too soft for us to take a regulatory position, because after all, the pressure on us has been to do just that.

DR. SIMON: I just will say a few more words in support of my position, I guess, for a yes vote on the question. I think we have to remember that what we used to

cleanse the skin was based on this kind of analysis. That is, we wouldn't have any prep at all as far as I know if we had as an endpoint, the desired one, of the infection of the unit.

So, we have sort of empirical choice of agents that remove bacteria from the skin, because that is what we want to do with this step of the procedure, and the data would indicate that tincture may be superior.

I was a little surprised at the skepticism about the blood culture studies because the reason we did the study at UBS back in 1994 was the literature on the blood culture studies, which indicated that povidone was inferior.

I might be somewhat influenced by this 1999 study by my former mentor at medical school from Barnes-Jewish, which showed tincture of iodine to be superior, and I don't believe that we would use povidone in our laboratory for blood cultures at this time. We would use either chlorhexidine or tincture of iodine.

So, I think that there is enough data there given that what our objective is with this step of the procedure is to remove bacteria from the arm. We may have to do other procedures to make sure that the platelets are absolutely sterile, but that would seem to be the most reasonable first step.

DR. FITZPATRICK: I would agree with Toby, but prior to making regulation, because really the only data we have for regulation is from the Vox Sang article, and since the tincture of iodine wasn't in that, there isn't a comparison to use, so you would need a comparison.

But as far as just surface contamination, I think there is ample evidence, and we did used to use tincture of iodine, and the biggest complaint was that techs and nurses were getting cut in their fingers when they broke the ampule initiative the tincture of iodine swab that was used to prepare the arm, and now there is a method where you don't have to break a glass ampule to do that.

Since it just says preferential, it is pretty soft as it is.

DR. LEW: I think maybe to be fair, to be more specific, though, because everyone is struggling with the fact, I think, that there is no good studies looking at many different types of preparations and saying that this is The superior with a capital T.

But if you can just say preferential, the tincture compared to what is used now as a recommended standard, I don't think anyone would have a major problem with that. It is just trying to imply this is the best overall. The data is not there, and it is not appropriate to I think regulate based on no data.

DR. NELSON: Are we ready to vote on this? It is now an open public hearing, but if you have got something critical that we haven't considered.

DR. WAGNER: Just a cautionary note, and that is of placing too much emphasis on whole blood cultures done at hospitals on patients who may already, some fraction of which would be bacteremic, to compare two different skin preparation methods.

The bacteremia in the population may overwhelm the differences.

DR. NELSON: The difference of differentiating a contaminant from a real infection. We have recorded that.

DR. ALLEN: Would the FDA consider an amendment, if we add at the end of this, the sentence as written, "for preparation of the donor's phlebotomy site compared with the current procedure using povidone-iodine"?

That compares this one versus that one without making a statement about any other preparation.

DR. LEE: We could do that, interpret the question in that light.

DR. NELSON: Right, since that is what is used, I guess. Okay.

DR. SMALLWOOD: Would you repeat that?

DR. ALLEN: Do available scientific data support preferential use of an isopropanol/tincture of iodine

procedure for preparation of the donor's phlebotomy site compared with the current standard procedure based on povidone-iodine preparation?

DR. SMALLWOOD: Voting will be by roll call as required.

The question as amended reads: Do available scientific data support preferential use of an isopropanol/tincture of iodine procedure for preparation of the donor's phlebotomy site compared with the current standard procedure based on povidone-iodine preparation?

Allen.

DR. ALLEN: I vote yes and I think we need to look at other preparations, and we need to study the donor acceptability of the tincture of iodine.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: I am going to vote no.

DR. SMALLWOOD: Davis.

DR. DAVIS: No.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: No.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: Yes.

DR. SMALLWOOD: Klein.

DR. KLEIN: No.

DR. SMALLWOOD: Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Stuver.

DR. STUVER: No.

DR. SMALLWOOD: Fallat.

DR. FALLAT: No.

DR. SMALLWOOD: Harvath.

DR. HARVATH: No.

DR. SMALLWOOD: Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon, you would--

DR. SIMON: Yes.

DR. SMALLWOOD: The results of the voting. There are 6 yes votes, 7 no votes, no abstentions, the acting non-voting industry representative agrees with the yes vote.

DR. NELSON: Now that we have solved that, do we have a second question?

DR. WILLIAMS: Just a very brief clarification. Like this question, several of the other questions deal with issues in which there is a developing industry

standard, as well as a potential developing regulatory policy.

Several of these initiatives are draft standards. They need to go through a membership comment period and final acceptance, so just to clarify, these are not existing industry standards at this time.

Committee Question 2. Do available data on the sterility of the sterile connecting device procedure support the use of this procedure to collect samples for bacterial detection from in-date platelet products?

DR. NELSON: Discussion? Yes.

DR. SIMON: I think the data were fairly overwhelming to answer this yes, however, just with the caveat that we are introducing another complexity into the system, which at a breakdown at some point, could lead to more bacterial infections than what we have now, but I think certainly the data we are presented support it and obviously, the FDA has approved this for products that remain in-date and can be infused.

So, I would think that we would vote yes on this one.

DR. NELSON: When it breaks down, that will lead to another question later on.

Are we ready to vote?

DR. SMALLWOOD: Question No. 2. Do available data on the sterility of the sterile connecting device procedure support the use of this procedure to collect samples for bacterial detection from in-date platelet products?

Allen?

DR. ALLEN: Yes.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: Yes.

DR. SMALLWOOD: Davis.

DR. DAVIS: Yes.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: Yes.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: Yes.

DR. SMALLWOOD: Klein.

DR. KLEIN: Yes.

DR. SMALLWOOD: Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Stuver.

DR. STUVER: Yes.

DR. SMALLWOOD: Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon?

DR. SIMON: Yes.

DR. SMALLWOOD: We have unanimous yes on the vote for the second question.

DR. WILLIAMS: Does the committee concur with FDA's proposed statistical approach to providing quality control for platelet contamination?

DR. NELSON: Discussion? Toby.

DR. SIMON: Well, I have a real problem with this, but in a way I think Dr. Epstein clarified it as a method for the agency to be certain that the regulated entities are performing their functions as they should. I guess it is something to go along with.

I just don't think that this kind of approach will ultimately improve safety, and it is going to cost a lot and small organizations will have to wind up culturing all their units. So, I think it probably logically leads you to what the AABB is proposing, which is a release criteria, but I don't see anything wrong with what the FDA

has proposed other than I think it is going to be a lot of data collection without a lot of value from it.

DR. FITZPATRICK: A comment and a question. I think Toby's comment about the small facilities having to culture every unit is very valid. In the past, FDA has attempted to find a means of providing those smaller facilities an alternate method, and I think it is essential that there be an alternate method for them especially if they demonstrate they are in control over a period of time.

The other question I have is when a facility finds itself above the 0.2 percent level, are they then to restrict the release of products until they sample enough products to come below the 0.2 percent level, and what is the impact on supply of that.

DR. WILLIAMS: That is a good question. If a process is deemed out of control, I think under normal circumstances, one would basically curtail production, reassess, and revalidate all the processes and continue, revalidate and resume production as soon as possible.

But I think to continue manufacture of product for a procedure that is significantly not meeting a current standard, it would probably be arguable that production should continue.

There is a supply issue and I think probably in that situation, approaching FDA for a potential solution is

probably the best impact. Jay may wish to comment, as well.

DR. EPSTEIN: Well, typically, industry establishes alert levels and action levels, and I think the discussion hasn't gone that far. It may depend what measure you get. You know, if the estimated rate is 0.4 percent, that is not the same thing as if it was 0.25.

I don't think we have all the answers there, but I think that Alan's answer is the correct one, a system that is clearly out of control shouldn't continue, and it does throw into question the quality of the products released.

But that said, more work is needed, more thought is needed to figure out what the appropriate actions are at any given level.

DR. SCHMIDT: I was struck by Dr. Bianco's comment about what do you do with the information, and the thing I thought back to is a recent event where a patient who had multiple transfusions, suffered from I think it was a Klebsiella, and the result of this, I just read the newspaper account, was shutting down the blood for the whole state more or less, and some strange things were said in the press.

I guess what I am saying is when you get to this type of iffy things and you are looking at the quality of

the entire place based on something that may or may not relate, this can be a pretty dangerous situation.

DR. FALLAT: I was impressed with the fact that there is such a variation in the literature and you really can't give a standard right now, so I am not sure how we can set up an industrywide standard when we don't know what the standard is.

I was also impressed with the comments made by the CDC representative that said that there may be several questions that need to be answered, and I think it would be much more reasonable that this be done as a pilot or a study to see what your response is with a certain number of centers that might be willing to cooperate in such a study rather than making it an industrywide quality control approach at this time.

DR. ALLEN: Thank you for saying that. I concur. I like this approach. It is certainly one that is analogous to what is used in industry for quality control. I think it ought to be pursued. As Dr. Epstein said, there is still a lot to be worked out on it, and I guess I am struggling how do I vote to encourage the further development of this and perhaps a pilot testing of it without indicating that I think it is anywhere close to being ready to be put into a regulatory mode.

DR. KLEIN: I don't think that this in any way as described is going to improve public health. First of all, we don't know what the right number is, and it is more likely that it is less common, which would put the facilities at risk of being out of compliance for no reason of their performance.

Second, as I stated earlier, a high percentage of the endpoints that we are looking at are not going to be addressed by what we do when we prepare platelets. They are from organisms that are circulating in the donor.

Point three, I think, is that what we are really looking for is a release criterion, and you obviously can't do that because the testings are not licensed for that, but I think that this is not a good compromise.

I think it will be laborious and potentially affect supply, and not improve public health in terms of bacterial contamination of platelets.

DR. NELSON: Is the Red Cross going to uniform culturing of platelet donors? If so, that could end up being a pretty good database to decide what the level should be.

DR. DODD: Ken, I take it I can comment on this?

DR. NELSON: Yes.

DR. DODD: The Red Cross is considering whether or how it could engage in 100 percent quality control of

apheresis platelets. That doesn't mean that we are actually going to do it although I think there are other blood agencies that are moving down that track, and I think it would give an opportunity for collecting appropriate data.

Ultimately, if and when we do that, we would like to do it in some way that prevented the usage of a bacterially contaminated product.

But I did want to take the opportunity of asking either the agency or the committee if it considered the fact that as of today, the two methods that have been approved for quality control, they are approved only for leukoreduced platelets. I wonder what impact that might have on answering this question.

DR. VOSTAL: I can actually address the question about leukoreduced platelets. The reason those devices are approved for that product is that is because that is the only type of data we saw when we were clearing the device.

DR. FITZPATRICK: I have Dr. Allen's same dilemma as to how do we answer this question. As I understand Dr. Epstein's desire for a way to measure compliance and encourage compliance, but we need a stepwise approach to that.

One of the key elements that I think came out today was the pooling random donor platelets and being able

to maintain them as a pooled product, and then test them. I think that would add to what we can do to ensure and reduce bacterial contamination for the patient, if we have a way of quarantining and release or testing prior to release.

As Dr. Epstein said, there are a number of unanswered dilemmas here with this, and the approach taken for the leukoreduction guidance, I think applies here, but because of the low incidence of positive units, the N becomes so large that it is very difficult to apply that statistical model to this.

I think future exploration and an alternative method to find a way to establish compliance and standards, and then monitor on a periodic basis might help, but I find it really difficult to say I concur with this as the appropriate approach at this point.

DR. CHAMBERLAND: I just find myself in the same dilemma. I would hope that the committee really wants to signal their strong endorsement as has been echoed by industry that the time is now to really take bacterial contamination seriously and to take steps in that direction to prevent and then appropriate monitoring.

I don't feel at this point comfortable enough that this proposed approach, exactly what it will accomplish, and will it incur any real risk related to

supply, et cetera, so I am concerned that if I vote no, that that might be viewed as not feeling that this is an important problem.

We are being asked to really vote on a really detailed, specific plan, and I think it takes a bit of time to sort of model that and work that out, and I just wonder if maybe you have all done that and done some real live kind of testing of this from a modeling perspective to see what might happen, but I just a little bit uncomfortable that a yes vote and develop a guidance and it's out there without thoroughly understanding the implication.

So, I feel somewhat caught here a bit.

DR. SIMON: I guess a question and a comment. Alan, could I ask, you are proposing this or FDA is proposing this for both apheresis and random donor, that is correct, isn't it?

DR. WILLIAMS: That's correct.

DR. SIMON: One other possibility, and I don't know how FDA feels about this, would be to table this question for now and at the next meeting, discuss this issue of quality control and the release issue together, and see which is the best direction to go to reduce risk, because I understand that AABB had some of these same kinds of discussions when they came up with their proposal.

Since industry is moving towards a sort of different approach for release, and since it raises all kinds of implications, and I think there, really where the supply issues get raised, both in terms of units being held and also in terms of what happens to random donor platelets in this setting, and are blood centers going to consider it too hazardous to provide these because they are not amenable to the same approach, so it has become a very complicated issue.

Although I don't see anything wrong with what FDA has proposed, it appears that it may need a more comprehensive discussion and taking into account both this approach and the release approach.

DR. DiMICHELE: I just wanted to echo the comments of several of the committee members. It seems to me, although I certainly defer to those members of the committee who are blood bankers and have had tremendous experience with this, but it seems to me that the issue of how we document sterility of platelets is still unclear.

So, therefore, it becomes very difficult to embark on this type of a study if we are really not clear on how we are really to measure platelet sterility in the first place.

I would agree with those committee members who suggest that maybe the next step is really to develop a

pilot study to really help us to understand how to measure platelet sterility before we embark on a widescale regulatory quality control measure that actually attempts to do this.

I don't know again the best design for this, but I know that there are many units of platelets, for instance, that would get discarded anyway because of hepatitis B core positivity, et cetera, units that would not be used, and the question is, is whether a study can actually be designed using units that cannot be salvaged, to start looking at this in kind of a pilot way.

DR. NELSON: There have been a few pilot studies on cultures, and they are not large enough. The issue is that to really get this number and to figure out what is acceptable would take a substantial size study I think.

DR. DiMICHELE: Well, that is if it were a natural history study, but one of the things that you can do with platelets that wouldn't be used anyway would be spiking experiments and manipulative studies that might be able to give you data in a very different way.

Again, I certainly can't comment on being an expert on the design of such a study, but it might be considered.

DR. NELSON: Are we ready to vote on this one?

DR. SMALLWOOD: Question No. 3. Does the committee concur with FDA's proposed statistical approach to providing quality control for platelet contamination?

Allen.

DR. ALLEN: I abstain with strong support for the FDA's continuing its work in this area.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: I also will abstain.

DR. SMALLWOOD: Davis.

DR. DAVIS: No.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: No.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: No.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: No.

DR. SMALLWOOD: Klein.

DR. KLEIN: No.

DR. SMALLWOOD: Lew.

DR. LEW: No.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: No.

DR. SMALLWOOD: Stuver.

DR. STUVER: No.

DR. SMALLWOOD: Fallat.

DR. FALLAT: No.

DR. SMALLWOOD: Harvath.

DR. HARVATH: No.

DR. SMALLWOOD: Nelson.

DR. NELSON: No.

DR. SMALLWOOD: Dr. Simon?

DR. SIMON: I would abstain.

DR. SMALLWOOD: Results of voting on Question 3. There were 11 no votes and 2 abstentions, and the industry representative took an abstention position.

DR. VOSTAL: We will move on to Question 4.

The question reads: Does the committee concur that data derived from FDA's proposed clinical trial design would be appropriate to support clearance of devices for pre-release screening of platelet products for transfusion?

DR. NELSON: Discussion?

DR. FITZPATRICK: Of the many designs that we were offered, which one would you like us to endorse?

DR. VOSTAL: I think the basic concept of whether we should require a clinical trial to evaluate these devices and whether the clinical trial should be of design where you have two cultures and you are looking for agreement between a culture early on in the storage period versus at the end of the storage period.

DR. FITZPATRICK: So, would you rephrase your question then?

DR. VOSTAL: I guess we could, if you don't like that one.

DR. KLEIN: If we answer yes to this, is it pretty nebulous. If you want to know if we think there should be a clinical trial, designed appropriately, I think that is a legitimate question, but it is hard for us to pick the appropriate design at this point from what you are offering.

DR. VOSTAL: So, we could change it just to say whether the committee would endorse that a clinical trial is necessary, and the second part of that question would be whether it should be of a design with the two cultures.

DR. KLEIN: I think that that would answer the question, and I think if you are going to do it, you need to do it with two cultures. Having said that and as a federal employee who looks at our budgets, I think this is going to be a very large study.

I think it is going to take a very long period of time, and I think it is going to be a very expensive study. I look at the culture technology really as a transient technology. We all want something that we can use at the endpoint of issue, and my guess is that in three to five years we are going to have something that we will be able

to do. Maybe by the time the study gets done, and we have the results of the study, we won't use this technology.

So, having said that I think you need a study in order to license this for that use, and that this study would be appropriate, I wouldn't participate in the study and I wouldn't spend any money on it.

DR. ALLEN: Thank you, Harvey, that's a hard one to follow.

I certainly am strongly supportive of the general concept. I think very definitely, clinical trials of in-use situation, using real live materials to the extent that that is possible is very helpful to support the evaluation approval of devices for this, as well a variety of other purposes.

I think the study designs that were presented were probably the purest in terms of sampling at the beginning and at the end, and maybe at a couple of mid-points, and I in general would be supportive. I am not quite as negative as Harvey on this. I agree that they will be large-scale studies and possibly fairly expensive and difficult to accomplish.

I think they could be important even in an area where technology will be evolving rapidly. Nonetheless, I think that the FDA, in terms of putting out trial designs, needs to be flexible, because I don't think that in every

instance that you have got to have exactly the same design and all of the bells and whistles.

I am supportive of the general concept. We did hear that there were many different clinical trial designs that were proposed, and I would urge flexibility on this, but I think the concept is one that I certainly am supportive of.

DR. FALLAT: Am I correct in understanding that one of the outcomes of this would be to get more data on the five- to seven-day platelet release and capability of release, and if so, I would be very much in favor of that sort of study design.

DR. VOSTAL: I think that it depends on the intent of the study, whether you want to have your device to be used for extension of the storage period, so that it will be designed to look at day 7 platelets.

DR. SIMON: I would agree and being supportive of clinical trials and design, but would also agree that this is going to be, the kinds of numbers we are talking about, it is going to be very costly.

Unlike Dr. Klein, I would do it if somebody gave me the money, but I think it would be a major task to do. What I am concerned about, because I think it would be advantageous to go to seven-day platelets having done the

studies in the '80s to support that before the bacterial contamination issue became in the foreground.

I would certainly like to see something done that would support seven-day platelets. From what I am gathering from your comments, somebody would need to do this type of study to get permission to do that extension or to get clearance from the FDA to sell seven-day platelet or to label their platelet product as being good for seven days.

I would certainly like us to find a less severe way to get to that point, because what I am afraid is going to happen with AABB instituting a voluntary standard for release of all products, and if the manufacturers see that their devices are being used on a national basis, they may not have an incentive to move to do this type of study.

So, I have the same concerns the other members of the committee have, but I certainly am supportive of doing clinical trials. I would hope that we could work through a model that wouldn't be quite as expensive to do.

DR. DOPPELT: In regards to the cost, how would this be funded? Would the banks be required to sort of absorb the cost?

DR. VOSTAL: I think we would be looking to the manufacturers to sponsor their studies because it will be for their device.

DR. CHAMBERLAND: Jim, did you propose a wording change, or it was just kind of--and I tend to agree with you that the idea of a study is something that I am in complete agreement with--but I would say that I am not sure we have the design that has been articulated and that there might be a need for some flexibility?

DR. ALLEN: You could perhaps add one word, the FDA's proposed clinical trial design concept.

DR. VOSTAL: Sure, that would make it plural.

DR. NELSON: Are we ready to vote on this?

DR. SMALLWOOD: I need to have the correct wording.

DR. VOSTAL: Clinical trial design concepts would be appropriate.

DR. DOPPELT: Is part of the proposed study that would give data to extend from five to seven, that is or is not included in the current proposal, because that was one of the four choices, so I just want to be sure what we are voting on.

DR. VOSTAL: There are several issues there. One would be having a device for release of platelets up to five days. Another one would be to have a device for release of platelets up to seven days. Or you could have a study that covers both, pushing storage out of seven days.

So, I think it depends on what the manufacturers want to have on their label and what kind of study they are willing to sponsor.

DR. SIMON: I take it we can take it for granted that somebody who came to you and asked to have extension of platelets to seven days, which I think people like Dr. Aubuchon are doing based on the bacterial detection device, you would not permit that with a culture at 24 days, and you would have to have follow-up studies at seven days.

DR. VOSTAL: Right. I mean if you wanted to be able to say that your device is capable of detecting or making sure that you have a culture-negative product at seven days, and you are going to be sampling at 24 hours, we would like to see data that supports that.

DR. FITZPATRICK: So, the key to the design of the study and the concept would be that you want a study designed to correlate the time of sampling and the result of that sampling to the bacterial condition of the product at the time of its out-date.

DR. VOSTAL: Right.

DR. FITZPATRICK: I think I could support that pretty well.

DR. SMALLWOOD: Question No. 4 as amended. Does the committee concur that data derived from FDA's proposed clinical trial design concepts would be appropriate to

support clearance of devices for pre-release screening of platelet products for transfusion?

Roll call. Allen.

DR. ALLEN: Yes.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: Yes.

DR. SMALLWOOD: Davis.

DR. DAVIS: Yes.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: Yes.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: Yes.

DR. SMALLWOOD: Klein.

DR. KLEIN: My answer to the question is yes. My caveats are in the record.

DR. SMALLWOOD: Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Stuver.

DR. STUVER: Yes.

DR. SMALLWOOD: Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: Yes.

DR. SMALLWOOD: The results of voting for Question No. 4, as amended, is a unanimous yes.

DR. NELSON: The next subject is Human Parvovirus B19 NAT Testing for Whole Blood and Source Plasma.

Dr. Yu will give an introduction and background.

DR. SMALLWOOD: We are now approximately an hour and 23 minutes behind. So, maybe if we move quickly, we may be able to meet our goal of 6:30 in completing this. If not, we will have a continued session regarding this discussion at a later meeting that we will announce.

II. Human Parvovirus B19 NAT Testing for Whole Blood and Source Plasma

A. Introduction and Background

Mei-ying W. Yu, Ph.D.

DR. YU: Hi. So, now the topics of the discussion is Parvovirus B19 NAT for Whole Blood and Source Plasma.

My name is Mei-ying Yu.

[Slide.]

I will provide the introduction and background and then Dr. Kevin Brown, who is a B19 expert from NIH, will present the overview of parvovirus B19 infection. Then, there will be industry data presentations.

They will update data presented at the December 2001 FDA NAT Workshop, and they will provide data for NAT sensitivity, testing algorithm, time to resolve to single donations or donors, prevalence and levels of both B19 DNA and anti-B19 antibodies and profile in serial bleeds, if any.

The presentations will be made by, first, Dr. Susan Stramer of American Red Cross, and then will be NGI, Dr. Andrew Conrad. However, Dr. Andrew Conrad is sick and he cannot make it here, so I think the committee has all his slides, so there will be no one to present his.

Then, there will be consolidated data presentations organized by the PPTA. There are three speakers: Dr. Barbee Whitaker, Dr. Steve Petteway, and Dr. Ed Gomperts.

Then, I will come back to address the FDA Perspective and Questions for the Committee.

[Slide.]

Now, I have a lot of background information I need to cover. We have talked about B19 NAT issues in quite a few meetings. They include the BPAC held in

September 1999, FDA NAT Workshops, and NHLBI Parvovirus B19 Workshop both held in December 1999, FDA NAT Workshops held in December 2001 and then the BPAC in this year, March, and another one is the ad hoc PHS Panel Committee Meeting held in July 2002.

Parvovirus B19 has been extensively discussed in September of 1999 BPAC. BPAC agreed then that pending a policy on screening whole blood donations, FDA need not require studies to validate the clinical effectiveness of NAT for B19 DNA under IND for plasma for further manufacturing.

So, parvovirus B19 NAT was considered as an in-process test, so it is unlike HIV, HCV, and HBV NAT, as a donor screen test, however, BPAC did not recommend resolving to the single donation or donor.

For S/D treated pooled plasma, the reactive 20 unit subpools were discarded when tests completed, labile components had expired.

[Slide.]

At that time, BPAC did recommend to quarantine and destroy in-date units when possible. So, FDA requires that the tests be reviewed under biologic license application--that is called BLA mechanism--for the manufactured product and that the tests be validated as

analytical procedures with respect to sensitivity, specificity, and reproducibility.

[Slide.]

At both the FDA NAT workshops and NHLBI Parvovirus B19 workshop held in December of 1999, a strategy for standardizing B19 NAT was outlined. FDA also proposed a B19 DNA limit that is less than 10^4 geq/per ml for manufacturing pools.

This limit was mainly derived from the B19 transmission associated S/D treated pool plasma in a Phase 4 study in healthy donors. In those product lots that have less than 10^4 genome equivalents, no B19 transmission in recipients. These are in zero-negative recipients.

The residual virus will be complex or neutralizing by anti-B19, always present in large pooled products, and also the manufacturer procedure, that is our viral clearance procedure to remove the residual B19 infectivity.

I want to mention one more point.

[Slide.]

We subsequently revised the limit. The limit was then set as 10^4 IU/ml because in year 2000, the WHO standard for B19 NAT and CBER working standards for B19 DNA are all available, so we have since then revised the limit to less than 10^4 IU/ml.

That limit seems to be technically achievable by most manufacturers.

[Slide.]

Fractionators are performing high titer B19 minipool NAT screening by in-house methods to lower the viral load in manufacturing pools. In the December 2001 FDA NAT Workshop, we learned that the sensitivity of NAT assay used to exclude donations ranged from 10^5 to 10^7 geq/ml. That is per original donation.

The reactive minipools are resolved to single donations. Testing results are used to reject reactive donations. Now, today, you will hear more the update by the industry speakers.

[Slide.]

Establishments collecting whole blood units that are used to prepare the recovered plasma and transfusible blood components would like to implement high titer B19 NAT screening similar to that used by source plasma fractionators.

So, Dr. Susan Stramer did present some retrospective data and some study data, and she described the Phase 1 approach that is not resolved to single donations, labile components would have expired, and in Phase 2 approach, that would resolve to the single donations by a free-standing test kit.

Now, Dr. Sue Stramer is going to update the data later.

[Slide.]

In March 2002, BPAC, FDA's current thinking on B19 NAT was presented. The recommendations that FDA is considering are the following. For plasma, when identified, high-titer B19 reactive units should not be used for further manufacturing into injectable products. This is to ensure that the FDA proposed limits less than 10^4 IU of B19 DNA/ml for manufacturing pools can be met.

Now, for whole blood, we say when feasible, B19 reactive minipools should be resolved to identify the individual reactive donors prior to release of the component for transfusion, and units from reactive donors should not be used for transfusion.

For whole blood, when testing is done subsequent to product release, in-date components from potentially reactive donors should be retrieved and discarded. Even when performing an in-process test, testing and identification of the individual reactive donors constitute medical diagnostic testing, therefore, such testing would require the use of an FDA-approved investigational mechanism.

[Slide.]

Informed consent should be obtained from blood and plasma donors subject to such high titer NAT testing. Reactive donors should be identified and be informed of their reactive status and be provided with medical counseling.

Lastly, because of the transient nature of the infection and rapid involvement of the immune response, such donors would be suitable to donate when they test nonreactive.

[Slide.]

So, in March 2002, BPAC, the discussion largely focused on the apparent lack of the medical benefits that might justify donor notification, so consequently, FDA convened an ad hoc PHS panel in July of this year.

The panel members include Drs. Harvey Klein and Kevin Brown of NIH, Larry Anderson, Mary Chamberland, and Bruce Evatt from the CDC, and CBER representatives.

[Slide.]

The conclusion by the PHS panels are regarding the donors, there is no medical benefit in identifying high titer B19 NAT-positive donors informing them of their reactive status and providing them medical counseling.

Regarding close contacts of the high titer B19 NAT-positive donors, there are potential medical benefits to donors contact especially those at risk, for example,

persons with certain anemias, pregnant women, and immune-suppressed or compromised individuals.

Now, Dr. Brown will elaborate on these medical benefits later in his talk.

[Slide.]

So, FDA is taking a stepwise approach in resolving B19 NAT issues concerning whole blood and source plasma. At this meeting, FDA is seeking advice on the issues that are listed here.

The need to reduce the risk to transfusion recipients by withholding high titer positive units of whole blood and its components from use. The need to temporarily defer the high titer donors and whether potential benefits to close contacts of B19 infected donors warrant notifying high titer donors, and if so, what would be the time frame for notification.

Accordingly, we ask four questions. Before you listen to Dr. Brown and industry presentations, I would like you to bear in mind these questions that we are going to ask.

[Slide.]

First, if donations of whole blood are tested for the presence of human parvovirus B19, are risks to transfusion recipients sufficient to warrant withholding

high titer positive units. These are equal or greater than 10^6 geq/ml from use for transfusion.

[Slide.]

The second question is, is temporary deferral of positive donors warranted in the setting of: (a) whole blood donation? (b) Apheresis donation?

[Slide.]

The third question. Do potential medical benefits to contacts of parvovirus B19 infected donors warrant identification and notification of positive donors?

[Slide.]

Finally, if yes to Question 3, should donor notification be limited to settings where testing and notification can be completed within several weeks of donation?

Thank you.

DR. NELSON: We will come back to these questions.

Dr. Brown.

B. Overview of Parvovirus B19 Infection

Kevin Brown, M.D.

DR. BROWN: I am going to give an overview of parvovirus B19 infection, mainly concentrating on the areas that I think you need to be able to sort of answer the questions that Mei-ying posed to you.

[Slide.]

So, what is parvovirus B19? It is a small, 22 to 24 nanometer diameter icosahedral virus. These are viruses by immune EM. They are non-enveloped, so solvent detergents don't work too well.

They are relatively heat resistant because of the small genome, which is only 5,500 nucleotides of single-stranded linear DNA.

It has a high conserved genome and up until a few years ago, it was said the variation was less than 2 percent of the DNA level. There have variants that have been described in the last two years, but I am not going to say very much more--I am not going to say anything more about it because they have not been isolated from blood except at extremely rarely, when we found them in liver samples and other people have found them in skin.

[Slide.]

So, the parvoviruses are divided into three genera. They are the true parvoviruses of which canine parvovirus or porcine parvovirus are members. There are the dependoviruses, also known as the adenoassociated viruses, but B19 comes into the third genera, which are erythroviruses, so-called because they are highly erythrotrophic and they are only known to replicate in erythroid progenitor cells.

So, the cells that the virus replicates in are these cells here. The precursors are the red cells, that is, the BFU-E and CFU-E.

[Slide.]

This is the virus itself. The virus encodes for one non-structural protein and two structural proteins. The two structural proteins are encode VP1 and VP2. VP2 is the major structural protein. It is 58 kilodaltons. There is about 60 copies in the virus.

Ninety-five percent of the variant, as I say, is VP2, and you can express this in baculovirus and it self-assembles to form capsids. These VP2 capsids hemagglutinate and it was using this property that was able to go on and show that the receptor for parvovirus B19 is globosidal, known as Blood Group P antigen.

The VP1, which is a minor component, has an additional 223 amino acids at the 5-prime end of the VP2. If this is expressed, it does not self-assemble, but it is thought to be the main site of neutralizing epitopes.

This is again to show you what the virus looks like, but also to make the point that it is even quite different, not at the DNA level, but even at the structural level, looks quite different from the true parvoviruses.

[Slide.]

As I said, I was able to show that parvovirus B19 uses globoside, that is a glucose single lipid, demonstrated here as its receptor for viral entry into cells. I was also able to show that individuals that do not have P antigen on their red cells or on their cell surface cannot be infected by B19 either in vivo or in vitro.

[Slide.]

The discovery at the receptor for B19 does go on to explain a few of the things that we didn't know about B19, a lot of the pathogenesis of which I am not going to say more about it, but globoside is found on erythroblasts, as you would expect. It is found on megakaryocytes, megakaryoblasts, vascular cells, on the cells in the placenta, does cause transplacental infection, which we will come to, and it is found in the thecal hematopoietic cells and myocardial cells.

[Slide.]

Turning to the epidemiology of the virus, the virus is a very common infection. Everywhere that people have looked, they have been able to find it apart from some isolated communities in South America and Africa.

Virtually, all countries where people have looked, 50 percent of adults have B19 antibody with seroconversion happening in childhood and also as young

adults. The calculations are that there is an annual seroconversion rate in women in the USA of about 1 percent. That is 1.5 percent per year.

[Slide.]

It shows classical epidemic behavior, with temperate countries, increased peaks in the spring. It also shows variability between the years, so some years there is a much higher peak of virus than others.

Looking at natural infection, the incubation period has been calculated to be between 4 and 14 days depending on the presentation of the infection, with a maximum up to 20 days.

[Slide.]

The major route of the natural infection is by the respiratory route and it is actually fairly infectious. In studies that have been done in susceptible individuals, there is a 50 percent attack rate in household contacts and 25 percent attack rate in schools or nurseries.

There also is a high level of viremia and blood products can have virus in them, and you have already heard about how pooled products can be a source of B19 infection, but there are cases of single component, which I am going to come to in a few minutes.

[Slide.]

The kinetics of B19 infection were really well established by some volunteer studies which were done in the UK in the 1980s. These were all adult volunteers who had different concentrations of virus dripped into their nose. They were then followed to see what would actually happen to them.

There were a couple of individuals who had pre-existing antibody to B19. They remained well, there was no viremia, and as I say, they have no symptoms. There were a couple individuals who had low levels, which were called equivocal IgG levels. They had a fever and chills, headache and myalgia, only they didn't develop the second stage infection. They also boosted their antibody response.

However, in those that were antibody-negative, and received more than 10^8 genome copies into their nose, they had this typical biphasic illness, so that there was this level which was associated with viremia, with fever, chills, headache, myalgia. At that time, there was a drop in their reticulocyte count, and then a second phase infection which resembled fifth disease as the antibody came up and the virus cleared.

However, it is important to note from this that these assays were done really before PCR was well established and the viremia was measured by a dot blot, and

the dot blot has a sensitivity of between 10^5 and 10^6 genome copies/ml. So, although the viremia could only be measured for about four or five days, the fact that it goes back to normal or back to the zero line doesn't mean to say there is no virus actually present, and that will become relevant in a few minutes.

Also, there were no infectious assays performed. It is actually very difficult to grow this virus, and there were no neutralization assays performed, so we don't know whether these antibodies actually are neutralizing or not.

[Slide.]

The virus can cause a wide range of different disease depending on the host characteristics, and I am just going to go through and illustrate each of these.

[Slide.]

The majority of infections caused by B19 are asymptomatic and it has been estimated between 25 percent and 50 percent of infections are asymptomatic even in an outbreak situation.

The commonest presentation of B19 infection is erythema infectiousum also known as fifth disease, slapped cheek disease because of this characteristic slapped cheek appearance that children get, and also academy rash, because of the outbreaks that are often seen in schools.

The prodrome, which is at the time of the viremia, is usually missed or there may be just mild symptoms, and the diagnosis is usually made at the appearance of the rash. In children, it is particularly the slapped cheek on the cheeks. In adults, this stage is usually missed, but then there is a second stage where you get this reticular pattern on the limbs. It comes and goes and pruritis is very common. There is no specific treatment. It is usually a fairly innocuous infection and often the parents are more worried about the rash than the children are about the symptoms.

[Slide.]

However, in adults, and especially in women for reasons that we don't understand, it is often associated with arthropathy or even a frank arthritis. This is a peripheral distribution especially in the small joints.

Again, it can persist for months. It often lasts between two weeks to two months, but can, in fact, last for six months or even up to several years. The problem is that it may resemble acute rheumatoid arthritis, especially as the rheumatoid factor can be positive and also autoantibodies are often present.

So, diagnosis, this is B19 as opposed to acute rheumatoid, does have implications especially for the

management of these patients. These patients respond to nonsteroidals.

[Slide.]

The first disease that was associated with parvovirus B19 was transient aplastic crisis, and this was seen in patients with increased red turnover. Basically, there is a transient arrest of erythroid production and in those who have a high erythroid turnover or dependent on that regular erythroid turnover, they develop this aplastic crisis, which was originally described in sickle cell disease, but it can be described, it has been seen in many cases of hemolytic anemia, in fact, any cases where there is increased erythropoiesis including even in acute hemorrhage.

Often pronormoblasts, such as are illustrated here, can be seen in the bone marrow, sometimes in the peripheral circulation. It is a self-limiting infection. As soon as the virus clears, which is about four to five days, the antibodies come up.

The reticulocytopenia results. There is a single episode in a lifetime, and treatment is supportive to get them through the aplastic crisis.

[Slide.]

However, in some individuals who can't mount an immune response or can't neutralize the virus, they will go

on to develop a persistent B19 infection. This is being described in a variety of different cases of congenital immunodeficiency. I am going to illustrate a case of Nezelof's in a minute.

In cases with iatrogenic immunodeficiency, such as chemotherapy or immunosuppressed patients, it is also quite commonly seen in patients with AIDS.

[Slide.]

So, this is a chart with Nezelof's syndrome who had dot blot positive instead of the usual three to four days, actually lasted for many months. This was associated with an anemia and a reticulocytopenia.

This was despite the presence of low levels of antibody. There was IgM and IgG present, but the virus was there at high titers.

[Slide.]

These cases are often very well treated and respond well to commercial immunoglobulin which has high titers of neutralizing antibody. This is a case of a patient with HIV infection who again had high levels of B19 DNA present for many months and was treated here with IVIG. There was a brisk reticulocyte response peaking and then coming down to normal and a response of the hemoglobin, and the virus actually disappears.

It is interesting to note at the time that the antibody responds, many of these patients have the symptoms of fifth disease. They have the arthropathy and they also have the rash.

[Slide.]

The next case I want to talk about is where you have a combined, where you have an immunocompromised or immunosuppressed individual with high erythropoiesis, by which I mean the fetus.

In fetal hydrops, there are many, many case reports now in the literature that are very similar. B19 can be found in all the tissues. In some of these cases, this is associated with myocarditis, globoside is actually found in the fetal heart. Some of these spontaneously resolve.

[Slide.]

This is a combined study again in the UK where they looked to see what the risk of B19 was or the outcome was of confirmed B19 infection in pregnant women. So, this is a stage that the mothers have their B19 infection. You can see there is an increased fetal risk due to B19 infection, particularly in weeks 9 to 20, so the first half of pregnancy. There is an excess of fetal hydrops at this stage.

[Slide.]

The conclusion of this double study was that both asymptomatic and symptomatic infection is associated with hydrops or fetal loss. There is a mean interval of about six weeks between the maternal infection and the fetal symptoms, but 1 in 10 infections, confirmed B19 infections before week 20 will result in fetal loss due to B19.

The treatment for hydrops, if it is early, and many of these cases have been treated with intrauterine blood transfusion with positive results.

There have been no studies that have confirmed congenital abnormalities due to B19. There is a few case reports. We have described three cases of congenital anemia following a maternal B19 infection. Different from what happens with the persistent infection, these congenital anemias did not respond to immunoglobulin treatment.

[Slide.]

Despite those well attested associations with B19, there are a number of different disease associations that have been described in the literature, often based on PCR results, and some of these are controversial as to whether this is a chance association.

Certainly, it is being proposed that B19 causes PCH. It definitely causes some cases of hemophagocytic syndrome, ITP, vasculitis, Kawasaki is more questionable,

some cases of hepatitis have been ascribed to B19. Recently, particularly in Japan, there is a group that is claiming that B19 may cause rheumatoid arthritis.

[Slide.]

This is returning to the picture that I showed earlier based on the data from the volunteers, which has held up to be fairly good, but as I say, the first studies were done in the absence of PCR, but when PCR is now actually added, instead of actually just being positive for three to four days, the PCR actually remains positive for months, if not years.

Again, these studies were done without quantitation, so the question is how high is that virus, is it infectious, and what is it doing. I just want to make the point that the viremia that people talk about in the old literature is associated with this dot blot sensitivity of about 10^6 genome copies/ml.

[Slide.]

The fact that that virus persists at low level detectable by PCR, it is not really surprising then that when people have gone back and looked in blood donors, you can actually find virus.

So, this is not supposed to be exhaustive, but just to show some of the studies where people have looked at healthy blood donors by a variety of different methods,

that do have different sensitivities, so it is not surprising that you get different prevalence rates with the highest sensitivity those based on PCR have given you the higher prevalence of the virus.

I am going to go and say more about this study by Yoto, but I want to make the point that these samples, 1,000 samples were taken at the time of an outbreak in the community, which is why they are probably higher than some of the other numbers that people have. I could allude to the study by Jordan.

[Slide.]

The fact that the virus is present, can go up to 10^{12}, 10^{14} genome copies/ml, it can be a problem in pooled products, and all these products, there have been cases in the literature where B19 has been said to be transmitted from them.

But single components, it is much rarer. There are some case reports, but there are not an awful lot of them.

[Slide.]

I want to go through some of them, and again this is not exhaustive, but it is supposed to be I think for the solitary. This was actually a study by Yoto, which is the group that did the prevalence of B19 by PCR at the time of an outbreak.

That was actually triggered by this case that they found. This was 14-year-old boy who had ALL, who was being well maintained on chemotherapy. He received two units of red cells. They have no additional information on the red cells, so they went back and looked at 1,000 blood units to see what the prevalence of B19 was, but they didn't test these two units.

The child actually developed a profound anemia. He actually went on and had a peripheral blood stem cell transplant, was treated with IVIG just as CMV prophylaxis, not actually because they had recognized that he had the B19 infection at that stage, but he had a viremia that lasted for a month.

Certainly, I can't imagine that they would have done a stem cell transplant if they had known that he had an acute B19 infection going on at the time, so this was an infection that was missed.

[Slide.]

This is a second case. This is a 22-year-old woman who had thalassemia major diagnosed at the age of 15 months, so had been receiving two units of red cells monthly, so estimated actually received probably about 500 units of blood at this point.

She again developed a transient aplastic crisis and severe heart failure. It turned out she had received

two units of red cells nine days previously, and one of the donors that they were able to show was IgM positive, DNA positive. Unfortunately, there is no information given as to what they mean by "positive."

This individual had an invasive esophageal echocardiography, was misdiagnosed as having subacute bacterial endocarditis, treated for a month with antibiotics before they actually realized what the diagnosis was.

So, again, a patient that was mistreated because the diagnosis wasn't thought about.

[Slide.]

This is a third case which was again picked up retrospectively. This was one of the cases that was found by Jordan in that study of looking at the prevalence of B19 in their blood donors.

What they did was they identified positive blood donors and then went back to see what happened to the recipients of that blood. One of the individuals had a severe anemia, and this was the individual.

This was 49-year-old man who had a liver transplant for chronic HCV. He received one unit of red cells two days post transplant. The donor was IgM negative, IgG negative, but DNA positive. Again,

unfortunately, they don't give a titer, but it was strongly positive on their ELISA-based assay.

Four months later, he was thought to have recurrent hepatitis, he was found to be anemic, found to have reticulocytopenia, was treated with red cells. B19 wasn't even considered.

Eight months later when Jordan contacts them to find out what happened to the recipient of this blood, they find out that he had a B19 infection at this stage. He has, in fact, seroconverted. He is IgM positive, IgG positive, B19 and DNA negative.

[Slide.]

These were the 10 recipients that they were able to follow up on. It is interesting to note that this was the only patient that received B19 DNA positive. Now, as I say, we don't know what they mean by that titer, because they don't actually give a titer. Had B19-like symptoms, so was followed up.

Interestingly, this patient was IgM, the donor was IgM negative and IgG negative, so presumably this was an acute B19 infection that the donor had, but was asymptomatic at the time.

[Slide.]

The last case I want to talk about is a case where there was transmission by platelets. This was a 36-

year-old who had CML treated with chemotherapy, received a bone marrow transplant, had been tested before and was shown to be B19 IgG prior to the transplant.

Over the next six months, he had increasing anemia and eight months later, B19 was diagnosed. The patient was treated with IVIG. They were able to go back, and he had had blood from 90 donors, and they were able to actually test all of those.

Two of them had B19 DNA. One of them, Donor A, it was greater than 10^6 genome copies/ml. I can say that because it was dot blot positive, and I used to work in this lab and I know the sensitivity of the test that they use.

They also sequenced the donor's virus, and he had the same B19 sequence as they found in the patient. There was a second donor that was positive. This had been given prior to the transplant. This had less than 10^6 genome copies/ml. It was only positive by PCR, not by dot blot.

But again this diagnosis was only made eight months after the event.

[Slide.]

So, what about levels of B19 DNA? As I say, there are not that many studies where people have published where they have looked at actual levels, but this is a group from Italy where they have taken blood.

I think it sort of makes the point they divided them into those that were DNA positive, IgM positive, and IgG negative at the early stage, and you can see they have relatively high viremia levels, those who were IgM positive and IgG positive, so within the first couple of months, following an acute B19 infection, lowered, but there are still some that are above this cutoff of 10^6, and then some that were IgG negative and IgG positive, which suggests they had a B19 infection more than two months earlier, and yet one of these individuals had greater than a 10^6 genome copies/ml.

So, the question that I think that we really don't know the answer is although we know that B19 can persist for months even at relatively high titers, if this level of B19 is infectious if it is given as a unit of blood.

[Slide.]

The problem is that we really don't have the answers to some of these questions. The virus is very difficult to grow in the culture. It can only grow in human bone marrow explants or thecal livers as a source of hematopoietic cells.

There are a few cell lines that have been described, but they really aren't that highly permissive. You can detect virus either by looking for inhibition of

colonies, but it is very insensitive looking by immunofluorescence for capsid proteins or NS proteins.

Some people have described in real-time PCR looking for DNA increase. We prefer to use RT-PCR looking for viral transcripts to distinguish replication RNA from viral DNA.

[Slide.]

I put this slide on really just to illustrate that even if you have an infection assay, this is using different concentrations of virus at three different cell lines that are said to be explicit for B19.

In the most highly sensitive, you can detect down to 10^4, 10^3 genome copies per ml, but in another cell line, you can't really detect anything even at 10^6, so even the cell lines themselves have problems in their sensitivity as to what you call infectious, and there is obviously limits to how much virus you can actually put in there.

[Slide.]

So, coming back to the FDA questions, who is at risk of parvovirus B19? Well, you could argue anybody who is seronegative is at risk of B19 infection, but fifth disease is a relatively innocuous disease and apart from the problems with arthritis or arthropathy, the main problems in these patient that have increased

erythropoiesis, patients who are immunosuppressed or immunocompromised, and the pregnant woman and the fetus.

By definition, these aren't going to be your blood donors, but they may well be your contacts of your blood donors.

[Slide.]

Is there any way that we can prevent B19? Well, there is a vaccine that is in Phase 1 trials, but it is going to be several years at the least before we actually have a vaccine.

What about passive immunotherapy? The only thing that we have is IVIG, we don't have any antivirals that we know work for B19. Again, you have got the problem with the time interval. If you are trying to actually stop the viremia, you have got four days to actually do anything about it. So, time is limited.

[Slide.]

This is my last slide. This again shows the time course of B19. What I tried to do here was to put when you expect to see the symptoms at the different risk presentations.

So, the transient aplastic crisis is really at day sort of 4 to 7 following your infectious exposure. You have not got a lot of time to do anything there. The persistent anemia starts probably just about the same time,

but lasts actually months, so even with the late notification, you might actually be able to go in and make a difference.

The fifth disease is usually at about sort of 21 days, but the arthropathy can last for several months.

So, what are the benefits of notification? Well, you might be able to intervene. I did mention pregnancy, but certainly in the pregnant woman, you might be able to monitor and see what is happening.

I think it is important for accurate diagnosis and may be important for treatment especially chronic infection and also for the monitoring of pregnant women who might be at risk of hydrops.

Thank you.

DR. NELSON: Thank you, Dr. Brown.

Questions? Mary.

DR. CHAMBERLAND: Thank you for that nice presentation. I had a question. It seemed, and I am sure this will come up in the discussion again, that the benefits of notification are going to be not so much with respect to the donor, but the close contact.

That is clearly going to probably be linked to the period of time over which notification can take place after the unit has been tested.

In your review article, which was distributed to the committee, under Transmission, it is stated that the case-to-case interval is 6 to 11 days irrespective of the type of B19 related disease.

Now, if I understand that correctly, it would suggest that let's say in a typical household setting, a contact setting, that there is really a fairly limited period of time in which you would have to, if you will, inform a donor and potentially interdict subsequent transmission.

Sort of tying that in with the other comment in your slide, you say the slide that looked at the titers of B19 DNA relative to IgM and IgG, you ask the question is this level of B19 infectious if given as a unit of blood.

Actually, I think the sort of complementary question is, is this level of B19 infectious through the traditional respiratory route.

I am just wondering if you could comment on that because I was quite struck by this statement in your article about this fairly tight time period.

DR. BROWN: It seems to have held us in sort of fairly good stead, this sort of illustration, because this time of the viremia does seem to correlate well to the time of infectiousness in close contacts. So, this seems to be, as I say, a very good estimate.

So, as soon as the IgM and especially the IgG starts to come up, then, you don't actually see exposures continuing to happen.

Maybe that sentence is a bit ambiguous. There is a slight difference in the time between exposure and the disease itself, because the transient aplastic crisis will appear earlier, which is the first phase. If you are looking for fifth disease, it's the second stage, and you see the viremic stage is missed, so that usually sort of comes up a little bit later. So, that is why you have quite a wide range, but the infectious time is actually very tight exactly.

DR. SIMON: If I put that in practical terms, so if we detected someone, and I gather that fairly insensitive techniques are being used because we are looking for high titer, so we would be likely to detect someone at about day 7 time frame. So, the infectious period, you are going back to day zero when you say 6 to 11 days?

DR. BROWN: Yes, these numbers are based on having high titer virus dripped into your nose, which is not really an every-day occurrence and probably doesn't mimic what is happening either if you get a unit of infected blood or if you are living with somebody who is actually copping the virus out.

DR. SIMON: So, unless we could get to that donor within four or five days, it probably would not have much utility.

DR. BROWN: Exactly. That is what I was sort of trying to get to here. If you actually want to actually go in and actually intervene before this viremic stage, you have got a very, vary narrow time cap, and I am not sure, quite frankly, that it is realistic.

However, if you are trying to actually go in and do something about patients who have persistent anemia, now, you have got a much longer time because they are being viremic, but they will continue to be having symptoms, and they would actually do well with actually being treated even if it quite a bit later on in their disease.

DR. SIMON: Treated with what?

DR. BROWN: The only treatment that we have is IVIG, and it actually works very well, as in the HIV case.

DR. SIMON: I am told by our expert that it is considered experimental therapy. I know it's off label and that not everyone accepts that it is beneficial particularly if you don't know the titer of parvovirus antibody in the preparation.

DR. BROWN: It is the only treatment that is available, there is nothing else. So, I think when people have actually looked for neutralizing antibodies in most

commercial sources of IVIG, they are actually at high titers. I don't know if anybody else wants to comment on that.

DR. WU: I think we ought to let other industry presenters to present and maybe they have some data, and if not, we do have some data that we can present later on to shed that light.

DR. DiMICHELE: I was really surprised to see the number of people who get infected in middle age and beyond. Is there any difference in the morbidity from this infection in the middle age and older age population compared to the younger population?

DR. BROWN: None that I am aware of other than the fact that women, and it doesn't seem to be particularly old or young, but certainly from 20 up would seem to be more likely to have the arthropathy and the arthritis, but otherwise, there doesn't appear to be any difference if you get your B19 when you are 80 as opposed to when you are 20.

If you get it when you are 8, you will probably have less symptoms and you will have the slapped cheek. That is all I can say.

DR. NELSON: Thank you, Dr. Brown.

Dr. Stramer.

C. Industry Data Presentations

Susan Stramer, Ph.D.

DR. STRAMER: Thank you very much.

This is a compilation of several presentations. Firstly, most of the data that I will present were presented at the AABB last year, then presented as Dr. Yu referenced, at the December 2001 FDA NAT Workshop, and I have added some new data and comments at the request of FDA.

I also want to mention that I am not only discussing B19, but I will be making some remarks about hepatitis A virus, because we really can't separate the two as we are trying to screen our plasma derivatives for nonenveloped viruses. Parvo is one, but so is HAV.

So, my presentation is contaminated with some HAV material, and I will try to limit those remarks.

[Slide.]

As we have heard, manufacturers of plasma derivatives have implemented NAT for nonenveloped viruses and such testing will likely be implemented for recovered plasma.

Most parvovirus B19 NAT programs target the elimination of equal to or greater than 1 million copies/ml as already referenced by Dr. Yu.

Studies of HAV and B19 frequencies in recovered plasma are limited. Dodd and coworkers at the 1997 AABB

reported some results from screening pools of 512 at NGI, and those results, we had zero positives for HAV out of 20,000 donations screened, but a frequency of 1 in 1,400 for B19. This was using a very sensitive test and as Dr. Brown referenced, the prevalence is very dependent on the sensitivity of the test that is used.

[Slide.]

Dr. Yu also mentioned solvent detergent treated plasma and through the three-year experience that has been reported at Vitex for NAT screening of S/D plasma and final product, which is 2,500 donations, and that is at NGI for HAV, or by their in-house testing for B19.

Now, they may screen pools of 100 that are comprised of five subpools of 20, and if a pool of 100 is found positive, they resolve to the subpool of 20, and if that subpool of 20 was found positive, they discarded all 20 individual units.

But from their testing, their frequency for HAV was about 1.5 million, and about 1 in 800 for B19 DNA. When we started to think about developing programs for B19, we tried to recover some of these positive units prior to discard, such that we could research the frequency of B19, the titers of B19, and try to get in-house some positive materials.

So, what we were provided was greater than 1,000 units, and we have tested these representing 20 positive subpools of 20, but to our surprise, of those subpools that we tested, the individual units comprising those subpools, only 23 of greater than 1,000 units tested were B19 positive at NGI using a standard test. Those were from 16 subpools.

So, of the 72 subpools tested, only 16 were positive. That indicated that we had a 77 percent false positive minipool test result using the sensitivity of the Vitex procedure.

[Slide.]

When I presented these data at AABB and at the FDA NAT Workshop, we only had a couple of positives identified to that point, and this again supports the data presented by the earlier speakers.

Here, you can see, even though these are separate units, if you align these by titer, and then you look at the IgM and the IgG concentrations or presence of those two antibodies, you can see that only in this very high titer positive unit there is no IgM or an IgG. Those that had lower titers had the presence of IgM. As titers decreased, IgM disappeared and then all were positive for IgG.

[Slide.]

For the 23 that we have identified at the conclusion of the study, we haven't completed the IgM and IgG testing, but I just present to you the titers of the positives of these 23 that we found.

You can see only five here of three years of Vitex screening, only five represented very high titer units. The rest were lower titers and they do what you would expect here, maybe had a mix of IgM, IgG, and perhaps some of these represented further contamination as 5 of 16 of these pools that contained these positives, contained multiple low level positives suggestive of contamination.

[Slide.]

So, from the Vitex studies, we know that HAV was infrequent, B19 NAT false positivity may be an occurrence that we have to deal with, especially when you are dealing with very high titer units.

Low level B19 DNA positive, IgG positive samples do occur, and individuals with early acute B19 infection have high viral titers and are likely to be IgG negative.

[Slide.]

So, in order to prepare for some type of screening program, which I should have said at the onset we are not yet doing anything for parvo. We have done a couple of pilot studies, and I am going to present results from two of those.

We did the first study with NGI, and it was an unlinked study to determine the frequency of HAV and B19 in recovered plasma. The testing was done from our surplus NAT negative tubes for HIV and HCV our NAT negative PPTs that were sent to NGI. Once at NGI, they were pooled and tested.

The testing used at NGI, and NGI won't be here to present, they use a four-test reaction for both HAV and B19. That is two different primer pairs that they run each in duplicate. So, each of the four tests, all four tests have to be negative for them to report out a negative result. If any of the primers or replicates to primers is reactive, it is considered a reactive.

So, we took a half million donations that we sent to NGI. They were pooled into 100 pools of 512, which is the standard matrix that NGI uses for pooling. We tested HAV without dilution and if there was a positive result, we would resolve to the individual donation and quantify.

For B19, NGI's standard algorithm is to take the pools of 512, perform a 1 to 1,000 dilution, and then test. So if we had a positive pool, we then would resolve to the individual donation, quantify, and look for antibody.

One point that we added to the study is if a pool was negative at 1 to 1,000 dilution, we wanted to see what

would be in those pools that they were tested undiluted. So, 1 to 1,000 dilution negative was further tested NEET.

NEET, that is the 512 pool was tested without dilution, and if that was positive, the same thing. Resolve to individual donation, quantified, and IgM and IgG testing performed.

I do want to comment because this is in your materials from NGI, that the sensitivity of the testing that we used at NGI was 20 copies/ml, actually 22.4 to be exact, and that is what is in NGI's presentation.

If you then multiply that by a pool of 512, multiply that by 1 to 1,000 dilution, you get a sensitivity for the donation of 1.2 times 10^7, so this is where we get the greater than or approximately equal to 10^6, but this is the sensitivity of the NGI test.

[Slide.]

So, the results. For HAV, these were easy. They were all negative. For B19 in performance of the 1 to 1,000 dilution, we had 3 positive pools including 4 positive donations. Two of the positive donations occurred in the same pool. So, the 4 positives gives you a frequency in the study of 1 in 12,800.

These are the 4 positives, the IgM present, results of IgM testing. All were IgG negative as you would

expect from relatively high titers especially in these two. No quantifiable IgG.

One of the high titer ones was IgM positive, and one of the lower titers was also IgM positive. Interestingly enough, these two were detected even though they were below the limit of sensitivity of the tests we were using, perhaps being in the same pool, there was some additive effect.

[Slide.]

Now, when we took the remaining 97 pools that were negative at 1 to 1,000 dilution and ran them without the 1 to 1,000 dilution, we had an additional 34 positive pools including 95 positive donations, which gave us really an unacceptable yield of 1 in 528.

Again, if you look at the titer of the samples found, IgM, IgG presence, and then this is the number of samples within these various titers, you see there are some high titer samples, actually 1, that probably should have been detected at the 1 to 1,000 dilution but wasn't, and that one was IgM positive, and plus/minus for IgG.

The lower titers had IgM as you expect, but also had IgG. The lower titer samples had a mix of IgM and again most of them have IgG.

[Slide.]

We did a similar study with GenProbe because since we are talking about a Phase 1 and Phase 2 approach, the NGI would represent the Phase 1 approach where samples would be sent out for testing, but we recognize in the future that in-house testing may occur, so we wanted to look at the GenProbe test.

So, what we did is we took NAT negative pools, pools of 16, about 2,500 of them, and representing April collections, and I should have said in the NGI study that I showed previously, those also represented springtime collections, and that is important because it is the highest time of reported parvovirus prevalence.

This represented about 40,000 donations. They were tested at GenProbe using a combination test for B19 and HAV, that had about 600 copies/ml test sensitivity. This was about 100 percent detection level, which in our pools of 16, was about 9,600.

Of those 2,547 pools tested, 24, just under 1 percent of these pools of 16 were reactive for B19. There were no reactives for HAV once again. If we assume that there was one B19 positive donation per reactive pool of 16, that would give us a prevalence of the sensitivity that we were using this test at 1 in 1,700 versus what I showed you for the NGI study, which used a less sensitive

procedure, of 1 in 12,800. So, in this case, it was 7-fold higher.

If you look at product loss, because again at a pool of 16, if we have a positive, we have to discard all products, due to discard of all members of a reactive pool when dealing with 16, would be about 1 in 100, which is unacceptable.

Based on the distribution of quantitative results for those 24 positive pools, the addition of the ones with 1,000 pre-dilution, which is what NGI does, would result in a prevalence that was comparable to NGI, of 1 in 13,000.

[Slide.]

If you look at the titers of the 24 positives that we got in the study, the vast majority would be expected to be below the limit of detection of the GenProbe test in the pool setting, so those are unexplainable findings or due to contamination, which is likely the outcome.

Here are some moderate level positives that were detected. We don't have antibody signal results on these. Again, we have 3, these are the 3 high titer positive samples.

[Slide.]

Currently, we are also doing--this is moving on to something else--we are doing manufacturing pool testing.

That is where many recovered plasma units are pooled, approximately 3,250 liters, and these manufacturing pools are tested for virus prior to final manufacturing.

I don't want to dwell on this because this is HAV, but again it shows you the type of result output that you get from NGI. This is audio radiogram, and I said that NGI performs two primer pairs, they do them in duplicate, so here you see a set of four results.

Lanes, all one are their positive controls, 17 through 19 are all positives, so this one they didn't have a positive. I mean there are certain criteria, and these all met the validity criteria.

But here you have an unknown and you can see here that it may not be positive on all of the four rafts, but in this case, it certainly was positive on three, constituting a positive result. So, that shows you the type of data output one would get.

[Slide.]

So, the conclusions from the presented studies is that blood collectors considering implementation of B19 screening will have to evaluate NAT methods that are relatively insensitive to prevent issues from contamination and detection of low level NAT positives.

The frequencies that I showed were 1 in 12,800 using the insensitive method at NGI. If you consider only

the two very high titer positives we had, the frequency is 1 in 25,600, and those were IgG negative.

The frequency, if we increase the sensitivity, was 1 in 528 with moderate titer samples that were plus/minus for IgG, but positive for IgM. Now, if you compare the GenProbe methods, we could get comparable results depending on whether we do a dilution, which would yield a 1 to 13,500 result, or 1 in 1,700 frequency if we used their sensitive method.

[Slide.]

High-titer screening methods may not capture all infections B19 positive units, however, the infectivity of antibody reactive, low-titer positives is unknown, as has already been referenced.

This study defines expected yields of B19 if sensitive and insensitive NAT methods are used.

This study also demonstrates the infrequent occurrence of HAV in recovered plasma, which is about 1.5 million to a million.

[Slide.]

So, where does that leave us? It leaves us with a discussion of Phase 1 and Phase 2, and I will try to answer some of the FDA's questions here.

One mechanism to do Phase 1 testing that the Red Cross will likely implement is the method with NGI where we

would outsource the testing to NGI, and the process time for the testing would exceed the dating of labile components.

So, by the time we got test results, the only thing we would have are frozen components.

[Slide.]

Now, how do we limit this, so we are only dealing with recovered plasma, and not the issues surrounding FFP?

Following the completion of our current HIV and HCV NAT testing, we would take our NAT tubes and identify those that correspond to recovered plasma. Those recovered plasma tubes would be pooled into pools of 16. They would be sent to NGI for further pooling, into pools of 512.

NGI would test for HAV and parvovirus, following a 1 to 1,000 dilution for the parvovirus. If negative, the product with the plasma would be fractionated. If positive, we would resolve to the pool of 16, and all in-date frozen products would be discarded, and the good news here is that we wouldn't have any FFP because they were never tested to begin with.

So, the question is then how do we address Phase 2, which would be testing in-house using a commercial kit. This would represent real-time testing in pools. Most likely in our scenario at the Red Cross, we would maintain our current pools of 16, and as I mentioned with the

GenProbe procedure, we could do a pre-dilution step as part of the assay, whether that is a 1 to 1,000 dilution to reach about a 10^7 copy/ml per donation level or 1 to 100 dilution, so we get to 10^6. That remains to be determined.

Reactives would be resolved to the individual donation within real time. So, what does that mean? For product release, in reactive pool resolution, for the latter involving usually 3 rounds of testing, we have anywhere from about a 10 to a 48 hour per donation turnaround time, and that is really based on our current NAT testing now.

If pools are negative, our turnaround time is about 10 hours. If a pool is reactive, requiring resolution testing, and then if it is a multiplexed test, discriminatory testing, final results may not be available for 24 to 48 hours. So, this really represents the range of when results are available. In this model, no product release would occur unless the units not only test HIV/HCV negative, and in the future West Nile, but also HAV and B19 negative.

[Slide.]

The B19 sensitivity level would initially be set for the removal of high-titer units that is greater than 10^6 copies/ml. We really couldn't make claims for labile

products because we are not removing all parvo, we are just removing high-titer units.

Really, again, as reference, we would really need to determine the needs for recipients of labile products, what the level of sensitivity should be, who should receive these products, et cetera.

Donor notification, management of products from NAT-reactive donors' previous donations and recipient tracing, which we hope won't have to occur, would have to be determined. But regarding donor notification, as has been addressed in the questions from Dr. Brown's presentation, is our time required for donor notification, varies by the marker, but it is generally two to three weeks and for some markers where we outsource supplemental testing, it may take the full 56 days or up to 8 weeks.

Our timeline for any type of Phase 2 implementation is dependent on the regulatory policies that FDA mandates, availability of test kits, and I didn't even list here all of the implementation issues, such as those outlined for West Nile virus.

Thank you.

DR. NELSON: Thank you, Dr. Stramer.

DR. SCHMIDT: What is NGI?

DR. STRAMER: Oh, I am sorry, National Genetics Institute. They are a clinical reference lab.

DR. SCHMIDT: Thank you.

DR. STRAMER: I was hoping to get a more challenging question than that.

DR. SCHMIDT: I thought maybe it was a new disease.

[Laughter.]

DR. STRAMER: It could be.

DR. NELSON: Actually, ironically, they were supposed to present next, but I understand Dr. Conrad isn't here.

DR. STRAMER: I tried to address two points in his talk because he presented differing sensitivity, but it is actually the same test at 20 copies/ml, pools of 512, and a 1 to 1,000 dilution. According to my $1.99 calculator, that comes out to 1.2 times 10^7, and I did it twice to verify my initial results, so it is about 10^7 sensitivity for their method.

DR. FALLAT: You have presented a lot of data and threw out an awful lot of numbers. Can you simplify it for me? What do you think is the best estimate from your large sample size of the general incidence of this virus in donor pools? I see numbers from 1 to 500 to 1 in 25,000, and what is the best number?

DR. STRAMER: Using sensitivity that I think is reasonable to eliminate the high titer units, I think we

will wind up with a prevalence between 1 in 10,000 and 1 in 15,000.

Now, if a cutoff of 10^6 or 10^7 is adequate, that is what the prevalence would be. If we dropped the cutoff, then, we are dealing with considerably different numbers.

DR. NELSON: Next, from the plasma industry, Barbee Whitaker.

Fractionators/PPTA

Barbee Whitaker, Ph.D.

DR. WHITAKER: Good afternoon. Thank you for the opportunity to present the PPTA approach to reducing parvovirus B19 load in fractionation pools.

I would like to mention that there have been a few changes to the slides that were distributed to the committee last week, and that you should have the current version, the version I am presenting now in front of you.

I would also like to mention that we have three presentations as a part of our industry presentation and I would like to respectfully request that you hold questions until the end because it's a comprehensive presentation. Thank you.

[Slide.]

PPTA is the international trade association and standard-setting organization for the world's major producers of plasma derived in recombinant analogue

therapies. Our members provide 60 percent of the world's needs for source plasma and protein therapies. These include clotting therapies, immune globulins, and alpha-1 antitrypsin among other products.

PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

[Slide.]

Although transmission of parvovirus B19 is uncommon through plasma therapies, PPTA recognized the particular vulnerability of specific therapy recipients including pregnant women and immunocompromised individuals. The industry opted to pursue a strategy of identification and removal of high-titer units as described already.

About the same time that we were looking at this, based on experiences observed with the solvent detergent treated plasma for transfusion, FDA encouraged the fractionation industry to limit viral loads in manufacturing pools.

About a year later, in 2000, the European Medicinal Evaluation Agency, the EMEA, held a workshop to address viral safety of nonenveloped viruses. It was concluded that given the current extent of knowledge, further introduction of regulatory requirements should be

carefully considered, and to date, there have been no further meetings on this subject.

Also, in 2000, the WHO released an International Laboratory standard for parvovirus B19, allowing the standardization of various laboratory tests particularly NAT.

PPTA released its voluntary industry standard for the management of parvovirus B19 in mid-2001. This standard is one of five critical standards in PPTA's Quality Standards of Leadership Excellence and Assurance Program.

The goal of our Standards Program is to enhance the margin of safety and quality of each and every product that reaches our consumers.

[Slide.]

PPTA's parvovirus B19 standard requires in-process control testing of incoming source plasma by NAT for parvovirus B19 DNA. Plasma that would result in a manufacturing pool exceeding 10^5 International Units/ml is removed.

Effective July 1st, 2002, manufacturing pools may not exceed 10^5 IU parvovirus B19 DNA/ml.

PPTA's standard is designed to enhance the safety of the finished product and is based upon the recommendations of the September 1999 Blood Products

Advisory Committee specifically and described by Mei-ying a little bit earlier.

The recommendation to treat parvovirus B19 is an in-process control that no studies were required to validate clinical efficacy of B19 NAT under IND for plasma for further manufacture. The validation should proceed as an analytical test only and that no clinical correlates were necessary if no decisions regarding donor or recipient management were taken.

[Slide.]

As Dr. Yu has described, FDA has requested additional data regarding specific industry practices, and I would like to introduce Dr. Steve Petteway of Bayer Biological Products, who will walk you through the requested data.

[Slide.]

As agreed with FDA, industry data will be presented in an anonymized fashion. Companies represented are as follows: Alpha Therapeutic Corporation, Aventis Behring, Baxter BioScience, and Bayer Biological Products.

Following Dr. Petteway's presentation, Dr. Edward Gomperts of Baxter BioScience will present the potential impact of donor notification.

Thank you.

DR. PETTEWAY: Thanks.

The FDA has requested that we provide an update for our in-process control testing of source plasma for parvovirus B19, but before I do that, I want to address the FDA issues that are specific here from testing algorithm through to profiles for B19 serial bleeds. I will address those. I think that you have them in front of you.

[Slide.]

However, before I do that, I want to remind everyone that pathogen safety is a comprehensive approach with effective redundant measures that provide a high margin of safety.

Beginning with the donor, with donor screening, management of donations, and management through testing donations and inventory hold and lookback, followed by manufacturing and specifically the management of plasma or manufacturing pools, coupled with virus inactivation and removal, and this coupling is very important in the whole safety profile.

Then, moving through the process ending with postmarketing surveillance in support of our patients.

[Slide.]

Specifically for parvovirus B19 management, we focus on two of these manufacturing safeguards, the plasma or manufacturing pool, and in-process control of the plasma

manufacturing pool again coupled with virus inactivation and virus removal through the purification and manufacturing processes.

I think to understand the value of this in-process test method that we have implemented, understanding the link between these two is critical.

[Slide.]

Prior to implementation of our testing paradigm, no plasm units were tested for B19. This resulted in manufacturing or production pools that ranged from 10^1 to 10^9 International Units/ml, followed by process viral reduction gave us a defined margin of safety, however, after implementation, high-titer units are identified through minipool testing and removed, now providing production or manufacturing pools with a titer of 10^5 International Units/ml when coupled with the same process viral reduction lead to an increased margin of safety.

That is really the target of this testing is increasing the margin of safety.

[Slide.]

To address the first issue that we were asked to address, the NAT sensitivities for minipool testing and original units, what we are presenting is targeted testing threshold for minipool testing as opposed to analytical sensitivity.

[Slide.]

The reason for that is that the sensitivities required to achieve reduced manufacturing pool loads are a function of minipool size and the manufacturing pool size. They are a volume factor. So, the differences in the size of the minipools i.e., the volume or the manufacturing pool greatly influence what this targeted cutoff is.

Minipool and manufacturing pool sizes vary across the industry. Therefore, each manufacturer has set the testing threshold based on the size of minipools and manufacturing pools to achieve the PPTA standard. That is why you see different threshold levels from company to company.

[Slide.]

The targeted threshold levels for original units we have calculated for you here because we don't actually test the original units. We back-extrapolated from the minipools. We remind you again that each manufacturer has set the testing threshold based on the size of the minipool and the manufacturing pool, and the goal is to achieve the PPTA voluntary standard.

You can see the differences, 5 times 10^5 to up to 10^7, and it's a volume related issue.

[Slide.]

So, minipools that are reactive and based on the targeted threshold are assessed and units are released or discarded based on individual company processes for carrying out that activity.

[Slide.]

Looking at the prevalence and levels of B19 DNA in minipools, as you can see, they range from 1 in 3 minipools down to 1 in 40 minipools. Of course, this is because the frequency in minipools is influenced by the size of the minipool and it varies across the industry.

[Slide.]

The B19 DNA levels can range up to 10^{11} International Units/ml depending, of course, on the titer and the donation.

[Slide.]

The next issue is the prevalence of reactive minipools, original units, manufacturing pools, and the levels of B19 DNA in each, and we will attempt to provide that for you.

[Slide.]

The frequency and levels of B19 DNA in original donations. What we are showing here is the frequency of discarded units, that is, in the testing paradigm, because of the logistics of testing, all the units that we discard

are not necessarily greater than the threshold, so what you are seeing is the units that we actually discard.

It ranges from 1 in 2,000 to 1 in 5,000, and you can see that it correlates with the threshold, and some companies have a lower threshold than other companies have for identifying and dealing with units.

[Slide.]

For B19 DNA in manufacturing pools, I think this is a very important slide and pretty graphically illustrates the whole point of this testing and what we gain from it and the value of it.

Prior to B19 in-process testing, this represents, each line, each data point represents the titer in a manufacturing pool and you can see that many manufacturing pools have titers as high as 10^8 to 10^9 International Units.

Following the implementation of the B19 in-process testing, however, there is a consistent reduction of the titer of B19 in the manufacturing pools across the same time frame. This data clearly demonstrates the value of the in-process control testing for manufacturing pools of B19 NAT, and this again is our whole goal, is to reduce the load in the manufacturing pools.

[Slide.]

Resolution Times. Now, you can interpret resolution times in many ways. Resolution time may be from

the time a sample is received in a laboratory to the time the result is available. So, we interpreted resolution time as from the time collection occurs, the collection of he unit, until a result is available.

You need to understand that this doesn't include time for confirmation testing and/or notification of donor, and the resolution times range from a mean of about 25 to 60 days.

As far as resolution times as it relates to the single donor, that is not done in our process.

[Slide.]

Now, there are factors influencing resolution time, and I think this is pretty critical in trying to understand how this works and what the issues are. These factors, of course, are shipping logistics, when samples are moved, when units are moved, and how they are managed.

Laboratory capacity and through-put and even seasonality of infection, and I will show you in the next slide exactly what I mean by that.

[Slide.]

This is from one member company. This is about two years, and this is the trends in the incidence of parvo-positive units over time. You can see that it is cyclic, as you would expect, and at certain points in time there is a very low incidence, i.e., the through-put

through a lab would be very rapid, at other points in time there can be 5 to 6 times as many positives to deal with, so that is certainly going to affect the through-put of a lab.

So, I think we have to be very cautious in describing or relating turnaround times, that they can be a little inconsistent and they can vary on us depending on the conditions.

[Slide.]

The next issue was the prevalence and levels of anti-parvovirus B19 antibodies, if any.

[Slide.]

To summarize, anti-B19 antibody level is not affected by the implemented in-process control measures, that is, removing the high titer donations. About 98 percent of manufacturing pools, whether before testing or after testing, are above 10 International Units/ml, and there are no manufacturing pools below 5.

This demonstrates appropriate strategy for effective management of parvovirus B19 loads in manufacturing pools while, importantly, retaining necessary antibody levels.

[Slide.]

I will just make a couple more comments about that. We were also asked if it was possible to look at

serial donations and look at the temporal relationship of positives, negatives relative to serial donations, and this happens to be a very high frequency donor, a profile from the high frequency donor.

There are about 12 of those, and this is one example, and this is meant to be a prototype. Each box represents a donation and the status of that donation relative to our threshold, whether it is above or below the threshold.

What you can see is that at this particular point, we were very lucky and we identified a donation actually at the point of initial infection, and the increase in titer was very rapid up to a very high titer, and then the next donations decreased very rapidly until it decreased below the threshold, and then went back to nondetection or non-elevated based on our tests.

This does not mean there is no titer. This means that it is non-elevated relative to our testing paradigm.

There is one important point to make here relative to antibody levels, and that is that what we have superimposed is the expected IgG profile based on publications based on the literature.

We also have data that actually confirms this, so we have got data where we actually looked at titer relative to donations, and we looked at IgG. What you can see, I

think the first speaker already pretty much said this, is that most of the high-titer donations that we remove are not likely to have an impact on B19 antibody titers in either manufacturing pools or immunoglobulin products.

However, if we remove a great deal of the low-titer donations, then, the possibility exists for a significant impact on the antibody titers in both manufacturing pools and final product, and that is clearly one of the main reasons why we have adopted this particular paradigm.

[Slide.]

So, in conclusion, then, PPTA member companies have implemented appropriate processes which have been shown to be effective in managing parvovirus B19 in manufacturing pools, thus achieving an increased margin of safety for life-saving plasma protein therapies.

Ed Gomperts is going to discuss public health impact of donor notification and counseling.

Edward Gomperts, M.D.

DR. GOMPERTS: Mr. Chairman, colleagues, thank you for the opportunity to talk to you this afternoon.

I will focus briefly on parvovirus B19 infection, summarizing briefly what actually you have already heard, and then talk about resolution times, as well as issues around donors and contacts.

[Slide.]

The infection itself and the virus is well documented, well reviewed in standards, infectious disease textbooks, such as The Principles and Practices of Infectious Diseases. Essentially, it is an acute self-limiting disease without chronic sequelae in normal individuals, normally transmitted by the respiratory route.

Most infections are asymptomatic. Where symptomatic, the donor would be deferred, symptomatic being fever, headache, malaise, myalgias, and rash.

Antibodies to parvovirus B19 confer life-long protective immunity. More significant sequelae are rare and usually occur in particularly susceptible non-donor populations with pre-existing conditions.

[Slide.]

Parvovirus B19 infections typically resolve with the appearance of neutralizing antibodies, in the case of IgM, approximately 10 days post infection and 17 days, IgG, post infection, with a period of viremia being about 14 days and in some cases this viremia may well persist for a substantial period of time.

The intense viremia, however, develops approximately one week after infection, and this usually lasts about a week.

[Slide.]

Focusing on the donor notification and the counseling issue, as we have heard from Steve Petteway, the average resolution time for NAT testing ranges from 25 to 60 days.

Additional time would be required to identify the unit, perform the necessary confirmatory testing, and then to locate and communicate with the donor.

This is a fairly substantial period of time relative to the infection and therefore an infected donor would already have cleared the virus and developed sufficient antibodies to confer life-long immunity by the time notification occurred.

The infected donor also, on the basis of this fair amount of time, will already have passed the infection to close contacts by the time of notification.

[Slide.]

Focusing on the at-risk populations and close contacts. From the point of view of the donor population, these individuals are deferred. There are standard questions, for example, "Are you feeling well and healthy today?" which ideally would exclude the individuals who have an acute infection, that are feeling ill.

Female donors, the question is asked, "In the past weeks, have you been pregnant or are you pregnant

now?" Certainly, the questions would exclude immunocompromised individuals.

From the point of view of prevention of transmission of infection to close contacts, as already mentioned, the turnaround time mean is about 25 to 60 days, and confirmation testing would be a minimum of additional 10 days and donor notification, anywhere from 3 days to months.

[Slide.]

In conclusion, this medical information related to an acute parvovirus B19 infection would be nonactionable for both the donor and his or her close contacts. On focusing on the ethics, we may question the ethic of notification of a donor regarding nonactionable medical information.

Certainly, counseling a donor regarding nonactionable medical information certainly presents difficulties.

Finally, donor notification and counseling lacks public health benefit as this is a non-chronic, acute, short duration viral infection which is highly prevalent in the general population.

[Slide.]

To conclude and bring the presentations together, in-process control measures are designed to enhance the safety margin of plasma therapies.

Parvovirus B19 NAT test lacks value as a diagnostic or donor screening method.

Thank you.

DR. NELSON: The last three speakers are open for questions or comments.

DR. SIMON: Just one quick one. What is the confirmatory testing for this virus?

DR. GOMPERTS: It would be a repeat B19 NAT test.

DR. SIMON: You would just repeat to make sure there wasn't an error?

DR. GOMPERTS: On the specific unit that is collected from that specific donor.

DR. DiMICHELE: I can ask you, but the question would be for anybody. Has anybody ever heard of the CDC identifying a contact parvovirus infection in a contact of a recipient of blood products at all?

In other words, has the CDC ever identified infection in the contact of a blood product recipient or a plasma product recipient to the best of your knowledge?

DR. GOMPERTS: I don't know.

DR. YU: I believe for CDC, B19 infection is not a reportable disease, right, Dr. Chamberland?

DR. CHAMBERLAND: We wouldn't have the data to answer that question. There may be isolated case reports that are in the literature that someone can speak to that talked about secondary transmission in a household where a transfusion recipient acquired it from transfusion.

DR. DOPPELT: I am a little confused. How are you setting your cutoff for what you consider as a high titer and a low titer?

DR. PETTEWAY: The cutoff, as I said, is coupled to the manufacturing process, and it is coupled to the target of achieving no greater than 10^5 International Units/ml in a manufacturing pool. If that manufacturing pool is 800 liters, then, the minipool screening and the cutoff is going to be different than if the manufacturing pool is 5,000 liters.

So, it is all linked together and it depends on the manufacturing process for any given company.

A cutoff at the minipool level or at the donor level, when that unit now is diluted into the manufacturing pool, the cutoff will be 10^5. The titer of that unit that is diluted will be dependent on the volume of the manufacturing pool. That is how companies are setting their cutoff, and the key is the specification or the target at the manufacturing pool.

DR. DOPPELT: How are you picking that particular target? I mean is this arbitrary?

DR. PETTEWAY: No, actually, it is not. Remember it's coupled to viral inactivation and removal, and we picked that target because we need to go below the target, so if we are at 10^5, in order to assure that we don't go above 10^5, then, we need to be around 10^4, so if we are around 10^4, so now we are excluding donations, some of which are actually below 10^5, if we were to go much lower than that, we would start excluding the low-titer donations that are high IgG, and we are trying to avoid that.

So, what we are trying to do is to eliminate the highest titer donations without eliminating the donations that are high in IgG antibody.

DR. NELSON: And by "viral inactivation," you mean antibody primarily, right?

DR. PETTEWAY: No. I mean within the purification process for manufacturing, we have the capacity to remove or eliminate virus to a certain level, and the idea is to get the manufacturing pool, reduce the load in the manufacturing pool, so the challenge on that capacity is less and the margin of safety is greater. They are coupled together, and I think that is important to understand.

DR. LEW: I think I have a question that may be linked to what was asked earlier. My understanding is when CDC did their presentation, they mentioned about genomic equivalents/ml based on a study that looked at healthy donors, and you wanted to avoid anything that was greater than 10^4 genomic equivalents/ml, because those were nontransmitting lots.

We didn't really get the details of that study where we get this cutoff from, 10^6, and that is a problem that I am having, as well. What are the studies that show 10^6 is the greatest, which is a little different issue looking at keeping antibodies in our plasma or IVIG.

So, the first question is what is the correlation between International Units/ml with genomic equivalents, is that 1 to 1? The second is could we get some details on how that particular cutoff was chosen, either the 10^4 or 10^6 based on how you manufacture?

DR. NELSON: Wasn't the cutoff chosen based upon a study that showed transmission of some pools that had very high titers?

DR. PETTEWAY: No, actually, that may not even be relevant to what we are doing, so I will put a slide back up and try to explain.

DR. LEW: There is a different issue between trying to keep good antibodies in these products versus

this cutoff of not wanting to transmit, and I would like better clarification on that.

DR. PETTEWAY: Let me see if I can help you here. Remember that prior to implementing testing, we had manufacturing pools or production pools that were up to 10^9 International Units/ml. During our purification processes, we are capable of removing virus, but removing virus to a certain level. That gives us a margin of safety, but it is based on the starting load, how much can you remove.

What we wanted to do was reduce this load, so by minipool testing and removing the high-titer units, we are able to reduce the load to a defined--we can call this a cutoff, but a defined specification for the manufacturing pool of 10^5 International Units/ml. That is the goal.

Now, when that is coupled with the process viral reduction that is the same here, but with a lower titer or a lower initial titer, then, we have increased the margin of safety for the product.

The transmissibility in solvent detergent plasma of 10^5 would not be a criteria for choosing the load here. The criteria for choosing the load here is a balance between removing the most virus possible while not eliminating the most IgG possible. That is why that was chosen, not based on the 10^4 S/D plasma experience.

DR. LEW: Could you just say what is equivalents between genomic equivalents versus International Units?

DR. PETTEWAY: Well, the reason you have an International standard is because people--John, go ahead.

DR. SALDANA: John Saldana from Canadian Blood Services.

The correlation between International Units and genome equivalents is about 1 to 0.6 or 0.8, and the reason we use International Units is to get away from the discrepancy of people using different units. I think it was quite clear at the West Nile Virus meeting in November that people were using copies/ml, genome equivalents/ml, et cetera, and it is very confusing, so the WHO has adopted the IU, which is an arbitrary unit.

I think that tends to standardize. It is completely arbitrary, but we try and make it as close to the genome equivalents as possible.

DR. GOLDING: Basil Golding, FDA. This cutoff of 10^6 is obviously arbitrary and it is true that most manufacturing processes will remove virus, but the ability to remove virus is variable and this virus is removed to a lesser extent than enveloped viruses, and most manufacturing processes that I am familiar with will remove possibly 4 logs of virus, so you are still going to have virus in the product.

The point about the antibody, the caveat there is if you are making immune globulin, sure, you will have antibody in the product and it is going to neutralize low levels of virus, but if your fractionation process separates your virus from your product like it could do for certain calculation products, you could end up with 3 or 4 logs of parvovirus in your product without any antibody in the product, so that product could presumably transmit the virus, and if you look at the hemophiliac population, the antibody titers compared to the rest of the population indicate that that is exactly what happens.

DR. PETTEWAY: Yes, that's true, and that is another reason why our paradigm and the cutoffs that we chose wasn't based on the plasma S/D experience. I would also note that in many processes, we have validated capability of removing parvovirus up to 10^8 or 10^9, and in others it is less, so that is correct.

DR. SCHMIDT: I would like to see us remove from the discussion of what we should do, the point about the contacts of the donors for three reasons. First, I think we are all interested in public health, but I don't think we should add to the cost of blood and blood products some public health activity, such as caring for or considering the contacts of our donors.

Secondly, I don't think it is within the authority of the FDA to consider that. We are supposed to be worrying about the product and we are already moving back to the donor's health, and now we are talking about the health of contacts of the donors.

Thirdly, I think nowadays is this whole question of invasion of privacy or not invasion of privacy depending which side of the fence you are on these days, but we might not have any business letting people know about those things when they didn't ask us for them.

DR. FALLAT: It seems to me, though, pertinent to that is there is a big difference I guess between the plasma fractionators and their time period and the blood center. We have to keep that in mind when we look at the time period where the donors or the recipients might be contacted.

DR. ALLEN: I would be very cautious about certainly voting negatively on this question, however, in the absence of some medical ethics considerations, in the current environment, if an organization or an agency has that kind of data, and it is taken down to the individual donor level, I think there are many people who would feel that there is an obligation to get that information back with an appropriate explanation ever if there isn't any necessary medical or public health significance to it.

I think that goes back to the question of if you have got minipools, is there an obligation to test back to the individual unit, and that perhaps could be the level of discussion. I think if you have taken it back to that level of identification, there may be an obligation to inform the person.

DR. KLEIN: I would agree with that, Jim. I think that if you have that information about a donor, and it was I who donated last week, and you told me, I might not visit my pregnant daughter next week or I might not go to the obstetrical unit or to the hospital where there are immunodeficient subjects.

I think that us not discussing this and deciding whether or not this is an issue, we would be punting on that one.

DR. SCHMIDT: I guess this goes back to one of my old arguments with Toby who presented the point of view that the plasma industry was considering serologic testing for syphilis as a good thing because if it's public health aspects, then, I see some relation here.

DR. SIMON: I never advocated that. From a historical perspective, that is the way it came about, you know, that the testing every several months at a time when syphilis was more prevalent, I don't know if you want us to start discussing this or not.

DR. NELSON: We will have time to discuss the questions raised by the FDA. Since we have come this far with all the presentations and people have flights and are going to have to leave, could you present the questions again?

DR. WHITAKER: Could I just answer the question that was raised a minute ago?

DR. NELSON: Go ahead.

DR. WHITAKER: I would like to remind the committee that the test is a threshold test. You are not going to identify every one who has parvovirus when you do the test, so you will be identifying individuals with high titer viremia, but you may also be not identifying people, individuals with high titer viremia just below the cutoff.

The purpose of the test is the product and assuring a high margin of safety and that not diagnosing a donor, and that there are some issues here that really do need to be discussed and considered.

It is not the same as an HIV test.

DR. NELSON: There are four people that wanted to make a statement in the open public hearing. If you could make a brief statement or even provide it for the record or what I would like to do is maybe discuss the questions, but the first is Kay Gregory.

DR. CHAMBERLAND: Ken, can I just ask a question because there is a time issue here. I think the committee really wants to give this a thorough discussion and it is a difficult issue, and there are four questions. There is also open public hearing that has to take place.

I think there is, by my watch, about 45 to 50 minutes left before the scheduled adjournment and I think many of us, those of us from out of town, scheduled flights to accommodate a 6:30 adjournment.

If people realistically think that all of that can happen in 45 to 50 minutes, then, that is what we planned for, but if it is not realistically able to happen, I think people are just feeling kind of at a loss as to what exactly to do here.

DR. NELSON: I think if we have come this far and then we discuss, let's say, the questions again at the next meeting, we would have to sort of revisit all the issues. I would like to try to do it in the next 45 minutes if we could.

D. Open Public Hearing

Kay Gregory, AABB, ABC, ARC

MS. GREGORY: You have the written statement and this time I am actually representing the AABB, America's Blood Centers, and the American Red Cross. I am happy to just let you have it on the record, but I think it may be

giving a little bit short shrift to the whole blood industry if you don't hear the statement.

Primarily, what I really want you to be aware of is that given the important and compelling competing safety priorities of implementing West Nile Virus donor screening and performing bacterial detection in platelets for the whole blood sector, and we are going to be doing this in the next six to nine months, the additional capacity and work that would be required to perform parvo B19 NAT as a donor screening test simply cannot be absorbed.

For example, performing it as a donor screening assay would require the addition of another on-line assay requiring completion prior to all product release, the pulling of samples and further testing to resolve positive pools, the need for a confirmatory assay, and the alteration of 510(k) cleared computer systems to accommodate parvovirus B19 results as a release criteria.

Furthermore, current FDA policy would require that donor screening be performed under an IND or an IDE, which would be an additional burden for test kit manufacturers who are turning their efforts to West Nile virus test development.

We believe that the practical solution of performing parvovirus B19 as an in-process control at this time is supported, and we are willing to look at doing

that, but we think going any further to call it a donor screening and requiring notification, et cetera, is more than we can absorb at this point in time.

DR. NELSON: Thank you. That was a good summary.

Let's move to the discussion and questions.

E. FDA Perspectives and Questions for the Committee

Mei-ying W. Yu, Ph.D.

DR. YU: I will try to be short.

[Slide.]

The first FDA perspective. For whole blood donations, risks to transfusion recipients are sufficient to warrant withholding high-titer individual positive units that is greater or equal to 10^6 genome equivalents/ml prior to release of blood components to use in transfusion.

This particular level was set, it is to minimize the risk of infection in recipients and to prevent serious consequences of B19 infections in high risk recipients and to avoid the removal of low titer units that may not be infectious and which contain protective antibodies.

[Slide.]

Now, this is B19 profiles of B19 DNA and antibodies from the serial bleeds from normal source plasma donors. Dr. Gerald Zerlauth of Baxter BioScience presented in December 2001 FDA Workshop, and we have been

collaborating with him very closely, so this is a very precious panel I just want to point out, but unfortunately, NGI also have similar panels from serial bleeds, I believe from 20 donors and show very similar pattern.

In red or reddish pink, that is the DNA level, and the B19 DNA level, and in yellow is an IgM profile, and the blue is the IgG profile. So, as you can see from this source plasma donor, the B19 level goes up very quickly to 10^{12} and then it drops quite sharply to 10^{6} or a little bit below when IgG became positive. This is at day 14, anti-B19 became positive, and the titer is around the 7 times 10^{5} genome equivalents/ml.

But the viremic period can be very, very long. See, it tapered off here, but then it remained very, very long time through 304 days, but that is his last bleed, so it is 10^{2} or 10^{3} genome equivalents/ml level.

The IgM was positive at day 10 and then the level is still very high, 2 times 10^{10} genome equivalents, so this 10^{6} genome equivalents/ml above, then most likely IgG will be negative.

Now, we really don't know what is the infectivity, the minimum infectious dose especially for those unpooled products that has no antibody, but I want to tell you that the IgM in this particular donor became negative at day 60 and this donor was positive at day 14,

like I said, and then later on it actually gradually increased and the level reached to about 50 to 60 between 70 to 90 days IU/ml, 50 to 60.

DR. NELSON: This has been presented before to the committee. I wonder, could you move to the questions that you want us to consider?

DR. YU: Okay. I will. This is the level of IgG became around 10^{30} or 10^{25}, that is what is found in IGIV level, in terms of 1 percent IgG concentration.

I wanted to answer Dr. Toby Simon's question.

The key thing I wanted to show that profile is to say that you cannot be too sensitive. When you are too sensitive of the NAT, then, you are getting those low level units that may not be infectious, and they contain IgG.

[Slide.]

The second one is a temporary deferral may be warranted for high-titer apheresis donors if positive donations can be resolved within several weeks. As you know, the donation intervals are 8 weeks for whole blood, 8 to 16 weeks for red blood cell apheresis, 48 hours for plateletpheresis, and every 48 hours for plasmapheresis.

Based on the industry presentation, we will see the resolution time. In Susan Stramer's presentation, she said that can be in 24 to 48 hours, the mean time, so I put down two days here for the Phase 2 approach. Now, NGI

unfortunately, Andy Conrad cannot come to present, but in one of his slides, the average time to resolve to single donation is 4.6 days to be exact.

Within such a short time, either two or five days, you can really notify the donor, defer the donor if necessary, and then if there is a medical benefit for the close benefit, they can be notified quickly.

FDA actually got inquiry from plasma centers and they asked how long they can defer these positive donors, but however based on the PPTA presentations, you can see various companies. The mean time, resolution time is ranging from 25 to 60 days, so within the time period, you really cannot do very much for donor deferral or medical benefit to the close contacts, but the range is very, very high, you know, A and B companies can be as short as 8 or 9 days.

[Slide.]

The third point is that FDA is seeking the BPAC's opinions on conclusions made by the Ad Hoc PHS panels that there are sufficient potential medical benefits to close contacts, but not to donors, to warrant notification of parvovirus B19 donors.

However, we believe such notification is likely to be useful only in setting where testing and notification

can be completed within, for example, less than four weeks of donation.

So, the questions for the committee.

First, if donations of whole blood are tested for the presence of human parvovirus B19, are risks to transfusion recipients sufficient to warrant withholding high titer positive units that is equal or greater than 10^6 genome equivalents/ml from use for transfusion?

Is temporary deferral of positive donors warranted in the setting of: (a) whole blood donation? (b) apheresis donation?

The third question is: Do potential medical benefits to contacts of parvovirus B19 infected donors warrant identification and notification of positive donors?

Fourth. If yes to Question 3, should donor notification be limited to settings where testing and notification can be completed within several weeks of donation?

That's it.

Committee Discussion

DR. NELSON: Discussion?

DR. SIMON: Did you want to do these one at a time? I think it is a philosophic issue here. We have started with a test which was an in-process control, and it has somehow evolved into consideration as a specific test

for the removal of in-date units and for counseling of donors.

It only detects people who are at very high titers, so if you donate a day or two, before you hit that titer, it won't detect you, if you donated a day or two after, it won' detect you, so its public health usefulness is very limited, it doesn't have the same kind of testing characteristics for HIV or hepatitis B or hepatitis C.

I think what has created a red herring here, I guess is the Red Cross's intention, in its Phase 3, to do this in concert with the other tests and to have a positive test result at the same time as they do for the other viral markers, in which case they could remove the units, and I guess it would make sense to do so, but that Phase 2 is a while away and as they pointed out, even in their situation, there is still more time needed before they would be able to contact the donor. They have to confirm the test result and then they have to put in the process all the measures to contact the donor, and there is just a lot of other time taken up.

I think in terms of the industry, the plasma industry, you know, this is coming way beyond any time for medical usefulness. So, I just think we have gotten off. I guess, number one, I think if you had the data within the same time frame as you do the others, I guess you would

pull in-date units, but I think it is unfortunate that we moved from looking at this as an in-process test for the plasma fractionation product, to begin to look at it for these other purposes, because obviously, a somewhat lower titer in that setting could cause the problem.

So, I think it is unfortunate. I mean I guess that the common sense answer to Question No. 1 is yes, but I certainly wouldn't defer the donor who will get over the problem, and I think contacting, it is true, of course, that you always have this ethical issue when you have information, but it is not very useful information and the timing of it is such that it is going to come at a time when it won' be useful to the donor or the contacts, because simply the time it takes to do all of this, whether you do it by certified letter or phone call that goes into a voice mail, and by the time it gets back into the system, so that I think is I guess representing industry, kind of my philosophic look at it.

I would hope we would not saddle the plasma industry with having to go back to tell people 30, 40 days after they have donated about this.

DR. SCHMIDT: Considering the whole blood, we have heard a statement from Ms. Gregory that they can't do it right now without impeding other perhaps more important activities.

Wouldn't it be sensible for the FDA to table this request for us to consider this? I know it means taking it up again next year, but that might be a cheaper alternative to having everybody working on this before then.

DR. KLEIN: We have spent a lot of time on the plasma industry, and as best I can tell, the questions aren't addressing that, and it doesn't make much sense, since they are not resolving to the single donor, and the time frame would make that--

DR. SIMON: I think they are resolving to the single donor.

DR. KLEIN: If they are resolving to the single donor, then, the time frame would make it impossible really to have any medical benefit either to a donor or to the donor's immediate contacts or even distant contacts.

However, if, in fact, we are going to be resolving to the individual donor within 48 hours, then, I think we need to address these issues even though we may not be doing that for the next two or three years.

I think we at least have to get on the track. I think the FDA is asking us for that advice. I am not saying that we need to do it tomorrow. It seems to me that if you have a unit of blood that has a high titer test positive confirmed for parvovirus, you simply don't want to transfuse it. I can't imagine that you would ignore that,

so I think the answer to No. 1, in my mind, is yes, and I presume we will get on to No. 2 eventually.

DR. NELSON: Let's vote on No. 1.

DR. BIANCO: Let me just ask Dr. Klein an important question. What if in the whole blood sector, this testing is done after expiration of the cell or components for the units that are going to recovered plasma, which is what Sue Stramer presented?

DR. KLEIN: I think again the question we are being asked is about if you have an in-date unit and you have a test result that indicates that it may be infectious, and not only infectious, but potentially cause morbidity and mortality. I mean that is the question.

If you want to pose the question differently, I may have a different answer.

DR. NELSON: Jay.

DR. EPSTEIN: It may be helpful to realize that the terms of debate have shifted over time. The source plasma standard has caused the need for whole blood collectors to implement parvovirus testing, so that they can sell recovered plasma.

This has caused the FDA to consider what is going on in the whole blood scenario, and the way we looked at it is, well, if you are now testing whole blood donors,

shouldn't you have a proactive position to interdict the at-risk unit.

Now, what has evolved is that it can't be done immediately, don't allow it, priorities may not allow it, but we are sort of looking ahead and it was not clear some months ago whether there was, in fact, an industry intent to do what is called real time testing, which basically means testing as a release test.

There is this gray zone where you may not be testing as a release test, but you have an in-date unit, and you might or might not get the opportunity to interdict it. That is an unpleasant place to be.

So, you know, you sort of have these three scenarios. You have testing of outdated units for the purpose of screening and recovery of plasma. There is nothing further you could be doing about transfused units, and a lot of time has passed with regard to any value notifying a donor.

At the other extreme you have testing within 48 hours compatible with other release testing, and then you have this gray zone in between where you have some delay in testing, but you still have some in-date units.

So, what the FDA is looking for is, first of all, an opinion whether it is important to interdict these units because they are not being interdicted now when there is no

testing. Then, we are looking for a direction whether we should be pushing from a regulatory standpoint that all the testing should, in fact, in whole blood, become pre-release testing eventually.

If testing is feasible and if ultimately, it is feasible as release testing, shouldn't that be what happens. So, that is where we are coming from, and we recognize that you can't necessarily have it overnight. I mean I think we understand that point.

DR. FITZPATRICK: To me, that is a different question. What Dr. Klein said was if we know, we should interdict. What you said is should we test to interdict, and that to me says does this represent enough of a risk to the patient population that we should advocate pre-release testing.

I didn't see presented today any more information than was available in 1999 on cases of transmission by transfusion. So, those are two different things to me, and I am not sure where you want us to go with that.

DR. EPSTEIN: Well, my feeling is that if whole blood donors are to be screened, that we should work toward pre-release testing for the purpose of interdicting potentially infectious units and that, as you say, you have already heard that high-titer units are almost certainly infectious.

We know that they are a serious threat to some recipients. We don't have good data on the frequency of clinically significant events. Now, we don't have any more data than we have previously prevented. I think that is part of the problem, but we were trying to focus today's meeting primarily on the issue of benefit or lack of benefit of donor notification.

I appreciate the discussion of Question 1 has raised the additional dimensions of that issue. I think we could split it into two questions if you like. One is, is there a benefit to interdicting parvovirus-positive units, and the other is, if testing is done now, should it become pre-release testing.

Is your feeling that you can't vote this question or you don't know what it means?

DR. FITZPATRICK: I am concerned about the phrase, "Are risks to transfusion recipients sufficient to warrant withholding high positive titer units?"

You know high-titer units are infectious. To me, if we answer yes to the question, we are advocating an effort by the industry to engage in an effort to do pre-release testing to protect the recipient.

DR. EPSTEIN: Well, I would say that there would likely be an evolution of policy and that the first step would be retrieving in-date units found to have high titers

and a vote in the affirmative would encourage FDA to push toward ultimately pre-release testing, yes, but it doesn't all have to happen at once.

But, yes, a vote in the affirmative would put us on that course to progress from retrieving in-date units potentially with lookback notifications to an ultimate pre-release testing scenario.

DR. FALLAT: We have data from the blood banking industry that there is 10^6 titers in perhaps 1 in 15,000. We give 1.5 million units of blood a year. That translates into quite a number of people getting that titer, of which a certain percentage will be in the high-risk group.

For me, it is no greater to vote yes on No. 1.

DR. SIMON: Well, for me, it is unfortunate, the implications in No. 1, because I think if somebody told me they had tested, and it was a high-titer unit and should they remove it, I would have to say yes.

I mean I can't imagine a different answer, but on the other hand, I would not want to encourage the FDA to move towards requiring this testing as a donor test, in other words, because I think it takes us off the track of the rationale for it, and I don't believe, as Dr. Fitzpatrick said, that data in the past have suggested a need to look for this virus or to prevent this virus transmission in whole blood, platelets, and so forth, but

rather as a problem in pooled product particularly to hemophilia patients.

So, I think it is unfortunate that there is that implication with a yes vote, but I agree with Dr. Fallat. I mean I don't see how one cannot vote yes to No. 1 if you have that information.

DR. EPSTEIN: Could I suggest that we add a question to give you the opportunity to clarify this, which would be: Has a value for screening of whole blood donors for parvovirus B19 been established?

In that way, if you wish to vote 1 in the affirmative, you can still vote 2 in the negative. I think that would clarify things if I understand the issue here.

DR. KLEIN: I would like to have that first part that is now split off, I like the wording, because I think the wording is very important. We really have never looked for this, so we don't know whether it is a problem or it isn't a problem, so you really don't want to exclude that any more than you want to press forward with it in the absence of data.

DR. NELSON: Great. Certainly, parvovirus B19 infections are a significant problem in patients with AIDS and sickle cell, and all the rest, but we don't know how much of it is transfusion transmitted, and I guess that is the real issue.

DR. SIMON: We can vote on No. 1, I think, while he is writing No. 2.

DR. NELSON: Let's vote on No. 1.

DR. SMALLWOOD: Question No. 1(a). If donations of whole blood are tested for presence of human parvovirus B19, are risks to transfusion recipients sufficient to warrant withholding high-titer positive units greater than 10^6 genome equivalents/ml from use for transfusion?

Allen.

DR. ALLEN: I think the data aren't certain, but I am convinced that the answer probably is best yes.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: Yes.

DR. SMALLWOOD: Davis.

DR. DAVIS: Yes.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: Yes.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: Yes.

DR. SMALLWOOD: Klein.

DR. KLEIN: Yes.

DR. SMALLWOOD: Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: Yes.

DR. SMALLWOOD: There is unanimous yes for Question 1(a).

Question No. 1(b). Has a value to blood transfusion recipient been established that is sufficient to warrant donor screening for human parvovirus B19?

DR. SCHMIDT: I am sorry. Would you read that again?

DR. SMALLWOOD: Yes. Has a value to blood transfusion recipient been established that is sufficient to warrant donor screening for human parvovirus B19?

DR. FALLAT: It that for whole blood transfusions or are you separating out transfusions? Yes? Okay.

DR. SMALLWOOD: Roll call.

Allen.

DR. ALLEN: I think most of the discussion I heard was really to the absence of data although we agree that there certainly is a potential risk out there especially from high-titer units.

I am going to have to, in terms of the way the question is worded, Has a value been established, the answer is no. We need studies. I think there is a potentially very significant risk out there to certain populations. It is a real concern. I don't think we have the data now. No.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: I would vote no for the same reasons.

DR. SMALLWOOD: Davis.

DR. DAVIS: No.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: I am going to abstain.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: No.

DR. SMALLWOOD: Klein.

DR. KLEIN: No.

DR. SMALLWOOD: Lew.

DR. LEW: No.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: No.

DR. SMALLWOOD: Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Harvath.

DR. HARVATH: No.

DR. SMALLWOOD: Nelson.

DR. NELSON: No.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: No.

DR. SMALLWOOD: The results of voting: 2 yes votes, 9 no votes, 1 abstention, and the industry representative agreed with the no vote.

Question No. 2. Is temporary deferral of positive donors warranted in the setting of:

(a) whole blood donation?

(b) apheresis donation?

DR. SIMON: Is apheresis here plasmapheresis? I am getting the word that it is, (b) is plasmapheresis as of the plasmapheresis industry.

DR. KLEIN: (b) could also be plateletpheresis.

DR. SCHMIDT: Do we know what a positive donor is?

DR. NELSON: No. It could be 10^{2} or 10^{40}.

DR. ALLEN: Remind me again. With the plasma industry, my understanding is we are really talking weeks or longer between the time that the testing is done and any results are available, so plasmapheresis, I mean it's a moot question. Plateletpheresis is the testing is done reasonably rapidly.

DR. SIMON: That is an interesting question. Ordinarily you wouldn't do it on plateletpheresis since there is no recovered plasma. I mean if you take our vote on 1(b), go with the majority, you wouldn't do it on plateletpheresis unless you are making recovered plasma with it, but ordinarily you wouldn't be.

DR. FITZPATRICK: With 1(b), to me, until you resolve 1(b), you can't move on to 2(a) and (b).

DR. KLEIN: I don't really agree with that. I think if you have got a positive unit, then, what do you do with that donor? You have got a high-titer positive unit sitting here, and you have a donor, someone who is going to come in 56 days later. Then, I think the answer is pretty obvious, but someone who might come in, in 48 hours, you have to think about it.

DR. SIMON: Well, 56 days later, I assume you are saying you would not defer, and 48 hours you would except you won't know that for three or four weeks.

DR. KLEIN: Not in plateletpheresis, should you be doing it for plateletpheresis, and I guess there are protocols where plasma and platelets are collected, are there not, Jay?

DR. EPSTEIN: I am thinking. Again, it is a case where splitting rather than lumping. FDA brought it forward this way because we were thinking about frequent collection, and we were neutral about how long could it take to do the whole cycle of testing, because there is so much variation going on. We are not making the assumption things stay the way they are.

But I think for the moment it would be helpful to split out apheresis from plasmapheresis. So, basically, the two scenarios come down to the whole blood apheresis donor to make transfusible components where that donor may indeed come back in 48 hours to give platelets again. Part (c) would be the scenario of source plasma donation.

So, if we would say whole blood and apheresis donation from whole blood donors, in other words, the donors who meet the whole blood standard, so apheresis donation to make transfusible components, and then (c) would be source plasma donation.

DR. FITZPATRICK: So, Jay, in following Dr. Klein's, would you consider this the same as 1(a), if you

had the result and knew the result in time to make a decision, would you make one?

DR. EPSTEIN: Well, I think having posed and heard the vote on 1(b), we are not now really thinking in terms of the scenario where it is all pre-release testing, so we are back to the scenario where you might be learning later.

On the other hand, the donor, even though you learned later, even though maybe it was 14 days, the donor could still be coming back, in other words, they are not on a 56-day cycle.

DR. NELSON: This all one question that includes (a), (b), and (c). Is that right? Vote separately?

DR. SIMON: Yes, separately.

DR. NELSON: Let's do the first, 2(a). This is a whole blood donor with an interval of 56 days?

DR. SIMON: 2(a) would be, I believe, a whole blood donor with interval of 56 days. 2(b) would be potentially plateletpheresis, which could be twice in a week. 2(c) would be plasma donor, which could be twice in a week, but you don't have the results for three to four weeks.

DR. NELSON: Right.

DR. DiMICHELE: The nuance of this, the time of notification I think is critical to answering this question

because I think in answering Question 1, I mean I think we were sort of looking at the data that was presented by the FDA and the American Red Cross, and the possibility of getting this information out in two days, which is very, very different, I think, given the period of viremia of someone who is determined to be positive.

So, given the overlapping period of viremia and basically the identification and notification time, I mean I think those two things are very, very critical. If the notification time extends past the period of viremia, the question is a moot point.

If the notification time is included in the period of viremia, then, you are absolutely right, then, we vote maybe the same or differently on 2(a) and 2(b). I mean I think that this is an issue that has to be clarified before we can vote rationally.

DR. SIMON: I think the information we were given is that the whole blood segment could at some time move to having the data available within 48 hours. The plasmapheresis situation would not. Those units are all shipped to central testing laboratories that take longer to do it, and also we have to keep in mind with (c), the level of antibody in the final product because the donors that are then forming IgG are people you would want as donors for IgG.

I think that suggests that (a) and (b) you would probably say yes, and (c) you would say no, and that would be my view of it.

DR. NELSON: (a), you would say yes with the 56 day?

DR. SIMON: I am sorry, I am getting confused. (a), I would say no because of the 56-day interval; (b), I guess you would have to say yes, if you had it; and then (c), I would say no for source plasma.

DR. DiMICHELE: If that is what the question is.

DR. STRAMER: I just wanted to clarify time frames. I said we would have products tested by 10 hours to 48 hours, which is about two days at the longest time, but for donor notification, by the time the donor gets the test results, we may owe them a letter that is going to be two to three weeks.

DR. SIMON: But if you wanted to defer a plateletpheresis donor, you could put that in your computer.

DR. STRAMER: Right, that's true.

DR. SMALLWOOD: Question 2(a). Is temporary deferral of positive donors warranted in the setting of whole blood donation? Vote.

Allen

DR. ALLEN: No.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: No.

DR. SMALLWOOD: Davis.

DR. DAVIS: No.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: No.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: No.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: No.

DR. SMALLWOOD: Klein.

DR. KLEIN: No.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: No.

DR. SMALLWOOD: Fallat.

DR. FALLAT: No.

DR. SMALLWOOD: Harvath.

DR. HARVATH: No.

DR. SMALLWOOD: Nelson.

DR. NELSON: No.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: No.

DR. SMALLWOOD: The results of voting for Question 2(a), unanimous no.

Question 2(b). Is temporary deferral of positive donors warranted in the setting of apheresis donation from whole blood donations for further components?

DR. EPSTEIN: Apheresis donation to make transfusible components.

DR. SMALLWOOD: To make, okay.

Corrected 2(b). Is temporary deferral of positive donors warranted in the setting of apheresis donation to make transfusible components?

Allen.

DR. ALLEN: Yes, and that's based on the assumption that the test results are known within a short period of time.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: Yes.

DR. SMALLWOOD: Davis.

DR. DAVIS: Yes.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: Yes.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: Yes.

DR. SMALLWOOD: Klein.

DR. KLEIN: Yes, assuming it's not two-unit red cell apheresis in which case it's 112 days.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: Yes.

DR. SMALLWOOD: The results of voting for Question 2(b), unanimous yes.

Question 2(c). Is temporary deferral of positive donors warranted in the setting of source plasma?

Allen.

DR. ALLEN: No.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: No.

DR. SMALLWOOD: Davis.

DR. DAVIS: No.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: No.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: No.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: No.

DR. SMALLWOOD: Klein.

DR. KLEIN: No.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: No.

DR. SMALLWOOD: Fallat.

DR. FALLAT: No.

DR. SMALLWOOD: Harvath.

DR. HARVATH: No.

DR. SMALLWOOD: Nelson.

DR. NELSON: No.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: No.

DR. SMALLWOOD: The results of voting for Question 2(c), unanimous no.

DR. NELSON: Question 3.

DR. SIMON: This is the notorious contact question.

DR. YU: Do potential medical benefits to contacts of parvovirus B19 infected donors warrant identification and notification of positive donors?

DR. CHAMBERLAND: My take on Dr. Brown's talk and when there was a little bit of discussion about this, is

that in terms of medical benefits, if you stratify it by prevention of secondary transmission, that just given the time frame, it is unlikely to happen.

So, in terms of potential medical benefits, you are unlikely to prevent secondary transmission to a contact simply because of the time considerations and the type period when there is likely to be high-level viremia that could be transmitted via the respiratory route.

However, I believe he did hold out the possibility that in selected situations, probably fairly rarely, that you might be able to have a benefit in terms of potential treatment with modalities, such as IVIG for some of the more severe manifestations of parvovirus B19.

That was my take on it. People are nodding their heads, they had a similar--

DR. BROWN: That was my intention.

DR. CHAMBERLAND: Okay. It is late in the day and I wanted to make sure I (a) heard it correctly; and (b) restated it correctly.

DR. NELSON: We have already voted yes on 1, didn't we, notify, or was that just defer? Remove the product.

DR. GOLDING: Basil Golding. Sorry, I will add it very quickly, I know it's getting late.

A clinical benefit I see for people who have HIV and are getting parvovirus infections and are getting anemia, aplastic anemia, and it is going to last for a long time, and they are going to get stem cell transplants, the doctor needs to know, so that they are not giving the wrong treatment, instead of giving stem cell transplant, as an example, where IGIV would have been much better.

The same thing, if you have a pregnant woman who had a contact early in the pregnancy, and the fetus is then getting into trouble, I think it would be helpful to know what the causation was, and an intrauterine transfusion would also be helpful.

Also, the question of arthritis where you get long-term arthritis in some woman, it would be helpful to know that it is not rheumatoid arthritis, so there are diagnostic and other modalities that are involved.

DR. SCHMIDT: I gave three reasons before why I thought no. I would just like to add to that. When we started testing for HIV, we told people not to come in just to find out if they were positive. Those are the bad guys, and we only wanted to be nice to the good guys, I guess.

An interesting situation in the UK now, they are worried about if they find a test for mad cow disease, that people will stop donating blood because they don't want to know that they are positive for this. I mean it's a switch

in the other direction. But that might change if there is some therapy for mad cow.

We have fights about whether we are doing the wrong thing by giving away free T-shirts, but also free cholesterol examinations. I just think we ought to stay out of the whole business and just do what we are supposed to do.

DR. BIANCO: Dr. Nelson, I am very concerned about the consequences of what is being discussed today. We started and actually, Dr. Simon presented it very well, with a process that was to try to make a product for patients that receive those plasma derivatives better.

Now, when we move to another way, that we created a complexity where maybe one or two contacts a year in the country will benefit from a process that will drive an entire community in the way they collect blood.

My concern is that those regulatory requirements will simply inhibit us, so instead, people get it, contacts happen at home, they happen in bed, husband and wife with a wife that is pregnant. It is rare that we have an event like Dr. Klein described. It is possible, it is plausible, but it is rare.

If those requirements are imposed, this is only going to delay the adoption of measures that could help make patients, certain patients receive or allow certain

patients to receive a safer product, because we simply are not going to do it.

It is so involved in so many requirements. Unless there is a regulation that tell us to do, and we know that that will take four or five years at least to have a pre-release screening test that would allow screening of all donors for testing for CMV, that would be an equivalent model here, is testing that is voluntary and is done in a relatively small number of units, which is what would probably be the approach to deal with those patients at higher risk.

I am just concerned about the implications that these will inhibit progress because of fear of the impact of the regulation.

DR. KLEIN: I am going to disagree with that point of view. I don't know whether it will stop testing of single units or not, but it seems to me that if you have tested individual donors, you have a test result that could, in fact, impact on health.

You (a) have a moral obligation to notify the donor of their test results; and (b) you have a moral obligation to indicate what action could be taken to prevent some infection, whether that is 100,000 of them or whether it is three of them.

If you just test pools, it becomes a moot point, but if you are testing individual donors, and you are not giving the donor that result when it may, in fact, impact upon either his or her health or someone else's, I don't think that is the appropriate thing.

Now, we are not talking about the ethical issue, we are talking about whether there is medical benefit. I think there might be a small medical benefit, but I think if you are thinking in the patient's interests, for those of us who are hospital based, I would want to do that.

DR. BIANCO: I am sorry, Dr. Klein, I agree with you 100 percent. We, in our proposal, and unfortunately, the discussion, we did not, AABB did not have a chance to present our joint program, our proposal has been for minipool testing, it has not been for individual donor screening.

If we come to the individual donor screening, even if we were doing this limited number like we do for CMV, I think it has to be communicated to donor on the basis of ethics and on the basis of medicine, and I agree with you.

But minipool is the issue today. We are discussing an issue that actually is going to impede the implementation of minipool because there is a question can we test in minipool without resolving to the single donor.

What we heard today in the summary from Dr. Meiying is that the understanding is that we should resolve those to the individual donor.

DR. SIMON: Maybe we should sort of divide this into what is and what may be, and I think right now the plasma industry does have widespread testing in order to provide safer product.

As I understand it, in order to avoid throwing out units that are perfectly good, they have in many cases gone down to the individual unit. They get this information about 20 or some days after the donor has donated and by the time you would have notification, and so forth, you would be talking about a month or so.

I think at that point, the utility of transmitting this information is extremely low, so I would hope that they would not be encumbered with this obligation for an action they have taken to make the product safer and for an in-process control because they happen to identify which unit.

I think if the blood banking organizations ultimately move to doing this, like was reported by Dr. Stramer in her Phase 2, where they are doing it along with HIV and hepatitis B before release of units, then, it becomes another factor, and I think Dr. Klein's arguments would carry much more weight.

DR. FALLAT: We are putting the scenario in Question 3, making the scenario very different from Question 1, and now we are saying it's minipools, and so we really don't know that the person that has the positive viremia, therefore, it is not going to be possible to remove that blood.

It seems to me if the only thing that is going to be done is minipools, then, we need data to find out just how big of a problem this is if you did it on single donors or resolved it to single donors perhaps more rapidly, because again if you go back to those figures, if you have 1 in 15,000 that have a high titer, and you are giving out in a year and a half, you have got 1,000 donors that are receiving high-titer B19.

I would guess that at least 10 percent of those will be people in high risk groups perhaps, but this is all guess work. I think we need that data before we can press forward with single donor identification.

DR. HEALY: Dr. Nelson, this is Chris Healy with PPTA. I just wanted to make the committee aware of a point, and that is that the issue of minipools and going down to the individual donations is really kind of a red herring here. The way that the testing is performed, the companies do have unit identification bleed numbers.

That can be accessed, whether you are down at the minipool level or whether you are down to an individual donation. What they do not have is donor identification information, but information about an individual unit, a bleed number, a unit identification number can be found out at any point throughout the process, whether you are looking at a minipool or whether you are looking at an individual donation. There is complete traceability throughout the entire process.

So, the distinction between minipool and individual donation is really immaterial here. The critical distinction is do you have a donor's name, do you have a donor's identification number, do you have the center where that person donated, and are you in a position to contact them.

That information does not exist in the current strategies used for NAT testing of parvovirus at the fractionator level.

DR. FALLAT: Would you clarify that then, is Dr. Simon correct in saying it would take 20 days before you would identify that single individual?

DR. HEALY: Yes, that is correct. It takes quite a bit of time because what we look at is from the time the collection is made to the time the individual donation is identified, the confirmation testing is done, the center is

contacted, the donor's file is pulled. They are identified. Notice is sent out to them.

By the time you add all that up, in addition to the inventory hold that is in place, and all these other measures, by the time you add that up, you are looking at quite a span of time, yes.

DR. EPSTEIN: I would like to ask Dr. Bianco a question. If testing is done on a minipool and you get a positive pool, will there be an effort or will there not be an effort to notify hospitals that they may have transfused a high-titer unit?

DR. BIANCO: That was not part of the program for the minipool, stopping at an average of 20 units.

DR. EPSTEIN: So, you would have knowledge that out of a pool of, say, 16, or 16 to 24, however the case may be, there was a high-titer unit, and the plan is not to tell the hospital?

DR. BIANCO: In that Phase 1, as we had planned, the intent was not to notify the hospital or the donor, and these would be done after the expiration of the cellular products, after 42 days of the collection.

In Phase 2, that is what Sue presented, that is a pre-release testing, and then it would be done like HIV or HCV.

DR. EPSTEIN: So, where does the scenario arise where there might be an in-date unit? It would not.

DR. BIANCO: In the minipool, in the way we proposed, it would not. If we resolve to the individual donor, then, the scenario that we are discussing here certainly would apply, but that is not the intent.

DR. EPSTEIN: Part of the issue is that there has been a moving target. You know, we hear different plans at different times. That is why the agency is focused on the question of whether we should be proactive and say that if whole blood donors are being screened, that we should be pushing toward interdicting the high-titer units either in an interim phase where it's product retrieval and lookback notification or ultimately pre-screening and upfront interdiction.

DR. BIANCO: That is appropriate. Let's say in this pool of average 20, there may be a frozen red cell. Certainly, that frozen red cell would be interdicted, but for all 20 units, not knowing which one of them is the positive one.

DR. EPSTEIN: I think that what is being overlooked here is that when you are transfusing units and you have knowledge that they may be at high titer or that they were, that drives toward a situation of lookback. You know, you want to tell the doctor that you used a high-

titer unit, and it drives toward a scenario of product retrievals from inventory.

That is the phenomenon that is driving you to work back toward the individual unit. So, you end up there, you end up either doing upfront screening as a release, in which case you identify individual units, so that you don't have to throw out dozens of units, or you end up identifying individual units because you are engaging in product retrievals or lookbacks.

DR. BIANCO: But we will do that for all the 20 units in the minipool regardless. We will lose the product.

DR. EPSTEIN: You will lose?

DR. BIANCO: The 20 frozen red cells.

DR. EPSTEIN: I am sorry. You would pitch 20-- well, 20 frozen red cells, yes.

DR. BIANCO: That is correct.

DR. EPSTEIN: But in the upfront screening scenario, if you use minipools--

DR. BIANCO: Then, that is different. If it is upfront, if it is for release, it would be treated like NAT today for HIV or HCV with resolution to the individual donor and all the actions taken.

DR. EPSTEIN: The whole idea of going from Phase 1 to Phase 2 implicitly strikes me as affirming Question 3.

Question 3 is whether you should work toward identifying individual units. Now, we are asking if you do, should you also notify, but the commitment to go from Phase 1 to Phase 2 is a commitment to break down to individual units. You are already there. The question then is should you notify.

DR. BIANCO: Oh, if we are in Phase 2, yes, I would be sitting there and saying yes.

DR. SIMON: Then, Dr. Epstein, should we then divide this also between the transfusible unit and the source plasma?

DR. EPSTEIN: Well, yes. Again, I think Questions 3 and 4 were intended to work together, and the answer for source plasma is really that it's impractical under Question 4.

DR. BIANCO: Under the scenario of the minipool for the whole blood, as Phase 1, would you include it under Question 4?

DR. EPSTEIN: Yes, I think if you in Phase 1 and you are in a scenario where you have delayed identification, then, it becomes under Question 4, yes. Again, the underlying issue is whether the goal here is to screen units for transfusion.

Now, Question 1(b) said we are not there yet, we shouldn't be taking that position, and I am saying that if,

in fact, you move to "real-time" testing at any point, you are faced with the scenario of Question 3.

DR. BIANCO: But that I think is as I affirmed even to Dr. Klein, is the scenario of all tests that we apply. I personally and my organization would have no objection.

DR. EPSTEIN: But it is not true, Celso. In CMV, you do not notify a donor. The one-time ALT, you don't notify a donor. With the one-time anti-core, you don't notify a donor. It is not automatic that we think you should notify a donor. It needs to be asked.

I have only been pointing out that to argue that we never get there because we only test pools is wrong thinking. We will end up, at some point, testing individual units at least for whole blood, and then the question becomes material whether we think we should notify.

Again, I would suggest that we do not always notify.

DR. BIANCO: I agree with you. I think that we are not distinguishing here clearly the minipool testing with no resolution of the minipool versus the individual unit testing in any scenario for the whole blood donor. Even if you have a very delayed testing for a whole blood donor to resolve to the individual unit, you certainly

would come with the ethical questions that Dr. Klein raised.

DR. EPSTEIN: I think we can disentangle this if we change it to B19 infected donors and just strike the word "identification," in other words, if you have found an individual donor is the point here.

DR. DiMICHELE: Are we talking about the donor, though, or the contact?

DR. EPSTEIN: No, no, no.

DR. DiMICHELE: The way it is framed, it is about the contact, and not about the donor.

DR. EPSTEIN: That is correct, but the issue is do the benefits to the contact warrant notifying an individual positive donor.

DR. NELSON: Right. So, you would notify the donor,

DR. EPSTEIN: What I am doing is I am removing the identification of because that is the whole issue of breaking down a minipool.

DR. NELSON: Right, exactly.

DR. EPSTEIN: So, I am splitting the issue out. If you find yourself in the situation of identifying an individual positive donor, should you notify based on potential benefit to contacts.

DR. BIANCO: If I were sitting there, I would vote yes.

DR. NELSON: Can we vote on that? Let's vote. Linda.

DR. SMALLWOOD: Question No. 3, as modified. Do potential medical benefits to contacts of parvovirus B19 infected donors warrant notification of positive donors?

Vote. Allen.

DR. ALLEN: Yes.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: Yes.

DR. SMALLWOOD: Davis.

DR. DAVIS: No.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: Yes.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: I am going to abstain because I think that notification is a due process of medical ethics and when you have a result, you need to notify the donor, and it is not because of the medical benefits to contacts.

DR. SMALLWOOD: Klein.

DR. KLEIN: Yes.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: No.

DR. SMALLWOOD: Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: Yes, under the assumption we will get to several weeks in No. 4.

DR. FALLAT: Dr. Nelson, are we going to consider the question of should we notify the recipient of a high titer B19?

DR. NELSON: That is a question we weren't asked, but theoretically, if you identified a high-titer specimen, you wouldn't transfuse it.

DR. SMALLWOOD: Results of voting for Question 3. There were 8 yes votes, 2 no votes, one abstention, and the industry representative agreed with the yes vote.

DR. NELSON: No. 4. I am ready to vote.

DR. CHAMBERLAND: Question 4, there is a lot of wiggle room. It says should donor notification be limited to settings where testing and notification can be completed within several weeks of donation.

What are people's view of what "several weeks" are?

DR. SIMON: I think the intention here would be to split--I hope I am interpreting correctly--the transfusible product situation where they are going to be doing this rather soon after donation and discriminating down to minipool individual unit versus the source plasma situation where it is going to be several weeks.

It might be clearer to say, if yes to Question 3, should this exclude the source plasma donation situation, or if that is how it is interpreted, I would say yes to Question 4. I know that several weeks is kind of questionable, but I think that is the intention, to discriminate between those two situations.

I would hope we agree that in the source plasma situation with this passage of time, that it would not be appropriate to notify.

DR. DiMICHELE: I think you could interpret that question in a different way. I mean the way you could also interpret it would be, you know, if it is past the two-week period of viremia, is it going to make any difference to the contact, if you notify them or you don't notify them.

I think based on some of the information that has been presented by Dr. Brown, I guess in some circumstances, it might still benefit the contact. It becomes a tricky

issue again the way it is stated and depending on how you interpret it.

DR. NELSON: If the contact is an AIDS patient who is now on erythropoietin, yes, it would make a difference.

DR. CHAMBERLAND: I think you are really stuck here because you can always come back to that. For some people, the rare person, there might be a potential medical benefit.

I totally share the concerns that have been raised about the implementation of this and the communication of these messages is just really extraordinarily difficult to think about, but I am no sure in all honesty that you can say, or unless people have--I mean there are ways to go about trying to model this and do all those sorts of things, these medical decision analyses, and things like that.

I don't know whether this is one of these situations where it is potentially amenable where you can try and put a quantifiable handle on it, although oftentimes in the setting of questions that relate to the safety of the blood and plasma supply, people are somewhat averse to reducing it to quantifiable estimates, but that is where I continue to just kind of get stuck at.

DR. SIMON: I think we haven't, in this discussion, talked about down sides of notification, and we are talking about a very rare benefit here, the AIDS patient, the immunocompromised who might get IVIG, which could still be considered experimental therapy, versus people are going to have consternation for no reason, get a lot of medical testing and evaluation for no reason, see the doctor, and accumulate bills they can ill afford.

So, there are significant down sides and when we are out several weeks and the contacts have already been made, it seems to me we have such elusive possible benefits that the down sides become--to me, they outweigh the benefits.

DR. NELSON: I am not sure about the down sides. A person could get a hemoglobin and if it's okay, or a reticulocyte count, if it's okay, then, the infection is over.

DR. SIMON: Those cost money. Often people don't have money for that, and there is medical-legal risks or people who don't think they have been notified appropriately. So, I mean I think there are down sides and I think the benefit here is so elusive and so minimal that I personally don't feel that, at this time level, that it is reasonable to ask the industry to make a contact.

DR. BIANCO: I would like to suggest a solution. It is not just the source plasma, Toby, it is also the minipool testing where we did not resolve to the individual donor.

What Dr. Epstein has suggested, remove identification from No. 3, I would transfer identification to No. 4. If yes to Question 3, if the donor is identified within several weeks of donations, or should notification be limited to settings where the donor has been identified within several weeks of donation, because then we focus on the individual that would be the object of that donation, can we notify the donor within a certain reasonable period of time or we miss the boat, or we did not resolve the minipool.

DR. DiMICHELE: It seems to me that Question 4 actually still refers to the contacts, which is what we answered in Question 3, you know, whether we should limit it to contacts is one issue, but I believe it refers to Question 3.

I just wanted to make one other statement, and that is, you know, when we try to resolve this on medical-ethical issues, it becomes very complicated, because the question involves expectation of the donor, expectation of donor contacts. It involves social good and ultimate

making decisions on the basis of good to society or making decisions on the basis of good to individual patients.

You know, do we develop a policy that protects the least among us or the greater good. I think this becomes a very, very complicated question. Certainly, the testing and notification policies that have gone on heretofore have certainly focused on the individual and the expectation of an individual and an individual donor, which is sort of a very individualistic approach to this philosophy, but it is a tricky question and I think we have to decide on which basis we are going to answer that question.

DR. FALLAT: Could I get a clarification? If you find something like this, do the blood banks consider that they have to go directly to the patient, and not through their physician? If you go through the physician, isn't that kind of helping resolve a lot of these ethical issues?

DR. SIMON: No, you go to the donor. The blood bank has a relationship with the donor. You have no idea who the physician is, and some organizations have the center physician assume that role, but you are definitely going to the donor.

DR. SCHMIDT: The question was about patient, not donor.

DR. SIMON: These are donors here.

DR. NELSON: The other big problem is this might be pretty frequent from some of the data that was presented.

DR. SIMON: It is only the high titer. I mean this is a hit or miss thing, which is the other thing. If somebody donates right before they hit their high titer, and their brother has AIDS, they are not going to be notified.

DR. NELSON: Right.

DR. DiMICHELE: Are we answering the question about the contacts, though, or the donors?

DR. NELSON: You are not notifying the contacts. It is the donor's responsibility if his wife is pregnant or if his roommate has AIDS, or something like that, in other words, you would educate him about what this means. The donor would almost always be healthy by the time you got to this.

DR. DiMICHELE: But we are notifying the donor based on potential medical benefit to the contact, even if it's beyond several weeks after donation. That's the question we are answering.

DR. NELSON: Right. That is the issue.

DR. KLEIN: This says within several weeks.

DR. CHAMBERLAND: Right, and so in Toby's shorthand, I mean it includes both the whole blood donors,

as well as the source plasma donors. That is what the shorthand here is for.

DR. SIMON: You are answering no, right? Yes would not include the plasma donors as I interpret it, and no would.

DR. NELSON: Because of the word "limited to."

DR. SMALLWOOD: Question 4. If yes to Question 3, should donor notification be limited to settings where testing and notification can be completed within several weeks of donation?

Vote. Allen.

DR. ALLEN: Yes.

DR. SMALLWOOD: Chamberland.

DR. CHAMBERLAND: No.

DR. SMALLWOOD: Davis.

DR. DAVIS: Abstain.

DR. SMALLWOOD: DiMichele.

DR. DiMICHELE: No, on the basis of a slightly different interpretation of the question that Toby has sort of iterated.

DR. SMALLWOOD: Doppelt.

DR. DOPPELT: Yes.

DR. SMALLWOOD: Fitzpatrick.

DR. FITZPATRICK: No.

DR. SMALLWOOD: Klein.

DR. KLEIN: Yes.

DR. SMALLWOOD: Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Nelson.

DR. NELSON: No.

DR. SMALLWOOD: Dr. Simon.

DR. SIMON: Yes.

DR. SMALLWOOD: Results of voting for Question No. 4. Six yes votes, 4 no votes, 1 abstention, and the industry representative agreed with the yes votes.

DR. NELSON: I guess that's it.

[Whereupon, at 7:00 p.m., the meeting was adjourned.]

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