DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

TWENTY-THIRD MEETING

VOLUME I

Wednesday, April 7, 2004

9:05 a.m.

Grand Hyatt Washington
1000 H Street, N.W.
Washington, D.C. 20001

P A R T I C I P A N T S

Mark Skinner, J.D., Acting Chairman

Jerry Holmberg, Ph.D.

Judy Angelbeck
Mark Brecher, M.D.
Edward Gomperts, M.D.
Paul F. Haas, Ph.D.
Christopher Healey, J.D.
William A. Heaton, M.D.
Jeanne Linden, M.D.
Karen Shoos Lipton, J.D.
Lola Lopes, Ph.D.
John Penner, M.D.
Merlyn Sayers, Ph.D.
John Walsh
Wing-Yen Wong, M.D.

Non-voting Government Representatives

James S. Bowman III, M.D.
Jesse Goodman, M.D.
Matthew Kuehnert, M.D.
Harvey Klein, M.D.
Karen Midthun, M.D.
Olga Nelson
LTC Ruth Sylvester

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. HOLMBERG: I'd like to call the Twenty-Third Meeting of the Advisory Committee for Blood Safety and Availability to order.

I've asked Ms. Olga Nelson if she would please read the conflict-of-interest statement.

MS. NELSON: This was sent to me by the Office of General Counsel. During your appointment, you may not personally and substantially participate, such as recommend, influence, or decide in official committee matters in which you, your spouse, your minor child, your general partner, or an organization which you serve as an officer, director, trustee, general partner, or employee as a financial interest. That's for each committee member.

Is that what you had in mind?

DR. HOLMBERG: Yes, that's fine. Thanks.

Dr. Brecher, would you like to make a statement?

DR. BRECHER: Thank you, Jerry.

Because this meeting revolves around the

question of bacteria contamination of blood, platelets specifically, and because of my position as an expert in this area and the fact that I have received grant funding from virtually every company that is interested in this area or served as an ad hoc consultant to these companies, in order to avoid any perception of conflict, I am going to recuse myself as Chair. Mark Skinner will chair this session, and I'll basically recuse myself from actively participating in this meeting.

That said, I do want to say that I have no proprietary interest in any of these products. I have no shares of stock, nor does my family. In fact, the only shares of stock my family have is each of my girls has one share of Disney stock.

[Laughter.]

DR. BRECHER: However, if there are any specific questions that the committee would like to put to me in my role as an expert in this area, I can answer those questions.

Thank you.

DR. HOLMBERG: Thank you. We're pleased

to have Mark Skinner as our Acting Chair for this meeting, and between Mark on one side and I on the other side, we'll try to make sure that things are guided smoothly, and I'm sure that he will do an extremely competent and great job.

I'd like to make a roll call at the present time. Mark Brecher?

DR. BRECHER: Present.

DR. HOLMBERG: Larry Allen?

[No response.]

DR. HOLMBERG: Judy Angelbeck?

DR. ANGELBECK: Present. And can I just make one other statement, Jerry?

DR. HOLMBERG: Yes.

DR. ANGELBECK: As we discussed on the phone, I am a conflicted member of the committee since I am an employee of Pall Corporation and will be presenting today.

DR. HOLMBERG: Thank you.

Celso Bianco cannot make it today. I have received e-mails from Celso, and he is recovering very well. Many of us went through that difficult

time with him, and I'm sure that many of you lifted up many prayers for him. He in his e-mail thanked everybody for their concerns and also mentioned that he hopes to be back in play by the end of the month. So we know that Celso will be missed today at this meeting.

Ed Gomperts?

DR. GOMPERTS: Present.

DR. HOLMBERG: Paul Haas?

DR. HAAS: Here.

DR. HOLMBERG: Christopher Healey?

MR. HEALEY: Here.

DR. HOLMBERG: William Heaton?

DR. HEATON: Here.

DR. HOLMBERG: Jeanne Linden?

DR. LINDEN: Present.

DR. HOLMBERG: Lola Lopes?

DR. LOPES: Here.

DR. HOLMBERG: Garji Pahuja?

[No response.]

DR. HOLMBERG: John Penner?

[No response.]

DR. HOLMBERG: Jerry Sandler?
[No response.]
DR. HOLMBERG: Merlyn Sayers?
DR. SAYERS: here.

DR. HOLMBERG: Mark Skinner?
MR. SKINNER: Here.
DR. HOLMBERG: John Walsh?
MR. WALSH: Here.
DR. HOLMBERG: Wing-Yen Wong?

DR. WONG: Here.
DR. HOLMBERG: Karen Lipton?
MS. LIPTON: Present. And could I also just state for the record that, after discussion, we were considering whether I should recuse myself from discussion today. It's my understanding that the discussion today will focus not on the AABB standard but on implementation of bacterial testing, and so it would be appropriate for me to continue to participate as a committee member.

DR. HOLMBERG: Yes, ma'am.
Okay. Non-voting members: Dr. Epstein could not make it for this meeting, and so in his

place we have Dr. Jesse Goodman, who is the Director of CBER. He will have to be leaving later today, and Dr. Midthun will be sitting in his place.

Dr. Klein?

[No response.]

DR. HOLMBERG: Jim Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Matthew Kuehnert?

DR. KUEHNERT: Here.

DR. HOLMBERG: Ruth Sylvester?

COLONEL SYLVESTER: Here.

DR. HOLMBERG: Did I miss anyone?

[No response.]

DR. HOLMBERG: Okay. Thank you.

I'll turn it over to Mark Skinner, please.

MR. SKINNER: The first item of business today is to recognize Dr. Holmberg, who is going to review the previous actions of this committee.

DR. HOLMBERG: Our January meeting was conducted on January 28th and 29th, and as most events here in January, weather was very

unpredictable. So we did have a cold meeting, but we got a lot accomplished.

The topic of that meeting was the role of the government in the national blood supply, whole blood and plasma, plasma fractions, both in daily medical/surgical use and local/national disasters.

What we looked at what the National Blood Policy of 1974. We also looked at how other national blood programs were developed in other countries, with overview by Dr. McCullough, and Canada, Israel, and the U.K. presenting their programs.

We also had a presentation from the National--or the Interorganizational Blood--I'm sorry, the AABB's International--Interorganizational Task Force--I'll get it right--on the National Blood Reserve, and I'll be highlighting some of those issues.

The Interorganizational Task Force on Domestic Disasters and Acts of Terrorism prepared a plan for the National Blood Reserve to respond to sudden and unpredictable civilian or military needs

from loss of donors or donations or increased use. Again, there's a typo there. Sorry.

The National Blood Reserve was a combination of government and private sector control, primarily looking at 2,000 units controlled by the government, held by government through the DOD, and 8,000 controlled by government, coordination by the Interorganizational Task Force, but held in regional blood centers.

The concept was explained to us as a surge capability with the DOD having the initial surge and the private sector having also a surge capability to have about 10,000 units available to be able to move into two major cities, and then the sustained support would be the adequate or the effective information exchange back to the blood centers to recruit donors and to build up the blood supply.

I have to say that in the interim of two months, we have presented this to the Acting Assistant Secretary for Health, Dr. Beato. We are moving ahead on some of these concepts. One of the

things that the committee has to understand is that, as each one of your organizations has to face a financial budget, we do also. And so we are looking at ways that we can support this and implement a National Blood Reserve.

At this time I don't have specifics how we would do it. We are taking the recommendations from the committee, and we are moving forward with those recommendations. Hopefully by the August meeting we will have more specifics for you.

I didn't see that. I thought I was building on a slide.

The recommendations from the committee were to take steps to increase the national daily availability to five to seven days, fully fund the DHHS Blood Action Plan in the area of private and government monitoring, and to increase the blood supply; and also to address funding needs at all levels of the blood system to support product safety, quality, availability, and access through targeting of additive resources and appropriate reform to the CMS reimbursement system for blood

and blood products, including plasma-derived therapies and their recombinant analogues; also to establish a National Blood Reserve consistent with the committee's recommendations of January 2002 by increasing daily collections through an enhanced program to expand and sustain volunteer donations. The committee endorses the element of the National Blood Reserve as developed by the AABB Interorganizational Task Force.

With that, I'll turn it over to Captain McMurtry to explain a little bit about our blood monitoring.

CAPTAIN McMURTRY: Good morning. I'm Mac McMurtry. I think I may have met a few of you in the past. I'm glad to be here to visit with you this morning. I want to talk about the blood monitoring. You realize or you know that this has been a gleam in everybody's eye for quite some time.

As you are aware, there was a recognition that there needed to be some sort of blood monitoring as far back as the 1960s when Doug

Serginore (ph) and Ted Wallace started a monitoring program. It was good for what it was; however, it was a very lengthy process. Some years they had funding for it; some years they didn't. And, over time, it just turned out to be not a practical plan.

The AABB and the National Blood Resource Center, of course, have done a lot of work with monitoring the blood supply. The annual survey that AABB does is sort of the gold standard for the amount of blood that's transfused in the country each year. But, once again, that's something that comes out once a year, and clearly, if it comes out once a year, it's not timely information. It's not the sort of information that the Department's looking for to make sort of on-the-fly decisions.

The FDA has come up with their plan, TransNet. TransNet certainly has its advantages. It has its disadvantages. It is a very good plan, one that the Department has considered at length, and, in fact, as we move forward with a monitoring plan, we're going to adopt a lot. I think we're

going to probably just take the whole thing over and fold it into our emergency response plans.

So, as I said, the TransNet system is very good and will be used in the future. And then there's the HHS Sentinel system. This is the plan that we've been working with now for about three years where we have 29 Sentinel sites throughout the country. Primarily they're hospitals with three transfusion centers. We receive daily blood inventory information from them. And while this is not a representative sample by a long stretch, it does illustrate variations in the blood supply. It was up and functioning in August of 2001, so when we had the 9/11 attack, we were able to illustrate very nicely what the blood supply did and how it--what the level of it was for the 42 days before the blood began to outdate.

What we have devised now is a new system, a representative sample of hospitals and blood collection centers, and we're calling it BASIS, the Blood Availability and--Blood Availability and Safety Inventory System. I'm sorry. I don't know

why that's not rolling off. I normally can say it fairly easily.

We're going to be collecting sample blood data--we're going to be collecting data from a representative sample of blood collection centers, and what I have got here is the table that we're using to explain what the stratification is that we're using to collect--to determine blood centers. We're looking at the number of units that the collection centers collect within a year's period of time and then taking--we have--let me back up.

We have contracted with Economic Systems, Incorporated, to look at our plan or to look at our program and devise a way to get a representative sample of collection centers and hospitals. And they have told us that of the collection centers that collect this amount of blood each year, we need two of those, and then right on straight through, so that we end up with a sample of 37 blood collection centers.

With the hospitals, we're using the American Hospital Association survey. We're using

the number of surgeries performed each year as a surrogate for the amount of blood that's used because we don't really have a correlation between surgeries and number of transfusions yet. So, as I said, the number of surgeries is what we're using to stratify.

It's interesting to me--and I don't really understand it, but there are a certain number of hospitals that respond to the AHA survey where they don't list the number of surgeries that they perform. So we have a category that we're going to collect of hospitals that we don't know how many surgeries they do. We have a low on up to a high number of surgeries. We're going to end up with 131 hospitals in that sample.

That will give us, what they tell us--and we believe it to be true--a sample of hospitals and collection centers in the country that will describe the universe very nicely. And so any conclusions that we draw about the blood supply should be accurate, with a 95-percent confidence interval.

In the past, with the Sentinel system what we have done is collect information on all blood types. We are told--and we believe this--that we don't need to have all blood types; that if we simply get information on Os and then this information on platelets, that will describe the blood supply quite nicely, also. What we'll collect, we'll collect different information from the hospitals than we will from the blood collection centers.

I have this--actually, this chart is a little out of date. We have a line here for wastage. We're not going to collect that information. But we will be collecting the rest of it. And that should be enough to tell us what we need to have to make conclusions about the blood supply.

We're also going to look at some qualitative data elements. There's going to be input fields where we will ask if surgery was delayed, was an order not filled completely. If that's the case, was the blood product purchased

from an alternate supplier? Was a non-standard protocol used in patient care because of shortage? These shortage comments have proven to be very valuable to us in the past, and we're going to continue to collect this sort of information.

When are we going to do this? Well, that's the big question, isn't it?

It is our intent to begin to phase this program in starting this year with a phase-in of blood collection centers, and then in next fiscal year we hope to phase in the remaining transfusion services, the other hospitals, which is another 103, something like that, that will come in next year.

I wanted to put up here what our principles are. What is BASIS going to do? We want to gather data that can support broader, longer-term assessments of the status and direction of the nation's blood supply and improve the knowledge base underlying consideration of departmental policy decisions.

There has been some thought about BASIS

and it having some added value for the reporting sites, and we've gotten conflicting messages on that. Some hospitals that are Sentinel sites now and report every day, they think this is wonderful, some of them do, because it tells them about blood usage that they weren't aware of in the past, and they use it as a tool on a monthly basis. Others don't see that value in it. The value in it for us is that it gives the Assistant Secretary of Health information about policy decisions made by the government.

One of the things that I want to stress is that the Assistant Secretary for Health is the national blood safety officer. Decisions about blood policy rest with her, and this gives her information that she can use on what's actually happening with the blood supply so that these policy decisions can be made.

An example of this is we have contractors and servicemen coming back from Iraq and Afghanistan. There's a leishmaniasis deferral for a year for those people. What's that doing to the blood

supply? Do we really know? I'll tell you the answer to that is no, we don't know what that deferral policy is doing to the blood supply.

We're involved in a discussion today about platelets. What is the new policy doing? How is it affecting platelet supply? We don't know. We don't know. It's our hope that with a fully functional BASIS operation going that we'll have answers to questions like that. Does this new AABB policy or the new bacterial detection policy affect platelet supply? What is leishmaniasis doing to the blood supply? And then in a minute, we're going to talk about a national blood policy, and we think that a monitoring program--we don't think. We know that a monitoring program is essential to any sort of national blood policy.

Let's see. There's a thing that BASIS doesn't do, and our plan is that it is not intended to support a regular direct governmental involvement in the day-to-day operations and decisions of blood centers, hospitals, and/or community transfusion services. I want to be real

clear about that. This is not a way for the government to meddle in the affairs of blood centers around the country. That's not our intent by any stretch of the imagination.

What we're hoping is that it will generate data to enhance discussions and decisionmaking broadly across the entire blood community, whether it's within the government or outside the government. There will be a good, strong database that people can use in their discussions about blood policy.

Another thing that BASIS will do will help with critical instant response. This actually is a fairly nasty slide so let me explain what it is. None of the print works.

This is a schematic of what we intend for BASIS to do. We're going to be collecting inventory data from hospitals and blood centers. The information that we collect here will go into a secure Web input. That then will be aggregated and transmitted into a database. This is the day-to-day, routine inventory information that

we're looking for. I'll explain this in a minute.

This database then will generate output reports, which is here, and these output reports will go to our office and the Assistant Secretary for Health, and this will be updated--this whole stream right here will be updated every four hours so that we're aware of fluctuations in the blood supply. As I said, this is the day-to-day, routine blood monitoring.

This side over here is in the event of a critical incident. This database, the information in this database will translate--does translate or transfer over to the database that's maintained in the Secretary's command center. The fact is this is just a mirror of this one. This will be available in the command center, once again, updated every four hours.

In the event of an event, affected areas, regardless of where it is--whether it's some hospital someplace or--what was it last night? There was a train wreck in Jackson, Mississippi. So if there's a problem in an area, we will

actively go to that area and ask them to input data. We'll give them a password where they can load onto the website and put their information into this secure website. This goes in and mixes with the day-to-day monitoring, comes down to output reports, and then, once again, goes to our office and the Assistant Secretary for Health so that if we have to make decisions about blood supply issues, that can be done down here.

What kind of decisions would we make? Well, back this past summer, we had a shortage issue. We got the Secretary of Health and Human Services to roll up his sleeve, and there were lots of cameras there. He made an appeal for donations. Apparently, people came out and the blood supply came back up. So these are the sort of things that we're expecting out of this right here.

And then, as I said, there's a National Blood Reserve. As Jerry just reviewed with you, this is the recommendation from last time that we establish a blood reserve. This is a critical part right down here that we need to increase the

national available inventory to five to seven days.

There's also the issue of ad campaigns, trying to get more people to come out and donate blood. That's what you need to do if you're going to increase the available inventory. But what is a five- to seven-day inventory? We're in a position right now that we don't know what a five- to seven-day inventory looks like.

There are studies that have been done--and I think you can probably see it yourself in your individual sites--that as supply goes up, demand goes up along with it, and they kind of go up together. So if you demand following supply, how do you know what a five- to seven-day inventory is? And then you add in the effect of any sort of ad campaigns that might be out there. Does that really increase--you can probably count and see if it increases donations, but does it actually increase supply? We don't know. And so we're hoping that with BASIS we'll be able to actually see a five- to seven--we'll be able to see what a five- to seven-day supply looks like?

So, anyway, we're hoping to get that implemented beginning this year with our phase-in and then the rest of it following in the next fiscal year.

So, anyway, that's it with the update on monitoring. If you have any questions, I'll be happy to answer them.

MR. SKINNER: Questions, Jeanne?

DR. LINDEN: Just a request. The tables didn't print out on the handouts of the slides. Would it be possible for the committee members to get a copy of those tables?

CAPTAIN McMURTRY: You bet.

DR. LINDEN: Thank you.

MR. SKINNER: Colonel Sylvester?

COLONEL SYLVESTER: On your system, it updates every four hours. Is this manually entered data?

CAPTAIN McMURTRY: Right now it is. There's a gleam in our eye that we'll be able to do, not a direct link but the plan is for the reporting sites to be able to dump into a file that

can then be accessed by our server.

There's a reluctance on the part of a lot of folks to have the government computer tap into the local computer. The IT guys get real skittish about that. So if we dump into a separate file, they're happy with that. That's what we're hoping to do.

MR. SKINNER: Dr. Holmberg?

DR. HOLMBERG: I just wanted to make a point of clarification. The update every four hours is primarily because it will not be entered at set times by all places across the country in different time zones. And so we want to be able to capture that throughout the day.

At some point in time during the day, it will be stabilized, the data will be stabilized, and we're working through some of the advantages of that.

However, one of the things I would like to make a point of clarification on is that Captain McMurtry mentioned as far as what would we do with the data. The data will be used to make decisions

in working with the AABB's Interorganizational Task Force. So I didn't want to give the perception that, you know, government is going out there doing their own thing and trying to control the issue.

The Assistant Secretary for Health is responsible for the blood activity within the country, and she would definitely be working with the AABB Interorganizational Task Force.

As we mentioned at the last meeting, this has to be a government/private sector endeavor, especially with the blood reserves.

MR. SKINNER: Jeanne?

DR. LINDEN: In terms of critical events, I understood you're talking about would occur at sites that are not part of your random--or, excuse me, representative sampling.

CAPTAIN McMURTRY: That's correct.

DR. LINDEN: So can you elaborate a little bit on how you would enroll these sites that are not set up to be communicating with your system, keeping in mind that communication systems may not be completely functional, so I assume you have

backup systems arranged. Can you just tell us a little bit more about what you have set up in your plan for that to get these sites able to communicate?

CAPTAIN McMURTRY: I wish I had my favorite cartoon. It's one that I just love. It shows this university president-type guy talking to two scientists with the Einstein hair and the lab coats, and on a blackboard there's a bunch of figures on one side and a bunch of figures on the other side, and in the middle it says, "Something magical happens." And one says to the other, "Somehow I was looking for something a little more specific."

We are aware that there can be some communication problems, and so that's one of the things that we're beginning to address, to figure out how we would get data in.

Setting that issue aside, the intent is that--and let's just use this train wreck last night. Let's say that we have a lot of casualties there. What we would do is identify the affected

hospitals and blood collection centers in that area. We would actively call them up on the phone, ask them if they would contribute data to the command center, give them the passwords necessary to log into BASIS, and then we would ask them to update on a regular basis--I keep using "basis" as a word and then "BASIS" as a name. But you understand.

So we would ask them to input data at regular intervals so that we would be able to know what's going on in that area to see if there was any action that needed to be taken in conjunction, as Jerry said, with the Interorganizational Task Force.

There might be things that need to be done. There might not be things that need to be done. But we would know without it being a helter-skelter arrangement.

MR. SKINNER: Karen?

MS. LIPTON: Jerry, I very much appreciate, and you, too, Mac, talking about coordination. The one thing we do have in place

now is an ability to communicate immediately, and we have a number of default mechanisms that allow us to get in contact when everything goes does, which it invariably will. But perhaps we could make sure that we coordinate on that end so that we're both not trying to collect information from blood centers and hospitals in this situation, because that actually is something that we do routinely in these situations.

MR. SKINNER: Other committee comments or discussion? Dr. Sayers?

DR. SAYERS: I'd like to say something promoting the value of knowing the availability of the national blood supply and endorsing the concept of BASIS. Some of us here were present at Blood Products Advisory Committee meetings and Transfusion Spongiform Encephalopathy Advisory Committee meetings when the whole concept of geographic deferral for donors who might have been exposed to variant CJD was being discussed. And what was disappointing was that when the deferral period for those donors was under discussion, it

became very obvious that some of those advisory committee members wanted to know how much additional donor deferral actually could be tolerated. And that was an important consideration when the decision was, well, shall we defer individuals who've spent two months overseas or should we defer individuals who've spent eight months overseas, when those discussions were on the table.

Alan Williams put together information for the TSEAC to review in deciding how long those deferral intervals should be, and it was obviously earnest information that he put together, but it was incomplete because we really did not know how robust the national blood supply was at the time. Had we had the information that BASIS might have been providing, I think we would have had a better handle on being able to satisfy committee members' needs to know what that deferral inventory should be without at the same time jeopardizing the availability of the blood supply by being too aggressive in deciding how long that overseas

period should be before donors earned deferral.

I think had we known some of the BASIS information back then, we probably would have been able to make better decisions when it came to deferring donors to reduce the hypothetical risk of variant CJD transmission.

I didn't intend that to be a sermon, so I apologize.

MR. SKINNER: Captain McMurtry, I'd like to ask you a question. Is the intent of this system at some point designed to be able to provide prospective answers? The scenarios you've talked about are going to give us a retrospective answer in terms of what's occurred. You posed the question originally in today's discussion we don't know what the impact will be of the bacterial contamination changes, which really is forecasting into the future. Can this system help us answer those questions as well?

CAPTAIN McMURTRY: It depends on who you talk to. No, actually, we feel that with a representative sample that we're going to have, and

as large a representative sample as we're going to have, once we establish a good, solid baseline, we can do a lot of predictive studies with this program.

MR. SKINNER: Other discussion?

[No response.]

MR. SKINNER: Thank you.

At this point the committee will turn its attention to CMS, and Dr. Bowman is going to give us a overview and update us on some of the issues related to the Medicare Modernization Act.

DR. J. BOWMAN: Hi. My name is Jim Bowman. Does everybody have a copy of the three-page paper handout that was available at the door? If anybody doesn't have a copy, raise your hand and I'll...

It'll be a little difficult to follow the music with the handout. It's probably going to be difficult to follow the music with the handout. But we'll try to stumble through that. As Captain Mac said earlier, when a bill gets passed by Congress, something magical happens, but I think

you're probably interested in more specifics, and that's basically what I'm going to try to do for you in the next few minutes.

Many of you are much more knowledgeable about specific sections of this bill than I am. I recognize that. And to the extent that you identify any inaccuracies, please point them out to us at the end of my discussion so that we can get it on the record.

There's a lot of background material that will be posted on the website for the committee meeting and also in your handbook. We're not going to go over that at this point because of time limitations. So that's why I have the paper handout.

The paper handout is not an official document. The Department and CMS has some very specific information that is available on the website that identifies and addresses the Medicare reform bill, which is now officially called the Medicare Modernization Act, or MMA. And I refer you to that for specific details of the overview of

the bill itself. I primarily want to address issues that most of you are interested in, which is how payments for blood products are affected by this bill. And so that's what I'm going to confine the discussion to at this time.

The bill itself is about 674 pages. If you count the front page, the inside cover, the backside cover, and the back page, 678 pages. I brought a copy along for everybody to see. It probably weighs about five pounds. It's a fairly hefty document. This is all double-spaced and single side. So if you put two sides to a page, you can reduce it a little bit.

You can access the bill on the CMS website, the URL address in the handout, and there's numerous other ways to access it, also. I would encourage you not to print it out. You'll probably go through $10 worth of paper, ruin your toner cartridge, and you may even break your printer if you do that. But you can certainly--it's a PDF file, and you can certainly print out specific sections of it to work with.

I'd also call your attention to another document that's available that is fairly helpful. It's call the "conference agreement." The conference agreement is a document that's put out by the Congress, and it basically summarizes in a fair amount of detail the intent of Congress, especially the conference committee, when the bill was passed, for each section of the bill. In each section, it addresses the current or present law prior to passage of the bill. It addresses in detail the House version, the Senate version, and then the agreed upon conference agreement that appeared in the final bill.

It does provide some detail and some insight into the intent of Congress. I would point out that it doesn't have the force of law that the bill itself has. And so that is another useful document.

Now, on the handout, the very first page is a fairly mundane and dry list of sections of the bill. It has a number of titles, Title I through, I believe, Title XII. And the reason I put these

there is just for your information so you won't get confused with the Social Security Act, which also has titles. In particular, Title XVIII of the Social Security is the title that authorizes the expenditures for the Medicare and Medicaid programs. So I just want to make sure people do not get confused about that. The new Medicare bill, MMA, has a number of sections. I believe it goes up to--I'm not sure--1,200 or so. But they're not all sequential, so there are certain sections that are dropped out in the conference agreement. So you won't see 1, 2, 3, 4. There may be some gaps. It doesn't mean they left anything out in the final bill when you see it printed out. It just means that those were not included in the final bill.

I'd ask you to take a look at the second page or the back of the first page on your handout. I want to provide some clarification because when we talk about payments for blood products, we're really talking about several different things. There's blood, which, you know, comes right out of

your vein when you bleed. Okay? That's whole blood. And I'm not meaning to, you know, talk down to anybody. Like I said, I want to try to get us all on the same page and singing from the same tune, if we can, even if it's a very simple tune.

The payment can be affected by whether it's blood, whether it's a plasma-derived therapy agent, or whether it's clotting factors. And even under clotting factors, a lot depends on certain payment systems as to whether it's a natural clotting factor that's derived originally from blood or whether it's recombinant and is not in any way at all associated with blood. So I just want to get that out in the open to begin with.

Basically our payment systems under the Medicare program depend on where the services are rendered and by whom. And so, for instance, blood primarily is provided in the inpatient hospital setting in acute care hospitals. At least the vast majority, more than 90 percent is. And that's a certain payment system. There's a certain authorization in the Social Security Act under

Title XVIII for that. And there's certain specifications of the way that's paid. Most of you are familiar with that. It's under the DRG system.

The hospital outpatient department is another setting, and, by and large, a good portion of the blood that is used in blood products used in the hospital outpatient department fall under the Hospital Outpatient Prospective Payment System, sometimes called HOPPS--not to be confused with the beverage category. And our division director over at CMS, Cindy Read, is going to address some of those issues in a few minutes.

Finally, there's the physician office setting, which is another setting that sometimes we find blood and blood products provided. And that's provided for under completely separate authorization, which is the physician fee schedule. It's provided for under a different section of Title XVIII of the Social Security Act. So those are three separate settings, and I'll try to run over those very briefly. And I provide a fair amount of background material under each section for you to

refer to later on.

Now, when we get into the MMA provisions, some of the payments are going to be determined by when this service is furnished. For instance, if it was furnished in 2003 or prior years--of course, that's before the MMA was passed. It was enacted December 8th of this past year, and most provisions don't start until, obviously, January 1, 2004. And a number of them start January 1, 2005, and January 1, 2006, and thereafter. So there are certain special provisions written into the bill to allow for a transition, if you will, for some of the payments for blood products. We'll get to those in just a few minutes. I don't want to say much about the inpatient hospital setting for blood transfusion payments because those are not really changed much at all by the MMA provisions.

Now, having said that, there are some significant changes for the hospital inpatient payments in general under the MMA, and I've listed a few of those. There's a lot of additional monies that are going to be infused--sorry for the

pun--into the hospital systems, but not specifically for blood products. So I want to make that clear.

The second setting I want to address, which some people think may be the most confusing, is the physician office setting. And that should be on the second page, I think, the second full page. I'm not going to go into the verbiage. That's just to provide some background information for you to refer to later.

Primarily the blood and blood products do not have a specific benefit written into legislation. However, most of the services that are provided in the physician office setting would be considered incident to the physician service. And that's where a lot of the payments are made for a lot of different kinds of services and products within the physician office setting, and that's where blood falls.

Now, the main sections that address this in MMA are Section 303(b), and basically what Section 303(b) does is it amends a section--and

again, we're getting confused somewhat because we're talking about sections of the MMA and then sections of the act. But it amends Section 1842(o) and then the paragraphs that fall under 1842(o).

And it amends these areas which address payment and physician office setting.

By and large, currently these products are provided in the physician office setting, 95 percent of something called AWP, which all of you are familiar with--average wholesale price. Most of you are aware it's not necessarily an average, it's not necessarily wholesale, and, actually, it's probably not necessarily a price. But, anyway, that's the way it's written right now.

That's going to change. The first thing that's probably most important is that it will stay at 95 percent AWP for certain categories of blood and blood products, and that's listed toward the bottom of that page. I'm not going to read all these off to you, but primarily these relate to products that are provided in the year 2004, our current year. Blood clotting factors are listed.

It does address certain vaccines and certain separately billable dialysis drugs that fall under the End-Stage Renal Disease program, which is a separate authorization.

Now, the next section toward the bottom there is that the blood and blood products are actually excluded, if you will, from most of these provisions. If you turn to the back of that page and look under paragraph (f), which is toward the top of that page, I put the quotes there directly from the act. What it says is, "In the case of blood and blood products, other than blood clotting factors, the amount of payment shall be determined in the same manner as such amount of payment was determined on October 1, 2003." Basically there's no change for the blood and blood products.

Clotting factors are put in parentheses there, and that's because it was the intent of Congress not to include that. And so clotting factors will fall under the rest of the changes to Section 1842(o).

There are certain provisions for payments

in 2004, and then payments afterwards fall under some changes to Section (o), which is the addition of a new paragraph, which is paragraph (4). And we're still toward the top of that page. You'll see a section where it says, "The default amount is 85 percent AWP, as AWP is defined on April 1, 2003." Okay.

Then there's a section right after that that says that except for the defaults, there's a Table 3 in the Federal Register that was published on August 20, 2003, and those percentage of AWP are the ones that will apply. So the default will apply if it's not listed in Table 3 of the Federal Register on August 20, 2003.

Then, finally, the Secretary may substitute other percentages, and that's based on some data and information that is supplied by the manufacturers to CMS prior to January 1, 2004. Well, it's obviously past January 1, 2004, so that probably doesn't help the manufacturers at this point. But any information that was supplied, the Secretary will take that into consideration, and at

any rate, it would not be less than 80 percent of AWP.

Now, we get into the bigger changes, which is something called the average sale price methodology, and we're about midway down the page. And this is a new section that's added to the Social Security called Section 1847A, and this is going to become effective beginning January 1, 2005. That's next year.

Basically what it does, it pays physicians a premium of 6 percent over an amount that is determined to be the acquisition cost for the physicians. In other words, the physicians are going to get 6 percent, if you will, to cover overhead, office expenses, and things like that.

Now, I would clarify that physicians also receive separate payments for actually infusion services themselves. That's a whole separate issue that's addressed by both CMS on an annual update basis as part of the physician fee schedule and also within the bill. But in terms of the cost of the drugs themselves, what we call the average sale

price as defined in the act, which is also--the methodology is actually described in the bill itself. The physicians will get a premium of 6 percent.

There basically are two types of drugs that are considered the multiple-source drugs and single-source drugs. There's details in the bill itself that describe how those average sale prices are determined. In the case of a single-source drug, actually it's the lesser of the average sale price or something called the wholesale acquisition cost, which, again, is described in the bill itself.

Now, there's another section that's added just after that called Section 1847B, and this is a section that basically is termed "the competitive bidding section" or "competitive acquisition."

First let me say that physicians do not have to choose to be paid or reimbursed under Section 1847B. They're allowed to revert back to the default system, which is Section 1847A, primarily. But that's up to the individual

physician for him or her to decide.

This will become effective January 1, 2006. It's basically a section where there's certain methodologies set up for different geographic areas of the country for identifying competitive bidding for certain drugs and biologicals.

There's a lot of details to be worked out. There will be some contracts that will be awarded based on competitive bidding. There has to be at least two bids. There are some other details involved with that section.

I would point out, there's a section in the bill--and that's down at the bottom of that page--that's called "exclusion authority." Basically it states, "The Secretary may exclude competitively biddable drugs and biologicals, including a class of such drugs and biologicals, from the competitive bidding system under this section. If the application of competitive bidding to such drugs or biologicals," and then it follows one of two separate criteria, "is not likely to

result in significant savings or is likely to have an adverse impact on access to such drugs or biologicals." In which case, if the Secretary so determines, then the payment for these agents and products will revert back to Section 1847A methodology.

So the competitive bidding is an option that physicians may or may not choose, at their choice, and also there's exclusion authority that we should be aware of.

The final section I want to cover is the Hospital Outpatient Prospective Payment System, OPPS or HOPPS. It's kind of complicated. I'm not going to go into the details of how it's currently paid for right now. Cindy Read is going to address some of these issues in a few minutes.

Prior to the passage of the MMA in December, Medicare basically paid for drugs in the outpatient hospital setting under three different methods. Primarily most drugs are basically bundled or incorporated into the payment for something called an ambulatory payment category,

which is--essentially it's a DRG for the outpatient setting, okay? DRGs came into the inpatient setting back in 1983. The ambulatory payment categories, APCs, came into effect as a result of--somebody help me here. It was several years ago under one of the acts of Congress. So it was as prospective payment system for the outpatient setting.

However, certain drugs were recognized as being high cost at the time of implementation of the Outpatient Prospective Payment System, and they were given something called transitional passthrough status or transitional passthrough payment.

And then there were certain others that even though they didn't qualify or meet the criteria for transitional passthrough, separate APC categories were identified and created for those drugs and products.

The most obvious--I think a lot of you are familiar with it--is whole blood and fresh blood products themselves--not fresh blood but cellular components of blood, are actually paid for with

separate APCs in the outpatient section.

Now, the new bill does make some changes to this. For one, it classifies radio-pharmaceutical as, in quotes, "specified covered outpatient drug," which basically qualifies it for a separate APC payment. It also makes those drugs or biologicals paid as passthroughs on or before December 31, 2002, also specified covered outpatient drugs. Now, these two classes of drugs are going to be paid in a very specified way, according to the MMA bill, and what I placed halfway through the page there is where it says "product type," there are several types. There's a sole-source product, there's multiple-source innovator and multiple-source non-innovator. Those are defined very specifically in the bill itself. And then the payments are going to fall within ranges, so there's upper bounds and lower bounds on the amount of percentage of AWP during 2004 and 2005 that those drugs can be paid at.

Beginning in 2006, all of these products will be paid an average acquisition cost, and,

again, average acquisition cost is a payment amount that's determined very specifically under a methodology defined in the bill itself. I included some background information regarding the multiple-source and the sole-source drugs themselves and the specifications for biologicals, just for your information.

Now, finally, I want to call your attention to two sections of the MMA, and that's on the last page of the handout, the very back page.

One is Section 303(e) of the MMA, and basically it provides a mechanism for the Secretary to make some adjustments in blood clotting factors payments. And what it does is it relates back to a report to Congress that was made in January 2003 on the payment for blood clotting factors, and it prescribes some options for the Secretary, which, of course, will end up being done by CMS, for determining separate payments for certain aspects related to administration and preparation of the clotting factors. And I wanted you to be aware of that.

Then, finally, toward the bottom of the page, I want to call your attention to a section in the MMA conference agreement, which, again, is sort of the document that accompanied the bill from the Congress, that, again, provides an intent of Congress, although it doesn't have the force of law. Basically it says the Secretary is directed to compile and clarify the procedures and policies for billing for blood and blood costs in the hospital inpatient and outpatient settings, as well as the operation of the collection of the blood deductibles.

Dr. Holmberg has already been in touch and made several visits to CMS with our staff there to begin at least the preliminary legwork for accomplishing this.

And then at the very bottom, in bold print, I want to call your attention to the disclaimer because, again, this is not an official CMS departmental or Federal Government document or paper. There's no liabilities or consequences that the Federal Government will incur because of this,

and there could be inaccuracies. So I would encourage you to consult your trusted sources before making any determinations or decisions based on this information.

Having said that, the staff at CMS are certainly available and willing, obviously, to work with anybody who is concerned or has issues to address regarding blood and blood products payments. That's what we are there for. If we weren't, we wouldn't need our jobs. And so our telephone lines are open, and you are more than welcome to address us by e-mail. I think the my e-mail is in the handout. If it isn't, you certainly can get that from Dr. Holmberg. And I think that will conclude my section for now.

Jerry, do you want to let Cindy go first before we have any questions or would you like me to--

DR. HOLMBERG: Why don't we take committee questions and discussion now and then we'll hear from Cindy. Let me just ask the first question, if I may, for purposes of just understanding.

The section that relates to competitive bidding and the opportunity for exclusions from that, could you comment on what the current thinking is or what the current status is of competitive bidding for blood and blood products?

DR. J. BOWMAN: The way I understand it, because of paragraph (f), which was addressed earlier before we got to the competitive bidding section--and this is under the physician payment section--blood and blood products, it says the payment amounts will be determined as they are as of October 1, 2003. I haven't consulted anybody at CMS because, for one reason, competitive bidding will not take effect until 2006, so this is fairly deep into the weeds of that.

But based on that section, paragraph (f), it looks like blood and blood products other than blood clotting factors are excluded from Section 1847B, which is the competitive bidding section.

I'll try to find somebody who can confirm that for me and get back to the committee on that.

DR. HOLMBERG: Chris?

MR. HEALEY: Thank you. Thanks for that presentation, Dr. Bowman. I think that was very helpful. It clarified what is a very complex statute.

To Mark's point, our understanding of the way blood clotting factors are handled is that they are not exempt from the competitive bidding process that takes place in '06, and that is a grave concern to, I believe, the using communities as well as the producers of these therapies.

It is worth noting that Congress recognized the unique nature of plasma-derived and recombinant therapies by carving out IVIg from the competitive bid process. So that is carved out. The A1PI products enjoy orphan status, so they're not subject to the competitive bid as well.

It's also our understanding that it was the congressional intent to exclude blood clotting factors from the competitive bid process, and that was discussed in the conference and was in the initial drafts of the conference agreement but, for whatever reason, was inadvertently dropped from the

final publication. So I'd just like to alert CMS to that fact and let you know that we're working with Congress presently to try and have a technical correction or find some means of making sure blood clotting factors are also excluded from the competitive bid process.

That said, even though they're excluded from the competitive bid, they are then subject to the ASP plus 6 percent, the 106 percent of ASP. And that is also a concern, frankly, because I think there is widespread recognition that ASP plus 6 percent is inadequate for these unique therapies. I think there is a recognition that the handling and storage conditions that are unique to plasma therapies and the distribution channels that they must go through are unlike many other products. And, therefore, there are added costs associated with them, and the 6-percent margin there is inadequate to assure that physicians are going to have a proper incentive to acquire those, stock them, and provide them to their patients. So we really view it as an access issue, and we are

concerned about the 6 percent.

Just one more point, if I could, and that is, you raised some of the terminology differences in the MMA and the need for kind of a consistent nomenclature. And I'd just like to echo that point. I think that there is a lot of work that can be done between both CMS and FDA to make sure that like terms are used in the same manner across the agencies. I think it is very easy for an agency to refer to one thing as an orphan drug and another agency to say it's an orphan drug when they mean entirely different things. So I'd just like to try and encourage CMS and FDA to work on that issue, and hopefully with Dr. McClellan's transfer to Administrator of CMS there will be some new avenues to make sure that happens.

But thank you for the summary. I think it's very good, and unlike the commercials that I've seen on TV, I don't think this is the same Medicare. I think it's a different Medicare. And I think at least for the plasma-using community, it's a better Medicare.

MR. SKINNER: Other questions of Dr. Bowman?

DR. J. BOWMAN: Thanks, Mr. Healey.

MR. SKINNER: I'm sorry. Did you want to respond?

DR. J. BOWMAN: No.

DR. SAYERS: Thanks, Jim. I have the sense that you saved the best for last. If you look at that paragraph before your disclaimer on the last page of the Secretary being directed to compile and clarify procedures and policies for billing of blood and blood costs in hospitals, is there any timeline for that clarification?

DR. J. BOWMAN: No, there is no timeline, to my knowledge.

DR. SAYERS: Well, that's kind of disappointing.

DR. J. BOWMAN: At least not to my knowledge right now, there's no timeline.

DR. HEATON: Andrew Heaton, Chiron. I've got a couple of specific questions related to the Section 303(b)(1), which amends 1842, and basically

that amends 1842(o)(1) to allocate 95 percent of AWP basically prior to January 1, 2004; and then Section 303(b)(2) amends this to a default of 85 percent of the AWP price for blood and blood products. So the default percentage then in physicians outpatient setting has just dropped 10 percent.

I notice that there is a provision in that under Section (C) of 303(b)(2) that would allow the Secretary to substitute other percentages based on data and information submitted by the manufacturer prior to January 1, 2004.

What procedures are available to provide guidance to manufacturers to submit this documentation in order to avoid a decrease to the default percentage?

DR. J. BOWMAN: Actually, Section (C) was--I abbreviated Section (C) somewhat because there were actually two deadlines. One was October 1, 2003, and the other deadline was January 1, 2004, for manufacturers to submit additional data or information.

Interestingly enough, obviously October 1, 2003, predated the passage of the act itself, which was signed into law by the President on December 8, 2003. I think Congress anticipated passage of that act a good deal earlier than it actually ended up passing.

However, having said all that, at this point I'm not aware of any guidance that the agency itself has for manufacturers on this particular issue. As some of you are aware, the agency itself is always open and accepts unsolicited information routinely in addition to the information that is solicited during the comment periods of both the Physician and the Outpatient Prospective Payment System proposed rulemaking process. But unsolicited information is also always welcome.

The different divisions of the agency that have responsibility for both the physician payment and the outpatient--and inpatient, for that matter--absolutely always welcome additional and supplementary information that can inform the agency and its staff. The staff are there to do

their job as best possible and carry out the intent of Congress and the law itself, the provisions of the law. So even though there is no specific guidance there, and even though the deadlines have passed--and, for the most part, the payments for 2004, as you know, are already in effect and there have been corrections made just recently to those payment schedules, at least under the outpatient setting, the agency is always willing to accept additional information to the extent possible, if there are egregious errors or if there are inequalities that should be addressed in the interest of the beneficiaries and access.

So kind of long-winded, but unfortunately we don't have any specific guidance on that very specific provision.

MR. SKINNER: Other questions or comments?

[No response.]

MR. SKINNER: There have been a number of issues raised relating to either needs for potential clarification or guidance from the Secretary or CMS as we go forward, as well as

potential clarifications of what may be congressional intent. Is there interest on the part of the committee of coming back to this tomorrow afternoon with a possible committee resolution giving the Secretary some preliminary recommendations on the committee's thinking at this point?

I'm seeing nods.

DR. HEATON: Since we're going to be discussing the need for bacterial screening, for example, which will significantly increase the wholesale acquisition cost, if the agency, the FDA follows up on the new recommendation to require this or recommend this, I do think that we need to propose to CMS that there be a formal mechanism for recognizing adjustments to the wholesale acquisition cost based on new regulatory guidelines or mandates. And I believe that our committee should make such a recommendation.

MR. SKINNER: Chris, is there something that could be done at this point on the issues that you raised would be needed?

MR. HEALEY: Absolutely. I think it would be important to let the Secretary know that we're concerned about the payment mechanism for blood clotting factors and assuring that access is preserved there through an exclusion from the competitive bid process.

MR. SKINNER: Okay. Well, maybe the committee could keep those items in mind, and then when we get to resolutions tomorrow afternoon, be thinking between now and tomorrow about how we might want to word such a recommendation.

At this point then, we'll move on and we'll recognize Cynthia Read to present on the corrections to the HOPPS ruling and the APC Panel recommendations.

MS. READ: Thank you. Thanks, Dr. Bowman and Dr. Holmberg, for inviting us down.

Before I start, I wanted to introduce a couple of members of my staff. I'm Cindy Read, Director of the Division of Outpatient Care, and I brought several of my colleagues with me: Sabrina Ahmed and Cindy Yen. And some of you I think may

have met in person or discussed issues with them over the phone.

I don't have any handouts, but I wanted to refer on a few issues to the handout that Jim provided you on the MMA. And, of course, we're involved in the setting of rates for the services provided in hospital outpatient departments, so the MMA provisions on the OPPS, of course, are very pertinent to what we do. And I'll refer you to the last page.

I just wanted to add a couple of other things. In addition, the MMA instituted a threshold for packaging services. For 2003, we packaged the cost of the lower-cost drugs, and the threshold we use for determining whether or not an item would be packaged was $150. And for 2004, for our final rule that we published November 7, 2003, we lowered that threshold to $50, and the MMA said that we should have a threshold of $50 for both 2005 and 2006.

The other thing is that for passthrough drugs, the existing law before the MMA passed

referred to Section 1842(o), which is the same section for establishing the payment rates for drugs and biologicals use in the physician office setting as the basis for establishing payments for passthrough drugs. So the changes to 1842(o) that are in the MMA also pertain to how we pay for passthrough drugs under the Outpatient Prospective Payment System. And those are new drugs, and they're drugs for which we established these payment rules for two to three years. That, again, is in statute.

So the MMA passed in December, and we had to implement many of these changes January 1. We had to publish a rule, which we did on January 6th. That was an interim final rule with comment. We had a 60-day comment period. And between the passage of the MMA and when we published our rule, we had to determine how we were going to classify all of the hundreds of drugs and biologicals in accordance with the MMA provisions.

So we recognized when we published our interim final rule that we may have missed some

things in the categorization of otherwise the specified covered outpatient drugs. And we offered the opportunity for the public to comment on the classification, and we said that, should we receive comments indicating that we misclassified some items, we would make those corrections as soon as possible. And in most cases, we would be able to do those in our April release.

At CMS under the Medicare program, we implement changes that requires systems modifications on a quarterly basis. So the next opportunity for making those changes was April 1. And we did implement some changes. I'll call your attention to several change requests that we published, and the most pertinent one, I think, to you all is transmittal 113 or change request 3145. And in that we describe payment rate changes for 28 drugs, biologicals, and radiopharmaceuticals, some of which resulted from the reclassification of those items from multiple-source to single-source drugs.

For example, we changed the classification

in the payment rates for several codes used to bill for immunoglobulin. And those changes, while they were implemented in the systems on April 1, actually are retroactive to January 1st, and where hospitals had already billed for those services for the three-month period prior to April 1, our systems are going to go ahead and make a mass adjustment to those particular claims so that hospitals receive the correct payment. If they hadn't billed for them, then the claims that they're submitting from this point forward will be paid in accordance with the correct payment amounts.

Now I'll get on to the rulemaking that we have to do for 2005 every year. As Dr. Bowman indicated, we go through rulemaking, and we propose a rule generally in the summertime. We're aiming for some time in July to publish our proposed rule for the 2005 update. We'll have a 60-day comment period. And then we will have our final rule that will base the final rule on the comments that we receive in response to our proposed rule.

We recognize the importance the blood products play in lifesaving therapy for the patients who are treated, the Medicare beneficiaries in the hospital outpatient setting, and since OPPS was first implemented in 2000, August 2002, we have made separate payment for blood and blood products in APCs rather than packaging them into the procedures with which they were administered.

The APCs for these products are intended to pay for costs for the products. The cost for storage and other administrative expenses are packaged into the APCs for the procedures with which the products are used.

In 2002, we used industry data that we received to develop payment rates for the products. In 2003, we applied a special dampening rule. For most services paid for under the Hospital Outpatient Prospective Payment System, we use relative hospital cost data that we get from our claims and cost report information from all of the hospitals. We start from a database of 50 or so

million claims to develop those.

When we were doing our rulemaking for 2003, we saw that some of the payment rates for blood and blood products were lower than what we felt we could tolerate, and we were concerned about the access issues. And so we applied some special dampening rules where the payment rates that resulted for 2003 were really sort of a combination of numbers from our median hospital cost data and the previous payments that were established on the basis of external data.

For 2004, we accepted our advisory committee's panel recommendations, Ambulatory Payment Classification Panel. And we froze our payment rates for blood and blood products at the 2003 level. This gave us some time to look further at our data and some of the issues that had been raised by the committee and presenters at the August meeting. The issue again came up in our February meeting, and Dr. Holmberg and representatives of the industry also came and made some presentations at that meeting.

The APC Panel recommendations were that we consider again external data in evaluating the costs of blood and blood products and make adjustments accordingly. And we will consider there--we are considering those recommendations as well as looking at ways of refining our own data to determine what payment amounts we will propose for 2005. And we are in the process of developing our proposed rule, and we have had a number of meetings with external bodies. We have another meeting coming up soon, and we welcome any comments that anybody has to provide us or any additional information they'd like to share with us.

So I think that covers everything that you wanted us to present, Dr. Holmberg. If there's any questions, we'll be glad to answer them.

MR. SKINNER: Questions from the committee? Chris?

MR. HEALEY: It's really more of a comment than anything. Ms. Read, I just wanted to thank you for all your work and the work of the folks at CMS who made that rapid technical correction to

IVIg, listing it as a single-source. I think that's a tremendous step forward in making sure that the patients who rely on that therapy are going to have access to it. Clearly, these are not generic products. None of them appear in the Orange Book, and so I was glad to see that CMS acted so quickly with your technical correction and changed that listing.

I also know in 2006 you are going to be relying on a GAO study of hospital acquisition cost to establish new payment rates, a step away from the claims-based data, and I applaud that method as well. And just to make you aware, we'll be discussing with GAO some of their methodologies and trying to have input in that process as well to make sure, once again, the unique nature of these therapies is reflected in the study that they undertake.

So thank you very much.

MS. READ: Thank you.

MR. SKINNER: Other questions or comments?

[No response.]

MR. SKINNER: I'm going to take just a moment and do something a little bit unusual. Given that we are going to shift topics now and move into bacterial contamination, public comment is not really until tomorrow, but given that these are two different subjects, I'm wondering, given the interest on these two subjects, if anybody from the public would like to address either of these two presentations or ask questions at this point in lieu of waiting until the public comment session tomorrow.

If you'd just identify yourself for the record, please.

MS. VOGEL: Sure. It's Michelle Vogel from the Immune Deficiency Foundation.

First, I would like to thank you for correcting the IVIg situation at CMS under HOPPS. But I'd like to make a comment under the physician side of things under the Medicare bill.

Basically what is going on is the reimbursement for physicians has been reduced to 80 percent of AWP, although Congress put in the report

language 95 percent of AWP. So as Chris Healey talked about competitive bidding and that there was a mistake and language was dropped, the same thing happened for IVIg.

And what that does to patients is that patients are being dropped out of physicians' offices, and it can't continue that way. And in some cases, there aren't local hospitals that do the infusions. So where do these patients go? And that's a big problem because this is a lifesaving therapy. It's not something that they can go without.

So I'd like that to be taken into consideration to look upon increasing that reimbursement.

Thank you.

MR. SKINNER: Thank you.

Any other comments at this time?

[No response.]

MR. SKINNER: Great. We are a little bit ahead of schedule, so we will take a break at this point, and we will return at 10:50, in 15 minutes.

[Recess.]

MR. SKINNER: The committee is now going to turn its attention to the final rule on bar code labeling, and at this time we are going to hear from Elizabeth Callaghan. She's the Deputy Director of the Division of Blood Applications in the Office of Blood Research and Reserve in CBER in the FDA. She's the project manager for the Blood Action Plan and has undertaken in CBER the developing of regulations as it relates to bar coding.

MS. CALLAGHAN: Good morning, everybody. I apologize for not bringing any handouts, but I have been told that the slides I have will be on the Web, in case anybody needs to see them.

I intend to give you a short summary of the bar coding rule and how it relates to blood and blood components.

The bar coding rule is entitled "Bar Code Label Requirements for Human Drug Products and Biological Products." The proposed regulation was published on March 14, 2003, and the final rule,

after reviewing comments that came to the docket, was published on February 26, 2004.

Now, any of you who have ever dealt with the FDA I'm sure realize that this is warp speed for us. But you'll be surprised what one can do when one has to.

The effective date of the rule is the 26th of this month, which means within two years all blood and blood components for transfusion must have bar codes on them, must have machine-readable information, and all human drugs must have bar codes.

In response to a GAO report on medical errors, Tommy Thompson mandated that FDA put together a rule to help reduce medication errors in hospitals and in other health care settings. In the scope of this rule, medication errors are defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, the patient, or the consumer.

It requires drugs to contain bar codes, allowing health care professionals to use scanning equipment to verify that the right drug is going at the right dose by the right route of administration, is going to the right patient at the right time. This is what they hope to accomplish by putting these codes on the blood products and drug products.

Now, in regard to human drug and biological products, they are required to have linear bar codes. They must adhere to the UCC, the Uniform Code Council, or HIBCC, the Health Industry Business Community Council, standards. The bar code that is required to be on these drugs is the national drug code number, or NDC number. These numbers are the numbers given to drugs that are registered with CDER, or our Center for Drugs.

Manufacturers are not required to put lot numbers of expiration dates. They can if they want to, but it is totally voluntary.

In regard to blood and blood components, they do not have NDC numbers because they do not

register with CDER. They register with CBER, and we do not issue NDC numbers. However, they will be required to have machine-readable information which is approved by the Director of CBER, and we have also required specific pertinent information to be encoded.

Prior to this rule, 606.121(c)(13) read, "The container label may bear encoded information in the form of machine-readable symbols approved by the Director of CBER." However, with the new rule, 606.121(c)(13) reads, "The container label must bear encoded information that is machine-readable and approved for such use by the Director of CBER."

And I've lost my slides down here.

Okay. You will notice two things. We've changed "may" to "must," which makes it now a requirement. And we have changed "symbols" to "information." We have done this to allow for advancements in technology in case other systems develop such as radiofrequency ID chips or other technology that people would like to use as identifying information.

And, of course, in order to embrace the plain language initiative, we have expanded the rule with five additional little sections. We couldn't leave well enough alone.

Who is subject to the machine-readable requirements? All blood establishments that manufacture, process, repack, or relabel blood or blood components intended for transfusion and who are regulated by the FD&C Act or the PSH Act.

Part two is what blood products are subject to the machine-readable requirements. All blood and blood components intended for transfusion are subject to the machine-readable information labeling requirements of this section.

What information must be machine readable? These are where we get into the specific requirements for our blood labels. Each label must have machine-readable information, at a minimum, which contains the unique facility identifier--this could be a registration number, a license number, and for facilities using ISBT, it would be their ISBT identifying number--the lot number relating to

the donor; the product code, telling us whether it's whole blood, red blood cells, fresh frozen plasma; and the ABO and Rh of the donor.

This section was put in to conform with a section in CDER's part of the rule, and it says: How must the machine-readable information appear? And it must be unique to the blood or blood component, it must be surrounded by sufficient space so that the machine-readable information can be scanned correctly, and it must remain intact under normal conditions.

And where does this information go? The machine-readable information must appear on the label of any blood or blood component which is or can be transfused to a patient or from which the blood or blood component can be taken and transfused to a patient.

The last part of this sentence is very important. There have been several inquiries since the final rule has been published asking just how far down the chain, if you want to look at it, the machine-readable requirements go. The answer is

all the way. All products for transfusion, whether they're aliquots, divided units, washed cells, transfusable products and syringes, pooled components, anything you can think of must have machine-readable information.

In order to keep up with the spirit of the rule, you must be able to scan the product at the bedside prior to transfusion. So, if you have a unit of blood that is divided into syringe components, those components must contain the bar code information so that it can be scanned at the patient's bedside.

I think that's it. Are there any questions?

MR. SKINNER: Questions from the committee?

DR. LOPES: What happens if what's read at the bedside is inappropriate for the patient in the bed. Is there some automatic like a bar code on the patient?

MS. CALLAGHAN: That's a good question. Unfortunately, FDA has no control over what

hospitals do with patients. That's really CMS's call. And this is the first part of what we hope will be an entire system so that hospitals will be required to scan patients at the bedside and scan products prior to them being infused or transfused or whatever drug you're using. It is the beginning of a system that we hope will be in place to prevent medical errors.

MR. SKINNER: I have two questions. You mentioned that expiration dates were optional on drugs, and you didn't mention expiration dates in relation to blood components, whether those will be required on the bar code.

And the second question is how does this apply to plasma products? You talked about blood and blood components, but you didn't talk about plasma products. So if you could address those, also, please.

MS. CALLAGHAN: The expiration date we didn't require to be bar-coded. Of course, you have to have an expiration date. That is one of the requirements in 606.121. But we didn't require

to be bar-coded because smaller facilities who may divide units, who may wash units, may not have bar-code capabilities so that they could put the expiration date in a bar-coded form. So it must be on there, but you can write it in. It doesn't have to be in a bar code.

If more people had bar-code facilities that they could use, it would be better, but, unfortunately, we thought that would be too much of a problem.

Now, I'm not quite sure what you mean by plasma products. Do you mean fresh frozen plasma or are you talking about IGIV and Factor VIII?

MR. SKINNER: The latter.

MS. CALLAGHAN: They are drugs, and they will have to have NDC numbers. After source plasma is collected and is further manufactured, it is no longer a blood component. It is a biological drug product, and it's registered with CDER. So they are required to have the CDER NDC bar number on their products.

MR. SKINNER: So they would fall under the

first part of the presentation, which doesn't require lot numbers or expiration dates.

MS. CALLAGHAN: That's correct.

MR. SKINNER: And the rationale for not including lot numbers and expiration dates on plasma products is what?

MS. CALLAGHAN: I think CDER decided that it was too complicated to begin with. Don't forget, they also said they wanted linear bar codes. The manufacturers, because this rule is extensive and even includes little blister packs of aspirins and one little tablet, they would not be able to put the expiration date and lot number, along with the NDC number, in a bar-coded form, except if they used two-dimensional bar codes, and CDER didn't want to go to two-dimensional bar codes yet.

If you read the entire rule, you will see that CDER intends to reevaluate this rule in another 2 years and see if they should include the lot number and expiration date.

Blood felt that we were ahead of ourselves

here, so we actually said machine-readable information. That way we could require additional information. And if people wanted to use two-dimensional bar codes, as long as the director of CBER approved it, that could be done.

MR. SKINNER: Other questions?

Dr. Gomperts?

DR. GOMPERTS: Would you comment on the Agency's thinking around the actual information systems or what are the requirements around those systems validation.

MS. CALLAGHAN: That's another good question.

CBER does review and approve BECS, Blood Establishment Information Systems. However, hospital information systems are reviewed or looked at by the Center of Radiological Health and Devices of Radiological Health. And I hesitate to say this, but they really do not have any requirements. They are considered waived instruments. Hopefully, that will change with time as the systems sort of get together and coordinate because it is very

important that all systems be validated, so that we make sure that medication errors are prevented.

DR. GOMPERTS: Thank you.

MR. SKINNER: One final question. Has CBER made any specific recommendations as to the bar-code technology and what should be used?

MS. CALLAGHAN: If you're referring specifically to ISBT, at this point, CBER has approved two different bar-code technologies, ISBT and Codabar. We have not made a specific requirement to go to ISBT for two reasons. One, we don't own the system, and if changes were made that we didn't agree with, by requiring the system in a reg, we would have to rewrite the reg in order to not require it any more. I realize this one only took a year, but it's kind of hard to backtrack on something that quickly.

And, secondly, we didn't want to impede any advancements in technology if another system became available which was even better.

MR. SKINNER: Yes?

DR. LINDEN: Can we just go back to the

previous question?

MS. CALLAGHAN: Sure.

DR. LINDEN: Why are the bar codes for plasma derivatives under CDER and not CBER?

MS. CALLAGHAN: Source plasma and recovered plasma are products of further manufacture. They are not required, under our part of the rule, to have bar codes because they are not transfusable products.

However, when they are manufactured into products for infusion or whatever you're going to use them for, they then become CDER's drugs. I realize they are reviewed in CBER, but they do register with CDER, and they have NDC numbers. So they fall under CDER's regulation in requiring linear bar codes.

DR. LINDEN: So you're saying, basically, they're regulated by both centers.

MS. CALLAGHAN: Sort of, yes. We review, and they register. I know it doesn't make sense, but this is the government.

[Laughter.]

MR. SKINNER: Any other questions or discussions on this topic?

[No response.]

* MR. SKINNER: Thank you very much.

Now, we're going to move on to the main event, the primary topic for this meeting, which is the "Impact and Assessment of Methods to Reduce the Risk of Bacterial Contamination of Platelet Products."

To begin our discussion, Dr. Holmberg is going to review the committee's previous recommendations and action on this topic in January of 2003.

DR. HOLMBERG: Before I do that, I would like to recognize that Dr. Penner has joined the table, and it's good to have you with us, John. Also, Dr. Midthun has replaced now Dr. Goodman, who has replaced Dr. Epstein.

This is a very difficult subject that has been around for a few years. And I do want to go back, for historical purposes, to review what the committee recommended in January of 2003. Bear

with me as I read this.

"The committee recognizes that the current leading causes of transfusion-related fatalities are: bacterial contamination of platelets, homolysis primarily due to errors, and Transfusion-Related Acute Lung Injury or TRALI. And efforts to address these threats have been made in comparison to other threats.

"The committee further recognizes that public attention remains highly focused on residual risk from HIV and hepatitis agents and, less quantifiable, known and theoretical risk.

"The committee also finds that technologies already exist that would effectively reduce the risk of bacterial contamination and homolysis, but there are no currently available technologies to reduce TRALI.

"Therefore, we recommend that the Secretary take steps to encourage and facilitate implementation of available measures that could reduce the risk of bacterial contamination and prevent errors that can result in hemolytic

transfusion reactions.

"The Secretary encourages research that possibly may improve the safety and extend the shelf life of stored platelets and may result in technologies or practices that could reduce the incidence of TRALI, an ad hoc subcommittee be formed to develop a process to identify and evaluate residual known and unknown risk affecting blood safety and, secondarily, availability, both in relation to etiological agents and the processes used in transfusion medicine.

"The subcommittee is tasked to use the process as one tool, combined with other relevant data, to propose prioritization of efforts by government, industry and the health care system to address these risks for further consideration by the committee."

I think that recommendation says a lot. It identifies clearly the three main causes of transfusion risk. Today, we're going to talk about the number one, which is the bacterial contamination of platelets, and I think we've

already gotten implication of the secondary risk, the homolysis due to errors, and hopefully what technology can do to help those areas as far as the bar-coding and Transfusion-Related Acute Lung Injury still needs to be an issue that needs to be addressed.

The issue before us really is an issue of eleventh hour concern at the Secretary's level. In February, the acting assistant secretary for health, Dr. Beato, was very concerned about what would happen to the availability of platelets, both apheresis and whole blood-derived platelets, as the new standards from the accreditation of facilities by the American Association of Blood Banks and also the College of American Pathologists Phase I requirement.

Dr. Beato, in the absence of data, asked that this committee look at the impact and assessment of methods to reduce the risk of bacterial contamination in platelet products. I want to make sure that everyone understands that, first of all, there are people sitting around the

table that do have conflicts, there are members here that are specific government or special government employees. There's also representation from other manufacturers. And as we already heard from Judy, Judy made mention that--Judy Angelbeck--made mention that she does work for Paul, and also Dr. Brecher made his statement earlier today.

I want to make sure that everyone understands that those people that are from a company are here for their subject matter expert knowledge. They are not here to represent their company. And so we have to make sure that there is a clear distinction on that.

And so even to the point of recognizing that, from a company's point of view, you have to separate that out and make sure that you're addressing the technology. We do have technology here, primarily the way the charter is written, to address leukoreduction, NAT, various bag manufacturers, the plasma industry and the blood community, the whole blood collection community.

I do not want this to become a session where we are trying to tear apart or dissect any standard that is out there or any regulation that is out there or I should say requirement from the College of American Pathology or the American Association of Blood Banks.

The intent is not to review their standard or their Phase I requirement. The whole idea today is to review the impact and the assessment of bacterial contamination. So I hope that is very clear.

Lieutenant Commander Henry, could you please put my slides up there. I would like to address some of the questions that we would like the committee to carefully consider as we move forward in these discussions.

Questions:

Has there been an impact on the availability of apheresis and whole blood-derived platelets for patient use?

Has there been a shift in type of platelets available? If so, has there been a shift

in economics as a result of the implementation of methods to reduce the risk of bacterial contamination and platelet products?

Has detection of bacterial contamination of whole blood-derived platelets been limited to hospitals?

Has the endpoint method to detect bacterial contamination of whole blood platelets been sufficient for sensitivity and specificity?

Does the federal government need to establish policies for methods for reduction of bacterial contamination and platelet products?

Are data sufficient to establish such a policy?

Is there additional research that needs to be conducted in the area of methods for reduction of bacterial contamination and platelet products?

I know that's a lot. What we'll do is we'll come back to those when we have our discussions.

Was there a question?

MS. LIPTON: Yes. I just wanted to

suggest, I know we're looking at policies, but I also think if we could add a question about assistance from some of the agencies, and specifically FDA, in addressing some of the needs that might help the implementation of this standard, I think that would be a very productive discussion.

DR. HOLMBERG: Okay. I will get back to you with that question, formerly on that question.

MR. SKINNER: Thank you.

Our first presentation on the topic, then, will be from Dr. Kathleen Sazama. She's president of the AABB, and she will present on the AABB standards. In her professional capacity, Dr. Sazama is a professional of laboratory medicine at the University of Texas and M.D. Anderson Center in Houston, but today I believe she's presenting as president of the AABB.

* DR. SAZAMA: Thank you, Mr. Skinner, and thank you, Dr. Holmberg, for the invitation to provide this information to the committee.

Just to put us in perspective, for

decades, bacterial contamination has been recognized as a significant risk associated with room temperature storage of platelets. As the blood banking community has succeeded in reducing the other obvious infectious risks of transfusion, the magnitude and relative importance of bacterial contamination of platelets has become more apparent. In fact, platelet bacterial contamination has long been recognized as the most common infectious risk of transfusion therapy.

The risks listed here is that from published literature in 1 in 1,000 to 1 in 3,000 platelets transfused. And over the course of several decades, it has been the second leading cause of death from transfusion, as reported to the FDA, with mortality rates approximating 1 in 60,000 transfusions.

The agencies themselves have been concerned about bacterial contamination, and the FDA has taken steps over the years, over more than a decade, a decade-and-a-half now, to highlight this issue.

In 1986, upon a recommendation from BPAC, the 7-day storage of platelets was reduced back to 5 days after only a year or so because of a concern about bacterial sepsis and deaths related to them.

There have been no less than four subsequent BPAC meetings, in which concerns over bacterial contamination have been identified.

In 1992, the CDC also weighed in, recommending improved surveillance for this very important cause of transfusion risk.

And in 1995, '99, and 2002, FDA conducted workshops on this very important issue.

In 1998, the CDC also weighed in with a very important study, the BaCon study, which was looking at voluntary reporting for this issue.

In 2002, the FDA actually approved two devices: the BacT/Alert culture bottles and the Pall Bacterial Detection System.

So these together provide an impetus for us to understand that this is a significant problem and the agencies have long recognized this.

Now, there has been a parallel effort, and

in August of 2002, the FDA conducted a workshop on pathogen reduction. And during the course of this workshop, it became increasingly apparent that the imminent introduction of technologies aimed at reducing or inactivating pathogens was not likely.

Therefore, as was stressed in the open letter to the transfusion medicine community, written by some of the nation's leading transfusion medicine physicians, including some who are or have been members of this committee, the need to act on bacterial detection became even more pressing. These physicians called for the blood collection committee to immediately initiate a program for detecting the presence of bacteria in units of platelets.

This plea was recognized, and the leading experts on AABB's committees identified bacterial contamination as a priority issue on which AABB should focus in order to improve patient care in the field of transfusion medicine.

Both the Clinical Transfusion Medicine Committee, which is comprised primarily of

physicians working in hospital transfusion services or other departments who actively treat patients needing transfusions, as well as the Transfusion-Transmitted Diseases Committee, which is a group of volunteer experts in the field of transfusion-related infectious risks, together, agreed that this was an area of concern that the AABB board of directors should act on as an important patient care issue.

In light of the science regarding this important health risk, these two committees worked with the AABB Standards Committee to develop a proposed standard to reduce the risk of bacterial contamination of platelets.

As initially proposed in November 2002, AABB's new standard would have required blood banks or transfusion services to have a method or methods to detect bacterial contamination in all platelet products. As is AABB's general practice, the standard did not prescribe any particular method by which facilities would meet this standard. With the introduction of this proposed standard, AABB

embarked on a one-and-a-half-year mission to understand, and address the concerns of and to educate our members about this critical patient care need.

In December 2002, AABB published an association bulletin, which is our means to provide information to members, providing helpful background information regarding bacterial contamination and outlining possible means of addressing this safety issue. This bulletin included an annotated bibliography of the published literature on this topic and was meant to assist members to a better understanding of the complexity of the issues surrounding bacterial contamination and to help them to develop productive comments to AABB's proposed standard. And, in fact, a comment period by our members is part of the usual process for creating new standards.

In response to these measures, the AABB's Blood Bank Transfusion Service Standards Program Unit received more than 50 comments. The AABB appreciated these thoughtful comments and thinks

that this type of scientific debate contributes positively to our standards development process and the resulting standards.

So the board of directors carefully considered the public comments we received and the advice of AABB's Blood Banks and Transfusion Services Standards Program Unit. In particular, we had extensive discussions about requests, that we limit the standard to requiring culturing of apheresis platelets only. The board thought that, as a matter of patient care, it was critical that bacterial contamination of both plateletpheresis and whole blood-derived platelets be addressed.

However, recognizing the complexities of this issue and the difficulties that some institutions might face in implementing the standard, the board agreed to allow an extended implementation period to March 1, 2004, instead of to the date the rest of the standards were implemented, which was November 2003.

In sum, the new standards address two areas related to bacterial contamination. Either

the blood bank or the transfusion service would have to implement methods to limit and detect bacterial contamination, and steps had to be taken to minimize the risk of bacterial contamination at the venipuncture site. Specifically, green soap would not be permitted.

In March 2003, a year before the implementation date, AABB announced this final standard. Again, AABB wrote to our member institutions outlining potential ways to meet the standard. Later, another association bulletin was produced in August and another in October 2003, both again providing background and suggestions for means by which the standard could be implemented.

In addition, a CD was developed to demonstrate how swirling could be detected, which is a longstanding method of looking for gross bacterial contamination.

As mentioned by Dr. Holmberg, less than a week before the standard was scheduled for implementation, specifically on February 26th, 2004, the acting assistant secretary for health,

Dr. Christina Beato, wrote to AABB requesting that we delay the March 1st implementation of this bacterial contamination standard, and the concerns that she outlined are listed here and should certainly be considered.

The list includes QC methods applicable to pre-released testing, potential extension of platelet dating, pooling of random donor platelets, and surveillance and reporting protocols for positive test results.

Given the fact that this standard had been proposed almost a year-and-a-half prior to this date, and that AABB had provided considerable opportunity for public comment, it came as a surprise to us that HHS would make this request at such an extremely late date. Prior to this time, HHS had not raised any official concerns about this standard and, in addition, there are government liaison personnel who sit or sat on all of the AABB committees that helped develop the standard and none of them voiced any concern during the extremely deliberative process of drafting this

standard.

After considering this request from the assistant secretary, AABB's board decided it would not be in the best interests of transfusion patients to delay implementation of this standard. Again, members of the blood banking community, both in the public and private sectors, had known for years that bacterial contamination of platelets posed a serious risk to transfusion recipients.

AABB recognizes that we need to do considerably more work to ensure that our standard is implemented in an effective manner that improves patient care without jeopardizing supply. As part of our standard implementation plan, we have done or plan to do the following to educate our members:

We have issued flow charts to assist members preparing for AABB assessments. We have published, and will continue to publish, articles in Weekly Report and other standard AABB publications about new issues as they arise about this standard. AABB staff are always available to answer questions from any members. Obviously, if

the need arises, additional association bulletins will also be published.

Tomorrow, I plan to share with the committee additional information about steps AABB is taking to collect data and identify important issues surrounding the implementation of this standard. There is no clear or easy path to be taken to reduce the risk of bacterial contamination of platelets. Rather, the Transfusion Medicine Committee is faced with a complex web of issues we need to address. However, just because there is no easy answer doesn't mean we shouldn't act. Our patients deserve more.

AABB strongly believes that the new bacterial contamination standard will help improve patient care and save lives. We believe that we should stop holding our patients hostage by allowing the perfect to be the enemy of the good.

Unfortunately, in the absence of regulations or standard setting, and in the face of limited reimbursement, there has been, and is, little incentive to invest in blood safety advances

such as this. AABB believed it was our responsibility to act to serve our patients, even if the FDA had not acted yet in this regard.

It is also interesting to note that since the publication of our standard, there has been an increased willingness by companies to consider developing technologies to reduce the threat of bacterial contamination.

Thank you.

MR. SKINNER: Are there any questions at this time from the committee? As Dr. Sazama mentioned, she will be returning tomorrow to talk on additional aspects of this, but there may be some issues on what she's presented now.

Yes, Judy?

DR. ANGELBECK: Kathleen, since one of the list of questions that Jerry listed in the deliberations that AABB had for their various committees, did you discuss this shift in the type of platelet product available? And I assume that means more apheresis versus the whole blood derived.

DR. SAZAMA: Certainly, the data, with respect to availability of platelets and the pattern of use of apheresis versus whole blood derived platelets was considered and considerable discussion ensued about that. Currently, the data are about 75 percent of platelets are transfused as apheresis platelets, 25 percent still as whole blood-derived platelets, and certainly that represents a significant minority of the use. So, yes, consideration was given to that potential.

DR. ANGELBECK: Did the committee deliberations think that there would be a shift toward a greater proportion of apheresis used?

DR. SAZAMA: I can't speak to the committee's thinking on that.

MR. SKINNER: Other questions?

Yes, Lola?

DR. LOPES: Do I understand correctly that HHS was thinking about moving the storage back to 7 days from 5, where you said potential extension of platelet dating?

DR. SAZAMA: Those were the concerns that

were identified by Assistant Secretary Beato in the letter that she sent to AABB, but that was among the considerations that should be looked at.

DR. LOPES: I was sitting here wondering what are the factors that would be involved in even trying to reduce the shelf-life requirement from 5 days to something smaller. It seems that the smaller that shelf life is the lower the chances of contamination or at least reproduction are.

DR. SAZAMA: I think you really would address a question of availability of the shelf life were shortened to 4 or 3 days from 5 days. Those of us who have been around long enough to remember those days, inventory would be a terrific challenge if a shortening of that shelf life would occur. I think that was part of the measure that looked at, well, can we do something else? Could we look at the threat? Which is with older platelets, the data seemed to suggest that there would be a greater risk to patients from bacteria that might be incubating in those bags. And so looking at that as the measure to both balance

supply and safety was part of the thinking that went into the standard setting.

MR. SKINNER: Other questions?

[No response.]

MR. SKINNER: Thank you.

The next presentation will be by James AuBuchon. Dr. AuBuchon will be presenting the College of American--be presenting on behalf of the College of American Pathologists, the Phase I Requirement on Bacterial Testing of Platelets and Implementation of Methods to Reduce Bacterial Contamination of Platelet Products.

* DR. AuBUCHON: Thank you. Thank you for the opportunity to present my views on how this country has succeeded and fallen short in addressing the problem of bacterial contamination of blood components, particularly platelets. Before I begin my remarks on this subject, I would like to clarify for whom I am and am not speaking.

I am a member of many professional associations and active in the governance of several. I am not speaking on behalf of the

American Association of Blood Banks. Dr. Kathleen Sazama, AABB president has already ably expressed the actions and intentions of that organization.

The Clinical Transfusion Medicine Committee of the AABB, which I chaired last year, identified, along with the Transfusion-Transmitted Diseases Committee, bacterial contamination of platelets as the leading cause of transfusion-recipient morbidity and mortality. I am pleased that the AABB's member institutions are taking positive steps to reduce this risk, nor should my remarks be taken as the official statement of the College of American Pathologists.

As the chair of the Transfusion Medicine Resource Committee of the CAP, I have been closely involved with the issue of bacterial detection in platelet units, and I am pleased that the accreditation program of the college addresses this issue directly. I would refer the committee members to the written statements submitted by the CAP.

I would now like to take a few moments to

make it clear that I am not representing any commercial entity. On this slide, I have listed all of the support that my laboratory has received in the last decade for research and development activities related to bacterial contamination of blood components. As you can see, the slide is blank.

[Laughter.]

DR. AuBUCHON: While we have been active in the field and have been able to make a variety of contributions, none of this work has had any commercial support.

For example, when our medical center undertook culturing of all platelet units in 1999, we did that because we felt it was an important addition to our procedures that would improve recipient safety. The preliminary validation protocol was undertaken using uncommitted reserves, and the ongoing procedures are supported by the medical center's operating budget. The money, about $30,000 a year has been well spent--we will get to that later--but no direct or in-kind

assistance came from any commercial source.

On this slide, I have listed all of the biomedical companies in which I hold or have held equities or salaried positions at any time. As you can see, this slide is also blank. There are none.

I have served as a consultant to a variety of commercial entities that do business in the field of blood banking. A number of these companies have an interest in detecting microorganisms that may be contaminating units of blood, although my input to these companies has extended to many other fields as well. Because these consultations take some of my time, I am compensated. However, none of the compensation is in the form of stock options or other equities, as I do not want my thoughts or future advice tainted by financial implications. In these interactions, I try to speak my mind and let the chips fall where they may.

To illustrate this, I note that I have served as a consultant to both Hemasure and Pall, both of which were involved in the manufacture and

sale of leukoreduction filters. As this committee is aware, I believe that the most appropriate use of leukoreduction technology is selectively; directing it toward those patients in whom it offers demonstrated benefits.

I was speaking out in opposition to the universal amplification of leukoreduction at the same time these companies were supporting it. I felt entirely unencumbered in offering my views publicly, and they appeared to appreciate my honesty. I am an academic, and my stock in trade is open and forthright expression of what I believe is the most appropriate approach to solving a problem. Bending my opinions for financial gain would be counterproductive.

So, then, why am I so passionate about the quality of what's in this bag? It's because these platelets go into patients over 4 million times each year in this country alone. And these are not abstract recipients. They are real patients, real people who deserve the best that I can provide for them. The soapbox that I have been wearing out

over the last few years has been dedicated to focusing our attention on the biggest risks in transfusion and then identifying ways to reduce them.

Over the last 2 decades, we have had enormous and enormously gratifying success in reducing the risks of the diseases the public understands and knows.

The low level of viral risks that we have achieved should allow us to focus on other larger, persistent problems that we haven't dealt with yet:

Problems such as missed transfusion that has continued to occur at the same rate for half a century and kills two dozen patients in this country every year and that most hospitals think or hope only happens somewhere else;

Or transfusion-related acute lung injury, thought to occur every 5,000 transfusions, with a fatality rate that claims at least 50 to 100 patients annually, but for which we don't yet have a good answer;

Or the topic of today's discussion,

bacterial contamination of platelets, which occurs at about 1,000 times the frequency of HIV transmission and which leads to the death of more than 100 patients every year in this country.

It is comparisons such as these that motivate me to try to improve the transfusion support that we provide.

Steps to limit and detect bacterial contamination carry the burdens of cost and logistic complexity. Are they worth it? Let's compare this risk to others this committee has discussed in the past.

West Nile Virus was recognized as a disease transmissible by transfusion in 2002. According to reports to the FDA, five transfusion recipients died due to meningoencephalitis in FY '02 because we had no way to test the blood supply then for this virus.

As a result, special deferral criteria were implemented in an attempt to identify infected donors. A massive push was initiated by the FDA and several companies to develop a nucleic acid

amplification test, and this entire effort, culminating in a precipitous implementation of a nationwide clinical trial, received substantial FDA oversight, assistance and encouragement.

In that same year, the Agency received reports of 17 deaths due to bacterial contamination of blood components. As this committee has heard previously, this is undoubtedly an underreporting because of the difficulty in recognizing the cause of infection in the thrombocytopenic and neutropenic patient. The true number is probably tenfold higher.

Another comparison: The first issue brought to this committee after its creation was that of HCV look-back. This was finally implemented as a substantial undertaking by blood suppliers, and hospitals and physicians, with a cost in excess of $330 million. Unfortunately, benefit was restricted to well less than 1 percent of those notified, approximately 2,200 patients from over 10 years of transfusion. Note that not all of those benefitting would have necessarily

died or suffered ill effects from their HCV infection.

Bacterial detection in platelets, on the other hand, offers the potential of avoiding the deaths of several hundred patients every year or several thousand over a 10-year period. Clearly, tackling the problem of bacterial contamination is a worthwhile endeavor.

This point is driven home by the experience reported from Johns Hopkins. The rates of post-transfusion death after transfusion with apheresis, that is, single-donor platelets, is huge--14 per million--and that after transfusion with platelet concentrates derived from whole blood units is astounding--62 per million units.

Given that about 50 to 60 percent of platelet transfusions in the U.S. are currently apheresis units, these data would predict more than 100 patient deaths annually from bacterial contamination.

However, for a long time, I have heard, "But we have never seen a case here." Recognition

of bacterial contamination is difficult because of the kinds of patients who usually receive platelets. Most of them also lack enough white cells to fight infections, and they have frequent fevers. So the cause of a fever or even sepsis after transfusion is usually not recognized.

For example, in a study of over 3,500 platelet transfusions, patients and units were cultured when there was a 2-degree rise in temperature or a 1-degree associated with other symptoms after a transfusion. Fully 1 percent of all transfusions met these criteria, and 10 cases of bacteremia and 4 cases of sepsis were uncovered.

Most telling to me were the observations that a 1-degree temperature rise and symptoms was associated with a contamination rate of 27 percent, and a 2-degree rise was associated with a contaminated unit 42 percent of the time. Bacterial contamination is not a rare problem. It is a common problem that is rarely recognized.

Once the problem was recognized for its magnitude, some felt there was no good way to deal

with it. Culturing techniques were foreign to blood bankers and did not provide an instantaneous answer, leaving the potential for having to recall a unit, after it had been sent to a hospital or transfused. Blood centers were concerned about having to utilize recall systems that might not interdict a hot unit before transfusion. However, these techniques have come to be adapted and adopted, particularly for apheresis units.

The promise of a rapid post-storage detection system remains in the future, leaving hospitals that transfuse platelets derived from whole blood units to use microscopy-based techniques or applying urine dipsticks to detect biochemical changes in infected units. Not only are these techniques much less sensitive than culturing, but they put hospital transfusion labs in the position of qualifying a unit for transfusion, a position they are unused to.

Hospital transfusion services would rather that blood centers take the responsibility for qualifying a whole blood-derived platelet unit for

transfusion, and blood centers feel that they do not have the right tools to address the problem with these kinds of units.

As a result, although apheresis units are generally being cultured today by the blood centers that collect them, whole blood-derived platelet units are not being cultured, but are being examined by techniques that are much less sensitive and more likely to give false positive results as well.

The College of American Pathologists and the AABB came to recognize the importance of the problem and the potential of the means available to address it. Around the same time, in the fall of 2002, both adopted requirements that steps be taken to detect bacteria and offered guidance regarding methods that could be utilized to do so. So the U.S. has begun to test its platelet supply for contaminating bacteria several years after this has become commonplace in much of Western Europe, but we are finally underway.

Probably because of the long lead time

given to blood centers holding AABB accreditation, and because of the variety of techniques available for hospital use, the implementation appears to have gone quite well. The CAP has not received reports of difficulties associated with the implementation of bacterial testing, and in the past year, the requirement for testing was being met in 97.4 percent of all laboratories inspected by the CAP.

So far so good, but there are still several important impediments to expanding the most sensitive testing technique currently available--culturing--to all units of platelets.

Culturing is usually performed on the day after collection in order for the bacterial inoculum to multiply to the point that it can be detected in a small sample.

Based on the work in our lab, and that of Dr. Brecher's, a culture that is truly positive, with the most commonly encountered contaminants, can usually be found to be detected in 12 to 20 hours. Therefore, most blood centers hold the

units for 24 hours after culturing before sending them to hospitals in order to prevent them having to recall a unit from the hospital or, even worse, having to deal with the transfusion of a unit that had bacteria in it.

Based on their experience with implementation of nucleic acid testing several years ago, blood centers want to stay away from the problems associated with trying to track down a unit that has been released to a hospital or issued to a patient for transfusion.

An impediment to the success of this system, now generally being used for apheresis units, would be an expectation that a cultured unit be made immediately available for release. Blood bankers understand that the culture systems on the market have been approved for QC use only and that no claims can be made about sterility.

Were the FDA to attempt to prohibit blood centers from hanging onto a cultured unit for 24 hours, the system would suffer significant disruption, and some patients would receive units

that would subsequently shown to be contaminated. That just doesn't make sense. Blood centers should be allowed to use these techniques in the most logical, efficient and effective manner without regulatory interference that holds the potential to decrease patient safety.

The limitation of storage of platelets to 5 days still applies, however. So the additional time taken up with culturing, and then holding the unit to ensure that it isn't really contaminated, takes 1 to 2 days off of an already short 5-day storage time. That could cause a shortage or increase the wastage rate due to increased out-dating. However, most centers that have adopted culturing as their method of detection have coped with this problem successfully, but at significant expense.

Ever since the field of blood banking began to recognize that there was a way to deal with bacterial contamination, it saw reextension of the storage period as an important side benefit of culturing. Do platelets stored for 7 days work?

Yes. In fact, the collection and storage systems currently available appear to be better than those that were approved for 7-day storage in the early 1980s.

The FDA has already indicated to two different companies that their systems can be used to store platelets for 7 days, as soon as the Agency licenses a bacterial detection system, and that's where the rub occurs. To license a culture system, the Agency is requiring a clinical trial with two cultures of every unit--one at the front end of storage and one at the back end--to document the sensitivity of the culturing technique early in storage.

That part of a trial protocol makes sense. The problem stems from the numbers. The Agency is looking for ironclad statistical proof, and that implies performing the trial on over 50,000 units at a cost of over $2 million. The manufacturers of culture systems have nothing to gain in this, and they have been unwilling so far to pay for the trial. A price tag of $2 million, and the

consumption in a trial of $50,000 units of platelets are expenses that the nation's funding-starved blood transfusion system can ill afford.

Another impediment to success is the prohibition of storing pools of whole blood-derived platelets for longer than 4 hours. This means that pooling can be performed only immediately before transfusion. This stems from a concern, never fully validated, that a more dangerous inoculum could arise if bacteria were given a larger volume into which to multiple during storage.

As a result, each unit must be cultured individually if culture is used as the detection system. This increases the expense of materials for culturing sixfold. More importantly, it increases the workload to the point that many blood centers just don't have enough staff to attempt this.

Also, the volume to culture, whatever that minimum is--usually, around 5 to 10 mls, must be taken from each unit. That's a minuscule

proportion of an apheresis unit, but it represents 10 percent of the small whole blood-derived units. Thus, this approach reduces the efficacy of transfusion by a similar proportion, an undesirable effect.

As I said, the Europeans have been using these techniques for some time, and they have evolved an efficient system. It is common practice, in most Western European countries, to pool platelets made from whole blood units on day one and take a single culture at that point. Great economic and logistic economies are achieved by this approach, and these allow the Europeans to culture their whole blood-derived platelets, unlike in the U.S.

It also allows for simple and efficient prestorage leukoreduction, since a single filter, rather than six, can be used. Because of the culturing, European blood bankers are then allowed to store cultured, pooled platelet units for 7 days. This system is light years ahead of what we are doing in this country. My European colleagues,

frankly, laugh at our using dipsticks and gram stain to try to find bacteria in platelets. "Don't you know that these techniques are insensitive?" they say. "Why don't you just pool and culture like we do?" Indeed.

Some investigators have generated data that allow us to see just how good the culture-based detection systems are. Dr. Gail Rock has published the results of a double-cultured study constructed similarly to the manner that is being discussed for this country.

Her hospital utilizes platelet units derived from whole blood. When they arrived at her facility, they were individually cultured by the Pall BDS. Although they were eventually transfused in pools usually of five or six units, each unit was cultured individually since it was not allowed to pool them. This early culture would be considered the test culture.

Just before issuance for transfusion, the units were pooled and a culture was performed again, this time using standard microbiologic

techniques. This would be considered the most sensitive or control culture, since the additional storage time would presumably have allowed any contaminating bacteria to grow to a higher concentration and not escape detection.

A negative culture at the later time allows one to verify that the test culture was indeed accurate when it did not identify any bacteria in the units. Twelve thousand sixty-two units were cultured in the Pall BDS, and four were found to be contaminated with bacteria, a rate of 3.3 per 10,000 units. An additional pool was found later to be positive, indicating a residual risk of 0.8 per 10,000.

I should also note that the Pall BDS has been improved since the time of this study. Also, as part of this study, I would note that storage was extended to 7 days, and as has been seen in Europe, the 7-day-old platelets provided good clinical support.

So the detection system was not perfect, but what had been gained?

Culture early in storage detected 3.3 contaminated units per 10,000, and culture later found an additional 0.8, indicating that the total contamination rate was approximately 4 per 10,000 or 1 per 2,500 units, well within the range that others have reported.

The protocol used detected 80 percent of the contaminated units. That is good. What worries me is the question, if these platelet units had not been cultured, how many would have been detected as contaminated? A year ago in this country, the answer would have been zero. With the insensitive techniques now generally being used for whole blood-derived platelets, the answer is probably closer to zero than to 3 or 4 per 10,000.

The culture-based systems clearly have the ability to detect bacteria. That is why they were approved by the FDA. Unless they can be applied to pools of whole blood-derived platelets, however, and unless we can extend the storage time of these units, I fear that this more sensitive approach will not be widely used, and patients receiving

whole blood-derived platelets will not have the benefit of the technology that is currently available.

So prestorage pooling is clearly an important link in extending culturing to whole blood-derived platelets, but extension of the storage of cultured units is more than just an academic concern. If all platelet transfusions were cultured, apheresis units individually and whole blood-derived units by pools, it would cost perhaps $30 million per year. This implementation would have health benefits, saving a substantial number of lives each year and saving the cost--about $6 million--of treating the infections that would have been caused by the contaminated units.

With the extension of platelet storage that could occur, there are savings to be realized as well. Currently, 17 percent of all platelet units outdate before they can be used. Based on this country's experience in the early 1980s, when platelet storage was authorized, briefly, to be 7 days, the outdate rate should drop by at least

two-thirds. This would save about 100,000 doses of platelets a year or more and result in savings to the blood production system that would cover the cost of performing the cultures all by itself even before considering the treatment costs that would be saved.

Furthermore, those donors who were donating by apheresis and were no longer needed, could be redirected into red cell donation programs to alleviate the increasing shortage of red cell units, another benefit for the system and for patients.

At the moment, though, it feels to blood bankers as if we are stuck in molasses. We are trying to do the right thing in culturing units, but we can't make the logistic changes in the system that are necessary in order to extend cultures to all units. What I would like to see is the entire field, the regulated and the regulators, work together to address these problems. We need to focus on the big picture of recipient safety and, as you heard before, not let the perfect be

the enemy of the good.

We can make scientifically reasonable inferences from in vitro data and from the experiences of Europeans and those who were onto this problem first to see what needs to be done.

What should be our goals?

First, every platelet unit should be subjected to a bacterial detection test that is sensitive. At the moment, that means culturing, although other techniques may become available in the future. To do this, we need to get approval for using testing systems in manners that will cause the least disruption to our platelet supply system. That means we need approval for prestorage pooling and for extension of storage to 7 days.

I first proposed a trial to document the sensitivity of culturing 4 years ago. Others have taken up the mantle since then, but we still haven't gotten started because of the enormity of the trial that is being required. We all want to improve recipient safety.

I would ask that the federal government

congratulate blood bankers for taking the lead and imposing a requirement on themselves that will benefit patients. I would ask that the federal government assist us to get to where we need to be.

Ladies and gentlemen, if we were transmitting HIV to several hundred or even 10 transfusion recipients each year, solutions to the problem would be sought at a fever pitch. There would be congressional inquiries into the problem, and the full attention of the FDA and this committee would be directed at the issue. Thankfully, we don't have that problem. Instead, we have several thousand patients who are suffering needless bacterial infections and several hundred patients who are dying from a problem that we have the means to address effectively.

The blood bankers are on top of this. We are doing all that we can to limit and detect bacterial contamination. We need the assistance of the federal government to improve what we are doing to limit the chance of the very problem the assistant secretary was worried about and to

accomplish all of this at the smallest expense. I believe that our patients and the taxpayers deserve no less.

Thank you.

MR. SKINNER: Questions or comments from the committee?

Yes, Dr. Wong.

DR. WONG: I just have a quick question. Is there inoculum size or dose every time you culture on day one that relates to disease morbidity and mortality, given that most of these patients are on antibiotics?

DR. AuBUCHON: Well, certainly, the larger the inoculum that is taken from the unit, at least up to some reasonable level, will increase the sensitivity of the technique. There was a paper published 2 years ago which questioned the sensitivity of culturing, but they used a very small inoculum. Most centers that are using a culturing system today are using somewhere around 5 mls. The Pall BDS has a defined volume that is withdrawn for culture, but those that are using a

bottle-based culture system are generally culturing 5 to 10 mls. That seems to give a very good sensitivity.

What the FDA would like to see is a double-culture study in order to document that sensitivity, and that's really the only way that it could be documented in a real-world situation. There have been numerous studies where units have been spiked--sterile units have been spiked--with bacteria, and then small volumes, between 3 and 5 mls, have been taken out on day one to culture. These have indicated that the systems that are approved for QC use are indeed sensitive. And it was on the basis of those data that the FDA issued that approval.

MR. SKINNER: Other committee questions?

Dr. Midthun.

DR. MIDTHUN: Karen Midthun, FDA.

I guess I would just like to make a few general comments and just say that obviously we are listening here with great interest. I think this is a complex problem, and we have really come here,

together with the other PHS and other agencies, to hear all of the information, gather as much data as we can and all, hopefully, work together to figure out what the best way forward is.

MR. SKINNER: Other questions?

DR. KUEHNERT: I wanted to commend you on an outstanding presentation, and I would echo sentiments that this is an extremely complex issue that people have been talking about for literally decades, and it is an issue that absolutely needs to be addressed.

I agree with the phrase we have heard multiple times already today to not let the perfect be the enemy of the good, but I would extend that to also mean that there are some issues that still need to be addressed, even beyond just the task of a method for detection, and we will get into some of those issues later in this committee meeting.

I want to ask you a specific question about some data I wasn't familiar with from Dr. Rock concerning screening of pooled platelets. Do you happen to know the organisms that were

identified in those four cultures that you mentioned? And I'm wondering if some of those could have been false positives, whether here was an evaluation of false positives as well as false negatives.

DR. AuBUCHON: If I recall the study, the units that were found to be positive on initial screening with the Pall BDS were cultured individually again in order to document whether or not there was truly a contaminant.

Initially, there were six units that gave a positive signal in the test system. One of them could not be recultured for reasons that I don't remember, and one of them, on reculture, was sterile. So it was assumed that that was a false positive, leaving the four true positives. If I recall correctly, they were all skin organisms--so one a bacillus and three staph.

DR. KUEHNERT: I just wanted to follow up on that and see if you had any comment of what the impact of false positives might be on the system because that's a possible downside, although I want

to couch that by saying that, again, I think that even finding one gram-negative organism, for a blood center to do that, would prevent a fatality.

And having been at CDC and heard about cases over the years, I have heard the same thing as you said, that somebody saying that they have been in blood banking for 20 years and never seen a case, and then they saw a case, and they now understand the importance of the problem.

DR. AuBUCHON: Yes. Well, it is important to shut the door before the horse leaves the barn.

The point about false positivity is an important one, and that is one of the advantages of the Pall BDS system, that the unit is never opened to the environment. It's never an open system. Sterile connecting devices can be used to obtain the sample and pass the sample into the collection and detection system, and so the rate of false positivity should be quite low or presumably should be zero, if used correctly. I'm not sure how the one false positive occurred in Dr. Rock's study.

The other system that is used for

culturing that employs a bottle by necessity has an open part of the system, although the sample is taken from the unit using sterile connecting devices and maintains the closed system of the unit. Ultimately, the sample has to be drawn up into a syringe, and then, with a needle, the sample is inserted through a rubber septum into the bottle. There is always the potential for contamination of the culture at that point. The system is not truly giving you a false positive result. The system is contained, but the unit isn't contaminated. The contamination occurred at the time of actually placing the aliquot into the bottle.

When we began our culturing in 1999, we intentionally did not use a laminar flow hood, as you saw in the photograph. We do this out on a laboratory bench in the general transfusion service laboratory, with all of the techs in rotation taking a turn.

We wanted to determine whether or not culturing was feasible in that kind of environment,

sort of a standard transfusion service lab environment, or whether we would get too many false positives. We certainly did have some false positives, initially running at a rate of about 1 per 200 units, and now down to about 1 in 1,000 units. That comes from some changes in sampling pouches that are available to us, and our techs becoming more familiar with the technique.

Dr. Brecher, who adopted a similar technique, but does the manipulations within a laminar flow hood, has a false positive rate that's about half or a third, if I remember, of ours; again, indicating that most of these contaminations are coming at the time that the culture is actually being injected into the bottle.

MR. SKINNER: Dr. Sayers had his hand up.

DR. SAYERS: Thanks.

Jim, what do the Europeans report about their experience reducing the risk of transfusion-transmitted bacterial infection?

DR. AuBUCHON: I haven't heard much in the way of hard data before and after comparisons. I

don't have that information.

MR. SKINNER: Dr. Heaton?

DR. HEATON: Jim, there's an economic conundrum here, in that the FDA has asked for an extraordinarily wide-ranging and very expensive trial to justify the creation of an intended use claim for a release test. And one of the ways that one might justify such an enormous expense would be to pursue a 7-day platelet dating extension and indeed pooling.

Since you're one of the world's experts on platelet storage, what's your opinion on 7-day platelet dating, the efficacy of platelets at 7 days and the efficacy of the BCPC pooling? By virtue of your experience, do you believe those to be effective products and therefore a realistic goal of the development for bacterial screening assay program?

DR. AuBUCHON: Our laboratory was involved in the performance of clinical trials for the two companies that I am aware of that have submitted for 7-day dating. We performed these studies under

contract to them. In both of those studies, platelets that had been stored for 7 days were compared to platelets that had been stored for 5 days. One of those companies used an apheresis collection device. The other company used a whole blood-derived platelet unit.

Certainly, there were differences between 7-day-old platelets and 5-day-old platelets, both in terms of recovery and survival. The difference was less than 15 percent for a drop in the recovery. This was felt, at that time, to be an acceptable tradeoff and, in fact, at least for the apheresis platelets, the recovery and survival of the 7-day platelets, 2 years ago in our hands, was better than the published radiolabeled recovery and survival from 20 years previous that led the FDA to license 7-day platelets in the early 1980s.

Since that time, Dr. Scott Murphy, who I believe is going to be talking tomorrow, has proposed a comparison of stored platelets or treated platelets, any future platelet product submitted to the FDA for licensure not in

comparison to what has previously been approved licensed by the Agency, but against an immutable standard--fresh platelets.

Scott has appropriately pointed out that if we always compare our next advance to our last approach, we may be on a slippery slope to someday where we are comparing something that is terrible to something that is only slightly worse, and that's not appropriate.

Instead, we should use fresh platelets from the same donor, reinfused tautologously, as the benchmark for that donor and then compare the treated or stored or however processed platelets at the end of their storage period to those fresh platelets from that same individual.

This appears very scientifically sound. We have been engaged in some studies looking at this approach, which we euphemistically call Murphy's Law, and it appears that at 7 days, compared to fresh platelets, we are still getting excellent survival. Scott suggested that at the end of the storage period, the recovery should be

at least two-thirds of fresh platelets. And even at 7 days, the currently available systems can meet that requirement.

MR. SKINNER: Colonel Sylvester?

COLONEL SYLVESTER: You said that the AABB members had to implement almost a full year before or the CAP implemented a full year before the AABB, and you reported a 97-percent compliance.

Do you believe that's because of perhaps your transfusion services are relying on the donor centers to do it or what would be the difference between what you are saying is the standard was accepted and implemented, and everybody's in compliance, and nobody's reported a supply shortage with your member organizations, and yet there's a concern there will be when--the shortage on the AABB's part.

DR. AuBUCHON: Well, I am gratified that both those institutions, accredited by the AABB for their blood banking and transfusion service activity, and those accredited by the CAP, have, in the main, taken up this responsibility and run with

it and have been successful in implementing one technique or another.

The CAP Transfusion Medicine Resource Committee approved this new requirement on the inspection checklist in the fall of 2002. It was published to initially become effective in December of 2002. So that does appear a little bit earlier than the AABB.

There is a slight difference in how the requirement is interpreted, and that with the AABB, it is expected that, as of March 1, an institution is performing an appropriate technique, a suitable technique, for detection of bacteria.

In the CAP checklist, there are two classifications of requirements called Phase I and Phase II. The Phase II requirements are most stringently enforced, and the laboratory has to do precisely what is in the checklist, essentially no exceptions allowed.

The bacterial detection requirement, as all new requirements entered as a Phase I requirement, that allows the laboratory and the

inspector a bit more leeway in how the laboratory is assimilating this new requirement. But the fact that 97 percent--over 97 percent--of the laboratories received a passing grade on that question indicates that they were taking steps to implement one or another of detection techniques. I don't have data to say exactly how they were doing that.

MR. SKINNER: If I could ask a follow-up question. The AABB standard, then, as I understand it, is mandatory implementation. Yet yours is permissive. Is there a specific reason why the CAP standard is not mandatory? Is it the same reasons that Dr. Beato indicated in her reply or is that you don't see a need to make it mandatory because of the voluntary compliance?

DR. AuBUCHON: It is anticipated that the CAP requirement will move from Phase I to Phase II within the next cycle of checklists or in approximately 1 to 2 years. That is the standard approach that the CAP uses, rather than the approach that the AABB uses, which is a more

delayed implementation and with a public comment period.

There are different approaches to dealing with the same problem, and that is any new requirement will impose changes in procedure, possibly changes in equipment availability, training, validation requirements and a host of other implementation steps that cannot happen overnight.

It would be unfair for a laboratory to be inspected a week after the CAP's first publication of this requirement, to expect them to have everything in place. As you saw, it took some AABB institutions a year to get ready.

So the two organizations work differently. The end result is the same, and the CAP will be, I'm certain, moving from a Phase I to a Phase II requirement very soon, but it appears that most institutions are already paying attention to it.

MR. SKINNER: Dr. Gomperts?

DR. GOMPERTS: Jim, just focusing on the failures of the 1-day bacterial screening

procedure, those that are identified as bacterial positive at day five, day seven, whatever, would you comment on that.

DR. AuBUCHON: I think it is unreasonable to expect culture-based techniques performed relatively early in storage to be 100 percent sensitive. It just won't happen. Not all bacteria are going to multiply quickly enough so that a small sample taken one day into storage will by chance happen to have a bacterium that can grow in the system and then be detected.

Working in our favor in that kind of situation is the fact that if the organism is a slow grower, it probably will continue to be a slow grower during storage and is less likely to grow to potentially lethal concentration before the time of transfusion. Checking the unit at the time of issue or at the end of outdate I think is an appropriate way to document the sensitivity. But I am not greatly concerned that a few contaminated units will be missed. It is better than not testing them at all.

The question in terms of what that means for extended storage and how we should proceed, I think the appropriate clinical trial endpoint would not be documentation of 100-percent sensitivity, that is, the second or control culture at the end of storage always being negative before the agency would approve extended storage. What I think would be appropriate is to ask the question: If we did no testing, no culturing, what would be the infection rate? And if we did this culture technique and extended the storage, what would be the contamination rate? And if they're the same or the contamination rate is lower with the addition of the culture early in storage, then that is a winner and, in my opinion, should be approved.

DR. GOMPERTS: So you are saying that the false negative is associated with the bacterial type and also the actual bacterial load, that there are no other factors that could impact this?

DR. AuBUCHON: Well, I am not a microbiologist, but those are the two big ones.

MR. SKINNER: Dr. Angelbeck?

DR. ANGELBECK: Jim, with your comments on pre-storage pooling of the whole blood-derived platelet, and one of the questions before the committee that Dr. Holmberg pointed out, the availability or shift in the type of platelet available, do you think that that pre-storage pooling is essential with bacterial detection to making the whole blood-derived platelet a continued viable option?

DR. AuBUCHON: I do. The workload involved with testing each--with culturing each and every whole blood-derived platelet unit is phenomenal. Some blood centers, as I believe you will hear tomorrow, have successfully done that, but it has been incredibly expensive and an incredible amount of work for them to do that. They should be congratulated for having accomplished it.

However, I think that culturing of a pool will give the same answer and is a less expensive approach.

MR. SKINNER: Dr. Linden?

DR. LINDEN: My question actually relates to the same issue. You mentioned in Europe that they were routinely pooling prior to storage and culturing. Are they using sterile docking systems similar to what or identical to what we have in this country, or do they have, you know, other mechanisms for pooling that are not available in this country?

DR. AuBUCHON: I am familiar with the techniques that are being used in the Netherlands and Belgium, in particular, but I think those techniques are fairly standard throughout Western Europe. There is a difference in the type of platelet product. They produce platelets through a different system called buffy coat platelets as opposed to platelet-rich plasma-derived platelets. That really should not have any bearing on the bacterial contamination risk.

But once the platelet units are prepared from the whole blood unit or the buffy coat units are prepared from the whole blood unit, the further processing is all handled by a sterile connecting

device. There are also instruments available in Europe to do the final centrifugation, pooling, and filtering all in one step. And the culturing is--the culture sample, the culture aliquot is taken from the pool using sterile connecting devices. At that point they enter the small sample pouch with needle and syringe and place it in a culture bottle just the way that we do.

MR. SKINNER: We will have a presentation tomorrow on the Dutch experience where we can probe some of the European issues a little bit more.

Dr. Penner?

DR. PENNER: Jim, we have been experiencing some platelet shortages, temporary, in our region. Is this something that is a little more common or is it just a local phenomenon?

DR. AuBUCHON: Well, platelets never seem to be in abundance, even in the best of circumstances. All I can tell you is that in my area of the country, in the Northeast, we have not experienced any shortages of platelets. However, our blood center is only culturing apheresis

products. They are not culturing whole blood-derived products. That leaves the individual hospital to fend for itself and either do nothing or to use one of the lesser sensitive techniques.

There have been periodic platelet shortages, whole blood-derived platelet shortages, even in my part of the country, even though they are not being cultured. So I don't have data on that, but I think Dr. Sazama will have data tomorrow from the AABB about that.

DR. PENNER: Because this has been very uncommon for us in the past, and actually I had never experienced it before until recently. So I am not sure what is creating this situation, and maybe it is local.

DR. AuBUCHON: I guess I would ask you, Dr. Penner, are your whole blood-derived platelets being cultured?

DR. PENNER: Yes, they are.

DR. AuBUCHON: Okay.

MR. SKINNER: If I could follow up just on that as well, again, thinking back to the

difference between the AABB and the CAP standard, have you seen a serious impact on availability as a result of implementation of the voluntary standard? And is it a concern about availability that is in any way slowing down moving to a mandatory standard, to the Phase II?

DR. AuBUCHON: No shortages--no concerns about shortages have been reported to the CAP. So I don't know of any, but you heard Dr. Penner note, you know, some difficulties in his area. I am not aware of any.

In terms of why the standard was not initiated as a Phase II, the concern really related more to the ability of institutions to implement the techniques than to any effect the techniques might have on platelet availability. That was not what was truly driving the issue.

MR. SKINNER: Other discussion? Dr. Gomperts?

DR. GOMPERTS: Jim, there was one particular figure that really hit me, and perhaps I didn't quite understand it. Did you say that

approximately half of individuals receiving platelets who have a febrile response with a 2-degree or above febrile response are associated with bacterial contamination? That is more or less what I remember, which means this is quite a remarkable statistic. I don't know the incidence of such an occurrence, but I suspect it is not that low frequency, in which case the bacterial testing that Dr. Rock(?) talked about is perhaps missing quite a few of these.

DR. AuBUCHON: In the study that I mentioned, 1 percent of transfusion recipients either had a 1-degree rise in temperature plus chills and rigors, or a 2-degree rise in temperature. So that was 1 percent of all the platelet transfusions.

After those clinical signs and symptoms were noted, the unit and the patient were both cultured. They documented--I believe I noted ten cases of bacteremia and four cases of sepsis. And if the patient had a 1-degree rise and chills and rigors, the chance that that was truly a

contaminated unit that could be documented through that parallel culturing approach, a patient and unit, the chance was 27 percent, and a 2-degree rise was 42 percent. But that's based on a proportion of individuals who met the initial criteria for the culturing study, which was 1 percent of all platelet transfusion recipients.

DR. GOMPERTS: Okay. Thank you.

MR. SKINNER: Other questions? Dr. Sayers?

DR. SAYERS: Thanks. This is follow-up to Ed's question. This study, Jim, were those leuko-filtered transfusion products?

DR. AuBUCHON: No, I do not believe they were. Not pre-storage filtered, anyway.

MR. SKINNER: Dr. Kuehnert?

DR. KUEHNERT: I just wondered on that study and also in general, I was wondering what the storage times were in that study concerning those that developed sepsis and bacteremia. And then the more general question was just about the whole issue of day five versus seven storage time. We

talk about the experience in the 1980s about how the storage time was extended and then it was realized that there was a problem--quote, problem--and then it was scaled back. But I wasn't ever sure what those data actually were and if there's any data currently existing comparing day five versus seven as far as contamination and whether there's a significant difference. What do we expect? I mean, in looking to do a study, what is the expectation based on the data?

DR. AuBUCHON: I don't recall from the paper by Chu, et al., whether or not they reported the storage times of those units. I just don't recall.

DR. BRECHER: To put factual information on the table, they did. They averaged 4.5 days. But the age of all of their platelets was also 4.5 days, the university system getting all the platelets and transfusing them.

DR. AuBUCHON: There certainly was attention focused on the age issue from the study reported by Morrow, et al., from Hopkins in the

early 1990s where they noted that most of their platelets were transfused on day two or day three, but most of their reports of fever and sepsis came from platelets that were transfused on day five.

It is not unreasonable to think that the longer you store a contaminated unit, the higher the bacterial inoculum will be. Ultimately it will reach a plateau. But for most organisms, particularly the gram negatives and the ones that we are most concerned about, they seem to have very rapid growth curves, and probably reach their maximum within two to three days. So for them, the storage time is less of an issue. Those units are always dangerous.

DR. KUEHNERT: That was something I wanted to point out. I think on the earlier discussion there was talk about, well, what would be the impact of then decreasing to day three, and from, you know, data that has been previously published, it has been shown that really, since fatalities are primarily associated with gram negative organisms, they grow so quickly that

reducing the storage time would not be an effective measure. And what we are talking about when we are talking about day five to seven are more likely gram-positive organisms, which do cause fatalities, although not in the same proportion as gram negatives.

So, again, I was just wondering what the data were as far as the difference between day five and seven, and it doesn't sound like there really is anything out there.

MR. SKINNER: I wonder if there are any more questions for Dr. AuBuchon. Yes, Dr. Holmberg?

DR. HOLMBERG: Jim, I just have a question. Again, I'm stuck on the CAP Phase I requirement of the 97 percent of the laboratories inspected had implemented the bacterial testing.

One of the concerns that the Assistant Secretary for Health has had is the impact this has had on the hospitals, especially in the endpoint testing. And so I have a real hard time understanding that 97 percent, that if that number

of 97 percent is accurate, then we don't have a problem at the hospitals.

DR. AuBUCHON: The mechanisms that the CAP authorizes in that question for a laboratory to use in order to detect bacteria, or several, it included swirling, which is not accepted by the AABB as a standard technique to be used for routine release of platelets. It's authorized by the AABB in emergency release when you don't have time to do another technique. But it is allowed by the CAP to be used routinely, and that may account for some of the difference.

There is still some debate in the blood banking community how sensitive looking for swirling is. For those around the table who are not blood bankers, swirling is sometimes referred to as a shimmering opalescence that one sees by holding the bag up to the light and rocking it back and forth. And if a platelet remains in normal disk form, they will line up one against the other and create a small diffraction grid and create a rainbow. And you get many little rainbows being

formed, billions of rainbows being formed in the bag, and it appears to be an opalescent bag.

That indicates that the pH is in the acceptable range, above 6.2, and the platelets are happy. If you have a bacterially contaminated unit, the pH usually--not always--will drop and cause the platelets to sphere up into balls, and they can no longer create the diffraction grid.

The technique is, in my opinion, and based on our experimentation in our own laboratory, about as sensitive as gram staining. But it is far from perfect. There are others who believe that it is less sensitive than gram staining and, therefore, did not want the AABB to accept it as a routine method.

It costs nothing. It can be performed at the end of storage. It takes two seconds. And, frankly, it's fun to do.

[Laughter.]

DR. AuBUCHON: So this may be the technique that many of those laboratories are using. Clearly, it is not as sensitive as culture.

DR. HOLMBERG: Again, I just want to echo some of your comments that you made as far as partnership and working together, and also Dr. Midthun's comments earlier. The whole intent of the letter that was sent to the AABB was also not only to ask about the delay but also to try to get a mechanism so that we could have some roundtable discussion. And the way that we are approaching this is that what we want to do is to have this public forum, which we are having today, and then we will follow up with a roundtable discussion with the parties, all available parties, including all the agencies, Federal Government agencies.

DR. AuBUCHON: I am happy to hear that, and I look forward to being able to help any way I can.

DR. HOLMBERG: Thank you.

MR. SKINNER: Just one last question. On Dr. Holmberg's comment, do you have any specific data that indicates how they're complying with the CAP test and how this 97.4 percent breaks out, which ones they're using, what percentage are using

swirling, what percent dipsticks, what percent cultures?

DR. AuBUCHON: No, I do not.

MR. SKINNER: Okay. Thank you very much.

DR. AuBUCHON: Thank you.

MR. SKINNER: We are a little bit ahead of schedule. I don't know if the committee wants to have any discussion among itself before we break for lunch. We can certainly do that if there are any comments or questions from the committee in general.

[No response.]

MR. SKINNER: If not, then we will break for lunch, and the agenda says we are to come back at 2:00, but we are a half-hour early, so let's reconvene at 1:30. Thank you.

[Luncheon recess.]

A F T E R N O O N S E S S I O N

[1:47 p.m.]

MR. SKINNER: I think a majority or more of the committee is back, so if people would take their seats, we will get ready to begin this afternoon's presentations. Thank you.

The next presentation, we are going to hear from the FDA. We are going to hear from Jaroslav Vostal, who is going to speak to us about the approved devices and procedures to reduce the risk of bacterial contamination in platelet products. Thank you.

DR. VOSTAL: Thank you. Good afternoon. It's my pleasure to be here and to present some of the FDA current thinking on actually quite a broad area that includes sample diversion pouches in whole blood collection kits, detection of bacteria and platelet products, and also alternate platelet storage such as platelet stored out to seven days or pre-storage pooling.

So let me start off by talking about the sample pouch. The sample pouch is an idea that

suggests that adding a separate bag to a collection set could open up the possibility that you collect your disease testing up front so you don't have to wait until the end of the product collection. And sometimes the venous access is lost at the end of a product collection, and then you have difficulty gaining those disease testing samples. So this way, if you collect them up front, this gets around that problem.

The additional benefit of this could be that if there is a contamination at the time of collection of the blood that's going through, if that blood could be diverted away from the product bag, you may have a reduction of bacterial contamination in the final product.

Now, there isn't that much data on this that actually proves this concept, but the benefit--but we are understanding of the potential benefits of this idea.

So approximately two years ago, FDA presented the concept of the design of a sample diversion pouch at a BPAC meeting, and our design

included characteristics such as: it has to be a closed system; the diverted blood is separated from the final blood product by unidirectional flow so it doesn't contaminate the final product; and the volume of diverted blood is sufficient to provide samples for disease testing and potentially reduce bacterial contamination in the transfusion product.

Since then, three companies have come forward and applied for NDA supplements for sample diversion pouches, and these are the Baxter Corporation in January 2003; Pall Corporation, December 2002; and Terumo in September 2003.

The criteria for approval of this bag has been conformance with the FDA design proposal to BPAC. We did not require any clinical data if the manufacturers didn't claim decrease for bacterial contamination through the use of their product.

These products are on the market currently. However, there have been some growing pains with implications of these products, and some of the initial approved designs continue to be improved based on clinical experience.

So let me talk about bacterial detection devices that have been cleared by the FDA. There are two devices that have been cleared: the BacT/Alert by BioMerieux, that was cleared in February 2002; and BDS Instrument by Pall Corporation, that was cleared October 2nd. Now, these are specifically cleared for quality control of the platelet collection process.

FDA current thinking for clearance of these devices is based on the intended use of the device, and it's the manufacturer that presents us with the intended use of their device. We recognize two intended uses. One is quality control indication, and quality control is the sampling of a small number of collected products to assure that the platelet collection process is in control. And this could be as few as four units per month.

Now, the decision here, the decision to transfuse actually does not depend on the results of this quality control testing. So you don't have to wait for the results. This is different from if

you want to come in for an indication that is intended for product release. Here you screen all of the product prior to release for transfusion, and your decision to transfuse depends on the results.

This slide summarizes some of the points to consider when you're reviewing bacterial detection by automatic culture devices. The contamination at the collection is very low, and there needs to be time to allow bacterial proliferation in the product to reach detectable levels. This usually is 24 to 48 hours.

On the other hand, to preserve shelf life of the product, you need to sample the product as soon as possible after collection. However if you sample too early, this can lead to a sampling error. If you take a larger sample of volume, this improves sensitivity of the device, but also depletes the product. So all these things have to be balanced against one another.

Now, also, detection in the device requires proliferation of bacteria in the device,

and this usually adds another 24 to 48 hours to the time before you can get a result. And, finally, detection is based on metabolically active bacteria in the device. It may not detect dead bacteria or endotoxin that was produced by bacteria that subsequently died.

Now, there are some unique characteristics to bacterial growth in transfusion products. There's a wide variety of bacterial species that has been reported, and this includes gram-negative and gram-positive bacteria. As I mentioned already, the initial inoculum, it was very low, probably in the 1 to 5 CFUs per ml or less. However, once bacteria do get into a platelet product, since it's stored at room temperature and has sufficient nutrients to support bacteria, they can quickly amplify and proliferate to tremendous levels, up to a million CFUs per ml. And the rate of this bacterial proliferation in a product is dependent on the bacterial species, the storage temperature of the product, and also donor characteristics, such as antibodies or complement

concentrations.

Now, FDA current thinking on clearance of bacterial detection devices used for QC of platelet products, this is the criteria that we've applied to approval or clearance of the two devices that are already on the market. We've relied on in vitro testing. This is laboratory testing. In these tests, the devices tested platelet products intentionally contaminated with variable levels of bacteria, which is commonly referred to as a spiking study.

This type of testing identifies device sensitivity for a particular bacterial species and also the optimal sampling time and the sample volume that the device works with to increase its sensitivity.

Now, devices with low sensitivity need to allow time for bacterial proliferation in the platelet product, and thus sampling is done later in the storage of the product.

Now, this is a graphic demonstration of what these type of spiking studies look like. If

this denotes the storage of the platelet product at room temperature, you would spike in bacteria. Usually it's 1 to 10 colony-forming units per ml. And then you'd take a sample of the contaminated unit, put it into your device, and read out the device, usually 24 to 48 hours later, and also determine the actual concentration of the bacteria at the time of sampling. It's a relatively straightforward type of an experiment.

We did have a lot of discussion early on to decide what was the appropriate list of bacteria that should be tested in these devices, and we finally settled down on a minimal list of bacteria that was actually put together by Dr. Mark Brecher when he was evaluating the BacT/Alert, and he used 15 organisms, and his report came out in Transfusion in 2001.

Now, other companies can use the same list or a smaller or a longer list of bacteria. However, the final labeling of the clear device will reflect the specific bacteria tested in that device.

So that was the criteria for approval of devices for quality control. Now we're going to move into devices approved for release of platelet products for transfusion. The criteria here is more stringent because the device assures that products are not contaminated with greater than a certain level of bacteria, and this is based on labeling of the device which is derived from some of the in vitro studies.

For culture-based detection devices, we need to establish the predictive value of an early culture sample. We also need to establish the false negative rate and the false positive rate for the device under actual use conditions.

So for these devices, for release of products, we would also request in vitro testing, same as was done for quality control indication. But in addition, we would request a field trial to demonstrate the performance of the devices under actual use conditions. This would involve sampling of transfusion products from routine collections. And particularly for culture-based devices, we want

to see a demonstration that culture is also the sample taken early in a storage period are predictive of results of a sample taken at the end of storage or at the time of release of the product.

Now, here's a schematic of what this type of study would look like, or at least the concept of a study that we envision, and this was presented at BPAC in December 2002.

These would be normal products collected as part of routine operation of a blood center. There would be the initial culture taken early on, probably 24 hours. Then at the time of release of the products or at outdate, a second sample would be taken and also put into the culture so that the results of the initial culture could be confirmed.

Now, because bacteria proliferate during this time, the second culture has an easier time to detect the level of bacteria because the levels do get higher and higher. So we consider this as the reference standard.

Now, the field trial would have several

characteristics. One would be a primary endpoint, and this would be a concordance of the first and second culture with 95 percent confidence. The study would establish the sensitivity, specificity, and also the predictive value of the first culture.

This study may require a large study due to a low level of contamination, and some of the estimates we've received would be that 30,000 to 50,000 units would have to be screened to determine with sufficient statistical power those criteria that we're looking for. Even though this is such a large hurdle, this approach was supported by the BPAC, Blood Products Advisory Committee.

Now, since the cost of the studies is so large and has been the limiting factor in getting these studies off the ground, we have also considered combining these types of trials with the extension of platelet storage. And, therefore, here are a couple of ideas how using bacterial screening can be used to approve future platelet products.

As I mentioned already, applying

culture-based bacterial detection for a product limits the shelf life by 24 to 48 hours. Now, it would be relatively easy to extend--or it would appear that it would be easy to extend the shelf life of platelets. However, the shelf life was already limited by concerns over bacterial contamination by the 1986 BPAC.

Therefore, application of bacterial screening and shelf life extension could be combined in field trials to reduce the cost of the trial and then eventually to combine them in clinical practice.

Now, one way of getting at this would be to look at the relative risk of the various products. Currently the risk that we have--and it's not clear exactly what it is, but we'll just call it current risk. And this is what you would get from five-day-old platelets.

Now, we know that there is a higher risk to seven-day platelets because of the decision and data that was presented to the 1986 BPAC. So seven-day platelets are at a higher risk. There's

also a potential for--that we're also talking about pre-storage polled platelets.

Now, there is a higher bacterial risk, and this was established by a paper by Steve Wagner in 1985, and he compared the bacteria growth rates in single units, single random donor units or the pooled units. And since the pooled units has a larger volume, the bacteria can actually proliferate to a higher load and, therefore, be a greater risk to a recipient if they receive that higher load.

So based on these two factors, we consider seven-day platelets and pre-storage pooled platelets a higher bacterial risk than the current risk.

Now, we're not comfortable with the current risk, and we understand all the concerns that were voiced today, and we agree with them. We think that this risk should be reduced to a lower risk that would be defined by or enabled by application of a bacterial detection method.

So once this is in place, this will become

the new current risk. And then any platelets, any platelet products that will be approved should have the same relative risk as the new lower risk established by bacterial screening.

Let me just summarize here. The bacterial risk of future products should not be greater than the risk of a five-day platelet screen for bacterial contamination with an FDA-approved method or device, and the relative bacterial risk of a novel platelet product should be demonstrated in a field trial.

Here is a schematic of what these field trials could look like, and this is just the concept that we present. We are open to suggestions and discussion about the design of the specifics of these trials.

This particular trial tries to combine transfusion of the products stored up to day six and day seven. This could be done under IND if these platelets are then screened prior to transfusion with some kind of a point-of-care screening device, such as gram stain. What we

suggest that this study should have, it should have a first culture, as done earlier, and then a second culture taken at day six or day seven. And then the results should be compared to see whether the first culture was predictive of those later cultures.

Now, we have also been approached with a study that's slightly different from this that utilizes outdated units. And here instead of transfusing the units that go beyond five days, they're allowed to outdate--outdate on the shelf. And then these are tested again to compare against the initial culture or against the day five culture. And the thought is that if you could demonstrate that the risk of day five and day seven is equivalent, that would be sufficient data to approve a device for release of platelets out to seven days.

So those types of studies are more suited for single-donor platelets, also referred to as apheresis platelets. We've already talked about whole blood-derived platelets, and these have a

slightly different collection scheme. Here you have, for whole blood-derived platelets, the single units that are collected from single donors are combined into a final pooled product. The current standard for this product is that it can be pooled only four hours prior to transfusion, and that's because there's concern about bacterial proliferation in the pool if it's stored beyond four hours.

Now, as Dr. AuBuchon mentioned, there's a lot of advantages to pooling up front. You could set it up so there would be only one bacterial detection or one leukoreduction filter. And so economically, those platelets would be better. However, there is that issue about bacterial contamination.

So here are a couple ideas about how devices could be tested against pre-storage pooled platelets. In this type of laboratory study or a spiking study, we would have five or six individual units, and we would like to see one of those units contaminated with bacteria. So one of these would

be spiked. These would then be combined together into a pool, and as you can see, there's about at least a five-fold dilution effect. And we're concerned about this dilution effect and how it would affect the sensitivity of the devices. So we'd like to see evaluation of the devices under these conditions, even in the laboratory situation.

Once this is established, I think the study that would demonstrate the--the field trial that would demonstrate the actual usability of this product under a clinical condition would be very similar to what we proposed for the other apheresis platelets. Again, there's an initial culture, and this is confirmed by a later culture to make sure that there's a predictive value to the first culture.

Now, solving of the bacteria problem is only half the story, and that's because when you have novel platelet products, you have to worry about the efficacy of the products as well as their risk of bacterial contamination.

So in order for these novel platelet

products to be approved, there has to be a demonstration of adequate platelet efficacy after storage. Platelets with extended shelf life or pre-storage pooled platelets need to function as well as the current platelet products when transfused. Storage containers need to be validated for extended storage or for pre-storage pooling.

I'm now going to describe to you how we evaluate the efficacy of platelet products that have been stored under novel conditions. This here is what we referred to as our pyramid of concern. You probably can't see that very well down here, but the level of testing is initiated by in vitro testing, such as tests for platelet biochemistry and platelet physiology. We would reserve that for minimal concerns about platelet efficacy.

As we move up to more serious concerns, we then get into in vivo studies, which involve radiolabeled platelets. The concept behind this is that a product that has been stored under novel conditions can be radiolabeled and infused into a

volunteer, and then you will look at the recovery and survival of those platelets in circulation. And if there is any level of damage, those platelets will most likely be removed faster than a standard platelet. So we do a comparison between control and novel platelet products in terms of how they circulate.

If there are significant concerns about platelets and platelet damage, we would move on to hemostasis clinical trials. These are trials that look at the ability of the platelet to prevent or stop bleeding in a thrombocytopenic patient. These are relatively expensive studies, so we reserve those studies only for cases of major concern.

This side of the slide, I've listed some of the examples of where different changes would fit in terms of our testing scheme. You'll notice there are two gray zones that the applications could fall into, where they could call into the higher zone or the lower zone.

Now, for very low levels of concerns, we can still use in vitro testing. However, as you

start to modify current platelet storage or the solutions that are used to collect platelets, we tend to move into radiolabeled studies. And products that fall under that would be five- to seven-day storage container or a new apheresis collection device.

Again, if you move up to designing a totally new storage media or storing platelets beyond seven days to 14 days and longer, then you start to wonder whether those platelets can still work. And, again, you might be convinced that they should be tested in a hemostasis type trial.

And, finally, if you have significantly modified platelets, like platelet substitutes, or chemically modified platelets, such as pathogen-reduced platelets, those would be used or evaluated in these type of hemostasis trials.

So in terms of pre-storage pooling, there's actually a bit of a problem with our current scheme. The current scheme is appropriate for validation of single-donor products because they're autologous, they can be reinfused into the

volunteer donors. Ethical issues prevent use of this approach with pooled products in healthy volunteers. Because you have five or six different donors that produced that final pool, there would be an issue of (?) immunization to the healthy volunteer. Therefore, we don't think that this radiolabeled approach can be used in evaluating of pre-storage pooled platelets.

To get around this problem, we suggested a new approach back in March 2003, and that was to use transfusion responses in thrombocytopenic patients receiving platelet products as therapy. So these patients are going to be receiving pooled products anyway, and it will be just a matter of designing a study around their therapy.

What we proposed was that there could be two arms of the study. One arm would be the four-hour pool, and the other arm would be a pool that was stored--pooled together pre-storage and stored out to five days.

The endpoints of the study would be corrected count increments and also the transfusion

frequencies between subsequent transfusion.

Now the study size will probably be larger than what we're used to with the radiolabeled platelets because the type of patient we're using, they're on chemotherapy and there's a lot of reasons for them to have increased platelet consumptions. So that will have to be figured into the design of the study, but probably would be on the order of about 50 patients per arm.

So, to summarize where we stand, I'd just like to point out the gaps in the current regulatory landscape.

For bacterial detection devices, so far these are not cleared for release of platelet products for either day five or day seven products. They're also not cleared for testing, and that's either release or QC testing, of pooled whole blood-derived platelets. Also, they're not cleared for platelet released based on point-of-care sampling.

Now, I didn't talk about these types of devices, but I think these will probably come in

the future.

And, finally, the efficacy of these products needs to be evaluated, and storage bags or devices are not cleared for pre-storage pooling of whole blood-derived platelets, either up to day five or day seven.

So these are the studies that we would propose that could fill some of these gaps:

A field trial of culture-based devices for screening platelets to determine the predictive value of a test, and this would be for day five, day seven, or for a pooled product.

We'd like to see in vitro tests for bacterial detection of pooled random donor platelets.

We'd like to see in vitro and field trial for point-of-care bacterial detection devices.

And, finally, we'd like to see evaluation of platelet efficacy for bags used for pre-storage pooled platelets.

Thank you very much.

MR. SKINNER: Thank you, Dr. Vostal.

Questions? Dr. Linden?

DR. LINDEN: On your pyramid of concerns about platelet efficacy, you didn't mention the extension from five days to seven days on there. You only mentioned extension beyond seven days. Is platelet efficacy a concern if one were looking at the five days to seven days?

DR. VOSTAL: The concern is still there because even though platelets were transfused out to seven days back in the mid-1980s, the platelet product has changed significantly since then. Now most of the platelets are leukoreduced. Back then, those were whole blood-derived platelets. Now we have apheresis platelets. And, also, the storage bags that are used to store these products have changed significantly since then in terms of gas transport.

So we like to see evaluation of the seven-day platelets as well with the current storage conditions, and actually I might have just raced over this, but those would fall under the radiolabeled type studies. We already have

approved one bag from Gambro Corporation for storage of apheresis platelets for seven-day platelets.

MR. SKINNER: Other questions? Yes?

DR. LOPES: Do policies in the United States allow us to use the experience of Europeans, who are apparently doing some of these things already? Do we have to start from scratch with the field studies?

DR. VOSTAL: Well, this is a very interesting point because Europe in some ways is ahead of us. The difference is that they collect platelets through a different methodology. They collect buffy coat platelets as opposed to platelet-rich-plasma platelets.

We currently feel that there is enough of a difference between the two products that the PRP platelets used in the U.S. would have to be evaluated on their own. Some of the differences are that there is a higher leukocyte collection for the buffy coat platelets. They get to sit with the product longer, with the white cells present, and

they may be able to take care of bacteria that are contaminating the unit from the beginning.

MR. SKINNER: Dr. Kuehnert?

DR. KUEHNERT: Could you go back to--you had a slide on risk that compared five-day screened to five-day not screened compared to seven-day. And I mentioned this before, earlier, about--I mean, I think this is a good way to quantify it, but what I'm struggling with is, again, this higher risk based on a 1986 BPAC decision and what the data actually were. And I think this is an important point rather than just sort of an academic point, because I think if you are trying to compare to say that five days compared with seven days is somehow a quantifiable risk and then you're saying that by screening you reduce that risk to some point, you want to know how much you're reducing by and what's acceptable.

So with screening at seven days, where are you between orange and red there? Are you 90 percent there or 95 percent there? You really don't know unless you know what the risk is at

seven days. So I just wondered if you knew what the data were in 1986, and if not, you know, how you're going to sort of estimate that risk there going in, because it makes a difference as far as the power, you know, I think needed to--the power of the study.

DR. VOSTAL: I think that the 1986 decision as based on a relatively small amount of data, and there were anecdotal concerns about sepsis due to platelet transfusions.

I don't think they had any type of surveillance in place that would tell them that this is the current bacterial risk across the country. I think we just sort of accept that they recognize the risk there and they move the storage back to sort of help alleviate that risk.

DR. KUEHNERT: Is there any idea about what that risk is, though, in terms of just relative risk between five and seven days? I mean, is it--you know, is there any expectation sort of going into a study to see, you know, what the effect might be?

DR. VOSTAL: I don't know what that risk is. I think, you know, if we talk about doing this kind of study, you know, where you can actually compare the contamination rate at day six and at day seven, it may be able to tell you what risk you are preventing--although, I mean, it's different because these will be platelets that are already screened up front, and the ones that are contaminated and picked up by the device will be eliminated from that study.

DR. KUEHNERT: One other point. The other concern I might have--and this gets to be a concern when you get to doing 50,000 units, 100,000 units. You are going to have some rate of false positives at each point, and so there might be a random chance of getting a false positive at one, the first sample and at the second sample, and I wondered how you might sort of deal with that in terms of trying to figure out what the true positive actually is.

DR. VOSTAL: I think that's a good point. You'd probably have to have a large enough study so

you'll pick up, you know, a significant number of true positives that would override your false negative or false positives.

MR. SKINNER: Dr. Sayers?

DR. SAYERS: Yes, can we make any predictions about the infectivity of products that do not have many bacteria in them, are falsely negative by culture on day one, but subsequently positive by culture say on day four?

DR. VOSTAL: The question was whether--what was the bacterial risk to those or what was the rate?

DR. SAYERS: I'm just wondering if we can make any predictions about those products. They're falsely negative, and you're ascribing positivity to them because they do subsequently become positive by culture. And presumably they're not positive by culture early on because there are few contaminating bacteria there.

So do we have any predictions we can make about how infective they are, you know, whether they would be positive in the biological test,

which would be transfusion transmission of bacteria in a patient?

DR. VOSTAL: Right, I think it all depends on the bacterial load that you end up transfusing. If it's a relatively low bacterial load, like if it's 100 CFUs per ml, you know, chances are it would not cause significant mortality/morbidity. But if you would miss a culture up front and those bacteria grow up to a million or greater per ml, you know, I think the chances of having a significant effect are good.

MR. SKINNER: Colonel Sylvester?

COLONEL SYLVESTER: Yes, two things. After the 1986 rollback of the date from seven years to five years, did FDA see a reduction in the number of bacteria-contaminated reports?

DR. VOSTAL: I'm not aware of any data like that.

COLONEL SYLVESTER: And then the other one was: Based on what you're showing, the only way this is going to happen, extension from five to seven days would be if they do the 30,000 to 50,000

study to get the device approved, correct?

DR. VOSTAL: Yes.

COLONEL SYLVESTER: So that study would have to be done first before any of the other studies would meet the FDA's standards because it has to be with a cleared device.

DR. VOSTAL: So the question is can you do the efficacy study first and then the bacterial detection later, or--

COLONEL SYLVESTER: Right. Well, the way I read it is that the studies for extending from five to seven days, they have to be done with a cleared device.

DR. VOSTAL: Yes, bacterial.

COLONEL SYLVESTER: The only way we're going to get a cleared device is if they do the study with the 50,000 sample, correct?

DR. VOSTAL: That's correct. I mean, the device we're talking about is the bacterial detection device, yes.

MR. SKINNER: Dr. Heaton?

DR. HEATON: A couple of points.

First, I was present at the 1986 BPAC discussion, and you made the statement that platelet storage has changed a lot since then. The reality is that in 1986 the commonly used random donor platelet containers was the Baxter PL732 container and then the Cutter (?) CLX, now the (?) CLX. So the random donor platelet containers have changed very, very little between now and then. It's true apheresis containers have changed a lot, but random donor platelet containers didn't.

Secondly, as I remember, the bulk of the platelet-contaminated events reported, nearly all were transfused at about four or five days. And if I remember correctly, there were almost none that were transfused at seven days. And the BPAC was concerned at the theoretical probability that there would be an extrapolated growth between five days and seven days. So to answer Matthew's question, there was remarkably little evidence about the incremental risk that you've got between five days and seven days.

The question I have for you, though, is a

little different, and that is that the standard that you've identified, the 95-percent concordance between day one and the second culture and the 50,000-unit trial in an operating environment and doing double cultures on day five and day seven, if you extrapolate the number of platelets that outdate in the entire U.S., this would take a manufacturer about a year to do this trial and it would be a multi-million-dollar trial.

My question to you is: Has any manufacturer stepped up to the FDA to suggest that they would care to fund such a trial?

DR. VOSTAL: Unfortunately, the manufacturers have not stepped forward and evaluated their devices for--

DR. HEATON: Are you surprised?

DR. VOSTAL: Well, I think actually under the current conditions, since the first culture is already being done on a routine basis, collecting the second culture should not add that much cost to this type of a study.

DR. HEATON: Yes, but you've got to have

that number of outdates platelets and presumably you couldn't use the platelet product in the interim. So you're actually diverting platelet production for the purpose of the trial as well as incurring at least two additional culture expenses, in the case of a Chiron assay and nucleic acid test.

DR. VOSTAL: True, but we've also suggested that you could do it in a way that you could actually transfuse those products if you did it under an IND type study.

MR. SKINNER: I think perhaps Roger Dodd could lend some additional information on the question.

MR. DODD: Thank you. I appreciate the opportunity, although I'll mention it tomorrow. Roger Dodd, Red Cross.

We've taken a fairly close look at both the logistics and costs of developing and performing such a study, and at today's rate of outdates, it will take at least two years nationwide to accumulate the outdates. And,

conservatively, it's going to cost about $5 million. And we feel that the difficulties of doing this under an IND are truly significant, both in terms of issues of consenting patients and charging hospitals to get older products. We don't think that's going to be too popular.

So I think that this is a real difficulty, and it may be easier for us to learn to live with what we've got now if we can't get the support of the agency to move ahead if we can only do it by logistically infeasible and unaffordable studies.

DR. VOSTAL: Thank you.

MR. SKINNER: Other committee questions?

DR. PENNER: Just a question on efficacy. How do you determine efficacy?

DR. VOSTAL: Well, efficacy, currently the way we look at efficacy, especially in radiolabeled studies, is we look at what the current standard is, which would be licensed platelets, and we try to make sure that the novel platelet doesn't differ from that current standard by more than 10, 20 percent.

Now, this approach gets you into trouble because subsequent comparisons, you always slide down the slippery slope, what Jim AuBuchon and Scott Murphy are talking about.

We are moving towards the new approach that Scott Murphy proposed, and that sets the fresh platelets as the standard. And then we will compare subsequent products to that uniform standard.

DR. PENNER: So you're just really measuring circulation time or at least how long these things stay in circulation, not hemostasis, you don't know whether they're functioning.

DR. VOSTAL: Well, let me get back to this. See, right here is actually what we do in terms of evaluating efficacy. We start off down at the bottom of this pyramid where we have minimal concerns with in vitro studies. As our concerns increase, we go to in vivo studies using radiolabeled platelets. If we have significant concerns about damage to the platelets, we move on to hemostasis type clinical trials, and this was

the case with pathogen-reduced platelets.

DR. PENNER: So there would be some hemostasis trials as well as just the NDM(?)-labeled platelet circulation?

DR. VOSTAL: It depends on how--if we felt that there was significant damage to the platelet caused by storage. For example, there are these gray zones that fall into these two areas. Say you have platelets that you want to store them out to 14 days or 21 days, you know, they may be able to circulate but there's no way of knowing whether they can still participate in hemostasis. I think at that point they would probably go into the hemostasis study category.

DR. PENNER: And that would be much more complex, obviously, because you're trying to see whether patients stop bleeding after you give the agents.

DR. VOSTAL: That's correct.

DR. PENNER: Okay.

MR. SKINNER: Colonel Sylvester?

COLONEL SYLVESTER: Could you go to the

hemostasis clinical trials in lieu of the radiolabeled trials? Like with the work we're doing with frozen platelets, we don't necessarily get a platelet increment, but we can stop bleeding. So if the intent is to stop bleeding, would we be prevented from getting to that point because they don't stay in circulation?

DR. VOSTAL: Right. Those platelets are almost a different type of a product from a normal platelet, so they may have to be considered under a separate category.

Most likely radiolabeling, they wouldn't stand up to the radiolabeled criteria, so they would have to be evaluated by a hemostasis type study.

MR. SKINNER: Dr. Holmberg?

DR. HOLMBERG: As far as the field trial for the pre-storage pooled platelets, would you consider that under an IND?

DR. VOSTAL: Yes, certainly.

DR. HOLMBERG: Okay. And do we have any evidence--I mean, was that the comment that the

BPAC in 1986 just extrapolated the data? Or was there a reduction once the dates were rolled back from seven to five?

DR. HEATON: I believe that there was perceived to be a reduction, but the bulk of the cases that led to the concern were, in fact, transfused between four and five days. There were a few at day seven.

MR. SKINNER: I believe Steve Wagner in the audience wanted to comment.

MR. WAGNER: Thank you. Steve Wagner, American Red Cross.

We've done some initial planning for such a study and included some statistical analysis of sample size. And if you adhere to a 95-percent confidence and you also believe that you want to do the study with a power of 80 percent, you'll have to look at over a million samples. Thirty or fifty thousand platelets will hardly give you any power for the study whatsoever.

MS. TOURAULT: If I could make a brief comment, I worked for the FDA--my name is Mary

Ann--

MR. SKINNER: If you could just identify--

MS. TOURAULT: I'm sorry?

MR. SKINNER: Just identify yourself for the record.

MS. TOURAULT: Mary Ann Tourault. I worked for the FDA at the time and collected the fatality reports when the rollback for the days was done.

If my memory serves me correctly, at that point in time the number of fatality reports coming into the agency were about 30 to 50 per year, and of those, there were usually six to seven due to bacterial contamination. The increase that caused the reduction I think was only three cases, if my memory serves me correctly.

MR. SKINNER: I think at this point, then, thank you very much, Jaro, for your presentation, and we will move on to hear from the two companies that have approved devices for bacterial detection, BioMerieux and Pall, and we'll first hear from Mr. A.C. Marchionne with BioMerieux.

MR. MARCHIONNE: Good afternoon. My name is A.C. Marchionne, and I would like to first begin by saying thank you to the committee for allowing me to present today. I must admit I am a paid employee of BioMerieux.

It is estimated that one to 1,000 to one to 2,000 platelets are contaminated annually with a fairly high frequency of occurrence, indicated here. What that means is of 4 million platelet bags transfused, about 2,000 to 4,000 are bacterially contaminated with about 200 to 1,600 cases resulting in clinical sepsis as well as 40 to 533 deaths potentially resulting.

We have designed a system called the BacT/Alert 3D. It consists of a two-bottle reagent system. The first bottle here is our BPA, blood products aerobic. The second bottle is called BPN, blood products anaerobic.

The automated portion of the instrumentation is a four-drawer incubator with a bar code scanner here and a touch screen here for loading bottles. Bottles are read continuously in

the drawers every ten minutes through the platelet shelf life.

If we take a closer look at the technology, this is the bottom of the bottles, and there is a sensor in there that will detect CO_2 production as a byproduct of a substrate. So as microorganisms grow and metabolize their substrates, CO_2 is produced and it is detected in a sensor at the bottom of the bottle, and the sensor will change from a greenish-gray to a yellow.

The system operates by measuring three different algorithms. The first one is sustained acceleration of bacterial growth. The second one is the rate of acceleration. And the third one is the initial threshold.

Along the left side here, we have images of the bottom of the sensor changing from gray to yellow in the course of five to seven days.

Within each cell that the bottle is placed into, there is a sensor at the bottom. There is an LED that's being shined off the base of the sensor and a photo diode that is measuring reflectance

units.

How do you get the sample into the bottle? We have worked with numerous companies--Gambro, ITL, and Charter--to develop sample devices that have been designed to reduce contamination. The bag on the left here is a Gambro bag, and the two devices here are from Charter Medical, and they do have an adapter on the end to cover the bottle as you inoculate the bottles. ITL is another company that manufactures the sampling device, and, unfortunately, I do not have a picture of that device to show you.

In this picture, we have a sample being collected from a platelet sampling bag via syringe that will be inoculated into two bottles in a hood, and then this is a side view of the drawer. A technician is loading a bottle into the drawer. There are 60 slots inside the drawer, each of which has a photo diode and LED. So each test is being conducted within each bottle in each cell.

These bottles have been shown to detect most organisms between nine and 36 hours here. And

the organisms listed below are organisms that have been known to contaminate platelets.

Bring your attention to strep viridans here. In this particular instance, the anaerobic bottle is detecting the organisms much quicker than the aerobic bottle.

Studies have been conducted in the U.S.--these are three papers from Dr. Brecher, who has done extensive studies on the BacT/Alert, and in the U.S. there are existing papers out there, but also internationally there are scientists who have studied the BacT/Alert. And the BacT/Alert has been in use as early as 1992, I believe, for platelet testing overseas.

Our clearance is currently for the two-bottle reagent system. The first bottle is the BacT/Alert BPA, and it is specifically used with the BacT/Alert microbial detection system for quality control testing of leukocyte-reduced apheresis platelet units and, as of March, single units of whole blood platelet concentrates. And the BPA culture bottles are used to detect aerobic

bacteria.

Again, the same applies to the BPN culture bottles. They are, again, used for quality control testing of leukocyte-reduced apheresis platelet units as well as single units of whole blood-derived platelet concentrates. And the BPN culture bottles are used for anaerobic bacteria and facultative anaerobes.

If we take a look at worldwide placements, as BioMerieux industry, we have approximately 421 systems installed worldwide, 386 of which are placed within blood banks. The others are placed within food companies for detection of bacteria in food products as well as in the pharmaceutical industry.

Outside of BioMerieux industry, we have our corporate headquarters in Durham, North Carolina, which handles the blood culture end of our business, and we have thousands of units placed. And what I mean by unit is a 240 equivalent or an incubator that holds 240 bottles. And there are approximately 6,000 240 equivalents

placed worldwide.

Dr. Brecher and Steve Rothenberg have found in practice that the true contamination rates have been three out of 2,397 and four out of 2,397 for aerobic and anaerobic bacteria, respectively. And all of these organisms were detected early on, which means that a late culture--no positives were detected with the late culture alone.

With respect to anaerobic organisms, we feel that these will be increasingly important with respect to potential platelet shelf life extension to seven days. And certainly while the verdict is still out on anaerobes like propioni and kerini(?) bacterium, there is at least one documented fatality from Clostridium perfringens.

We also have a product in development right now that I thought I would tell you about. It is called BacT/Notify, and it is a real-time notification system for transfusion centers. The BacT/Alert will transmit results to the Internet, and on the transfusion side, transfusion services and centers can scan a bar code and get a real-time

result through the Internet. We believe that that is going to help make the platelets even safer.

A positive test result would look something like this. It's customizable and it would have the product number or any other data that you would determine important on that page.

Does anyone have any questions?

MR. SKINNER: Dr. Linden?

DR. LINDEN: Could you tell us a little bit more scientifically about your system and how it works? You mentioned detecting bacterial acceleration, but I believe you're not really detecting the bacteria directly. Can you speak to us more scientifically?

MR. MARCHIONNE: Sure I can. There is media inside of these bottles that promote the growth and sustain the growth of bacteria if they're present and inoculated. And those organisms will metabolize substrates that will result in CO_2 production that the sensor in the bottom of that bottle will detect and begin to change in color.

DR. LINDEN: Okay. What substrates? I mean, can you give us a little bit more detail. Your talk was very generic.

MR. MARCHIONNE: Are you talking specifically about the contents of the reagents?

DR. LINDEN: Well, whatever additional detail you can give us without being overly proprietary.

MR. MARCHIONNE: I can tell you about some of the contents of the reagents, if that would satisfy.

For example, in the product insert, in the aerobic culture bottles, the media formulation consists of pancreatic digest of casein, papayic (?) digest of soybean meal, sodium polyanethol sulfonate, pyridoxine and other complex amino acids.

MR. SKINNER: Dr. Lopes?

DR. LOPES: Can you tell us something about the cost per unit of the processed product, tested product?

MR. MARCHIONNE: Currently, the average

sales price of the reagents is $3.50 per bottle, and the system is being sold--and when I say "system," I mean an incubator with a control module. That is being sold for approximately $60,000 to $62,000.

DR. KUEHNERT: I had two questions. One, you presented some information at the end about this BacT/Notify, which looked interesting as far as electronic notification. But I just wanted to clarify. What this system does, it tells you you have a positive result. It doesn't tell you what the identity of the bacteria is. Is that right?

MR. MARCHIONNE: That is correct, and it doesn't tell you if it is perhaps a false positive or a true positive at that point.

DR. KUEHNERT: So the system gets to the point of saying you have a positive as indicated by the system as a yellow light, but it's up to the blood center or whoever is operating the system to speciate the organism--or see if an organism is present and then to speciate the organism, provide antimicrobial susceptibilities, things that would

be clinically important. Is that right?

MR. MARCHIONNE: That is correct.

DR. KUEHNERT: The second question I had was about false positives. Do you have a sense of, on average, what the false positive rate is and what the effect is of doing the sampling under a laminar flow hood? Because I saw that in there and I wondered what the difference is, and this sort of has relevance, again, to trying to do some sort of evaluation study because if the false positive rate is high enough, it would overwhelm any true positive that you'd see at day five or day seven. So I just wondered if you had a sense of the numbers.

MR. MARCHIONNE: the false positive rate that we've experienced in-house--and I can speak to that, and I think we have some customers here today that will speak on their experiences. But we have seen less than 1 percent contamination rates as false positives. And in terms of the hood, sterile hood, I believe that the sterile hood does indeed help lower that, as well as the sampling devices.

But what we've seen in terms of training facilities is that we have seen that there is a learning curve in terms of false positives and initially getting started with the system. And those that have a hood have seen a lower amount of false positives.

DR. KUEHNERT: I hope the subsequent presenters will give more precise numbers, because one of out 100 would be very concerning. So we'll look forward to that.

MR. SKINNER: Dr. Holmberg?

DR. HOLMBERG: Your system was approved for the two vials, the anaerobic and aerobic?

MR. MARCHIONNE: Yes.

DR. HOLMBERG: So every facility that has implemented this are using both the aerobic and the anaerobic?

MR. MARCHIONNE: Unfortunately not. I am seeing approximately 14 percent of our customers using the two-bottle system.

DR. HOLMBERG: So you're telling me that 86 percent of your customers are using aerobic or--

MR. MARCHIONNE: They have chosen to

aerobic, and the product insert, just to clarify, makes a strong recommendation to use two bottles for optimal detection. But it has been interpreted as not being a requirement.

DR. KUEHNERT: Just a point of clarification on Dr. Holmberg's question. Is that two aerobic bottles, or is that--they're using two aerobic bottles or one aerobic bottle?

MR. MARCHIONNE: Good question. They're using one aerobic bottle, for the most part. I don't know of anyone using two aerobic bottles.

DR. HOLMBERG: But the package insert strongly recommends one aerobic and one anaerobic?

MR. MARCHIONNE: Yes.

DR. HOLMBERG: And that's what it was cleared with?

MR. MARCHIONNE: Yes.

MR. SKINNER: Have there been any in-house studies with pooled platelets with your product?

MR. MARCHIONNE: I have not been involved with those studies, but there have been studies with pooled products, definitely.

MR. SKINNER: I believe Dr. Brecher might be able to comment on those studies.

DR. BRECHER: It's a factual answer here. We have looked at nine bacteria in my lab in a pooled platelet matrix, pools of six platelets. Eight of the bacteria species were inoculated at five CFUs or less into the pool, and the pickup time was on the order of 10 to 12 hours.

Interestingly, that set of experiments, like the previous set of experiments, showed that a lot of the organisms were picked up earlier with the anaerobic bottle than the aerobic bottle, even though we think of these organisms as being aerobic. Usually it's been an hour difference, but with strep viridans, you know, we're talking about 12, 13 hours faster.

Now, we had some informal discussions with the FDA as to the design of that experiment, and the question revolved around what were we looking for. Could we detect low levels of bacteria in a pooled platelet matrix. If that was the main question, then we thought we would go ahead and

just pool the platelets and then put in the bacteria. And they had agreed to that informally. But as Jaro outlined today, now they say, no, we want to see bacteria in just one bag and then pool them. So all these experiments will have to be redone.

MR. SKINNER: Dr. Holmberg?

DR. HOLMBERG: Do you also strongly advocate that the laboratory identify the organism?

MR. MARCHIONNE: Yes, we do. Upon the alert from the system of a positive, we recommend sub-culturing that bottle as well as gram staining.

MR. SKINNER: I don't see additional questions, so at this point we will move on to the presentation from Pall.

MR. MARCHIONNE: Thank you.

MR. SKINNER: Thank you.

Dr. Jerry Ortolano? I got that one right. I apologize for mispronouncing the others.

DR. ORTOLANO: I want to thank the committee for the opportunity to present this information, and basically we're here to discuss

current issues of bacterial detection, well recognized as the number one threat of infectious complications associated with the transfusion of platelets.

I will touch upon four areas. First, I have been asked to really address potential availability problems with implementation of CAP and AABB, and I'll discuss what I know about bacterial detection and how it might impinge upon this question; practical issues of bacterial detection, the pool and store as a solution to the problem; and, finally, I'll give you some data concerning the performance of the eBDS, which is the Enhanced Bacterial Detection System.

First, with respect to the unintended consequences of bacterial detection, as you know and as this committee is addressing, with the market moving towards implementing bacterial detection and in many cases using it as a release criteria, this was not the intention of the FDA. They approved the product for QC and not release criteria.

But there are fallouts with this. Given the fact that the market wants to do this, the concerns that were addressed as a consequence were: Would this divert the availability of platelets? Basically would people prefer to use apheresis platelets as opposed to random donor because of the cost-related issues. If they're six-unit pools and you have to do six unit bacterial detections, that's six times the cost. So it is a legitimate concern.

Hospitals may implement alternative methods of bacterial detection, and as we know, we've heard discussed here today that some are indeed using dipsticks, some are using pH meters, some are using glucose analyzers. So those will have to be considered as well.

The implication however is that there is some kind of a tradeoff between safety and availability, and we submit that pool and store makes all that go away.

With respect to the two products, apheresis deriving from a single donor, we have

good experience about what the cost is, what the logistics are to use this product, and its safety and availability. I'll also submit that whole blood-derived pool and story, there's a body of experience from Europe that we can latch on to which would suggest that they're comparable, comparable in cost and maybe even less costly, comparable with respect to logistics and safety and availability. This is something we have yet to prove to the FDA, of course.

Pool and story, the current status for our company is that we are discussing with the FDA--and we'll met again with them on April 15th to discuss our data. We have 24-hour corrected count increment data which shows very strongly that we can pool and store for five and seven days and get good data at 24 hours.

The literature is replete with comparisons of one and 24 hours with respect to corrected count increment and basically show that 24 hour CCI is pretty predictive of what you see at one hour. So since we limited our data collection to 24 hours,

we'll offer that and hope that they would accept it.

The pool and store systems have been in routine use in Europe, as I mentioned, for years.

This is what a pool and store system would look like. There are two separate configurations. System one is for a leukoreduced random donor platelet concentrate. You see the legs on the left? You can actually sterile connect six units onto that system, and you could sequentially express them into the bag. These are already leukoreduced. All you need is a sample pouch to collect the sample for bacteria detection, and that's what you see hanging off.

With respect to system two for non-leukoreduced random donor platelet concentrate, you have, again, the six legs so that you could express up to six units into a bag. You would then pass that pooled material through a leukoreducing filter and then onwards into the bag. And then from that you can actually take a sample for bacterial detection.

You'll notice that there's a larger bag off in a T configuration, and that's basically to eliminate all of the air that would accrue as a result of processing six individual units. You always get a lot of air in the bag. You need to express that air out, and that's what that bag is for.

The studies completed to date include in vitro data for both five and seven days; in vivo data for five-day studies that have been performed for both systems. There is no effect of pre-storage pooling on lymphocyte activity, plasma activation complement, coagulation factors, et cetera, during storage. And we have some satisfactory in vivo data for five days and in vitro for five and seven days on storage quality.

I'll now kind of summarize the reflection of the problem. This is a recent paper published by Brecher and Hay, and basically it shows the results of the hemovigilance activity, the BaCon study, the SHOT study, and the French study.

I just want to point out that the six

units associated with fatalities have been further analyzed from the BaCon study. And what they show basically is that the platelet product only has to be somewhere between two and four days old to confer serious--to confer mortality.

If we look at the practical issues concerning platelet transfusions, we'll use Brecher's data at the University of North Carolina where we can see that the vast majority of blood products transfused for platelets are three and five days old. If we look at M.D. Anderson's published experience, which is a little bit different from what we hear, the vast majority is three days old. I actually hear it is now closer to two days old. So two to three to five, in that area, you're going to see platelets transfused.

What do we know about observation of bacterial growth in platelet concentrate? This derives from early literature. Basically it's generally agreed from that literature that the bio-burden is usually low. Rarely is it greater than 10 CFU per ml. So that's a target that we

could start thinking about.

Concentrations less than 5 CFU per ml are often complicated by inconsistent growth. This is the so-called auto-sterilization effect, and that has implications for spiking studies. If you go much below 5 CFU per ml, you're going to have to spike a lot of units of blood because they will not often grow.

If we look at sampling error, which has been addressed here, this little cartoon kind of demonstrates the point at its extreme. If we had one CFU in an entire bag of apheresis product, 300 mls, and we took out a 2-ml sample, the probability of capturing that one bacterium is 2 in 300, or 0.7 percent.

Even if we were to capture that, if the bug is captured, it leaves the platelet bag sterile, and the result would be a false positive. Again, that is extreme. If the bug is not captured, then the result is really a false negative. So this kind of represents the absolute extreme, what could happen.

As a result, we have to allow organisms sufficient time to grow to levels to avoid the sampling error. Now exactly how much time you have to allow is not really known. It's suspected that you'll start to get growth within 24 hours up to a significant level, and we'll actually see what the results of spiking studies are. But, again, looking at this in the clinical situation is a little bit different.

This is applicable to both single-donor platelets and random donors alike, and it's hard to imagine its avoidance, regardless of the method of detection. So whatever technique you choose, you're going to have to allow a certain amount of growth to be able to capture that in your sample.

This is data from Brecher and coworkers which basically show the results of spiking studies. These are six bacterium. On the Y axis, you see the log CFU per ml, and on the X axis is your days in storage, PCs at room temperature. And for many organisms, the initial bio burden doesn't make much difference. The growth is pretty

consistent. The one notable exception here is in staph epi, where you see that an increase in the bio-burden at time zero results in a more rapid attainment of the plateau phase.

If we were to impose upon this an arbitrary value of 10 7 CFU per ml and make that a detection limit, let's say--for practical purposes, I'm going to say for dipsticks. Then there are times when even at one day or at two days we may to be able to detect the bacteria.

If we look at a similar study we published out of our lab, the same kind of growth curves, and, again, impose that 10 7 CFU per ml, you can see that there will be times when we will miss bacteria.

So the culture-based methodology relies on taking a sample, so you have to allow a certain period of growth to occur to make sure that your sample is representative of what's in the bag. It also includes an incubation environment such that we foster the growth of bacteria in the sample to get detection sooner than would be possible you

measuring it in the platelet concentrate itself, which is stored at room temperature.

This is the Pall enhanced Bacterial Detection System, and I'll just briefly describe for you what the differences are between the old and the new. And many of you may not know what the old one was so I'll try to be a bit descriptive about it.

It is really comprised of two components: a sampling set that's disposable, and a bunch of equipment. That equipment includes an oxygen analyzer, a bar code reader to enter data, an incubator with an agitator. The agitator is actually an enhancement. We used to incubate these statically, and we found that results are better with agitation, and you'll see why in a minute.

Then there is a computer program that's represented by the monitor there which basically allows you to harvest or capture the data.

The idea behind this, the technical idea, is that we will express, after a suitable period of incubation at room temperature, a 2-ml to 3-ml

sample into a disposable--a sample pouch. In that pouch, we incubate the platelet concentrate with sodium polyanethol sulfonate, which is known to be an inhibitor of complement. It also inhibits lysozymes and some lipoproteins, which are normally anti-bacterial in nature. So that will foster--you inhibit the inhibitors. You'll foster the growth of the bacteria. We also add triptocase(?) soy broth as a nutrient enrichment. And we agitate the sample and incubate at 35 degrees centigrade.

Now, the bacteria will consume oxygen in this setting, and the oxygen will become depleted in the plasma. We then shake the sample so that we can redistribute this, and we can set up an equilibrium between oxygen in the plasma and oxygen in the air, in the head space just above it. So the idea is to measure the percent oxygen in air and use that as a surrogate marker of bacterial growth.

Here the Pall eBDS measures oxygen in the head space and compares it to some predetermined threshold limit.

The old Pall BDS system you see on the left, and basically what we have here is--we used to entrain a sample of the platelet concentrate through a filter, and the purpose of the filter was to reduce the burden of platelets. These are all leukoreduced blood products. So we reduced the burden of platelets because respiring platelets will consume oxygen. And if they consume oxygen, then that would contribute to the likelihood of developing a false positive.

So we take the platelets out, allow the bacteria to pass. Unfortunately, the bacteria transmission was not 100 percent. Sometimes it would be as low as 15 percent, sometimes as high as 80 percent. On average it was about 50 percent. And if you have a low bio-burden of bacteria to begin with, you can see how, by utilizing this filter, you would actually trap some of the bacteria and maybe not get as good a sensitivity as you would like or your thresholded section would be higher than you would like. So we actually in the enhanced version removed that filter.

We replaced the function of the filter with another additive in the sample pouch. This is an agent which actually causes the aggregation of platelets and minimizes their respiration. And so we actually remove that confounding variable in just a different way.

What you'll also see is that there's a probe that actually gets insert into a little septum up there, and the septum and the sample entry occurs in the same column. And we found that to be a problem, too, and so we replaced that by putting the sample inlet and the probe sampling port on opposite sides of the sample pouch.

These are data of low-level spiking studies. What you see are ten organisms which constitute 98 percent of all fatalities reported to the FDA associated with contaminated platelet products. What you also see are bins--bins of the number of units that we tested, which were less than 5 CFU per ml, between 6 and 15, 16 and 50, and greater than 51. If I draw your attention to the bottom of the column on the right, you can see that

the detection now--this is just spiking and then retrieving a sample, incubating for 24 hours at 35 degrees, and measuring percent oxygen, demonstrates 96.6 percent of the samples were detected positive.

Now, this is not the way the product is instructed to be used. This was really just a reflection of the robustness of the eBDS system. The way we recommend it to be used is to wait that 24-hour incubation period where, if you spike with a low bio-burden, now you can see many of the organisms have grown to higher levels. You can see that there are a lot of numbers now in the column that are greater than 51, whereas before, you saw no values greater than 51. So you could see that extra 24 hours allows for a lot of opportunity for sample growth, bacterial growth, and now the detection sensitivity, if you will, under this condition is 100 percent.

MR. GIROLAMO: So with respect to our summary of limitations to the BDS. All are addressed by the enhanced BDS. The original product had a limitation with respect to

sensitivity, or threshold detection. We removed the filter--the platelet-removing filter--and we actually increased our sensitivity or limit of detection.

The ease of use issue related to the probe and aspirating plasma into the probe, which caused the machine some concerns--we actually placed a hydrophobic membrane at the sample port, which allows you to now withdraw a sample without taking any fluid up. And so that problem's eliminated.

We had something called a "system 6.2 error." Basically this was just naive on our part, never realizing that it would be possible that the oxygen concentration would be zero percent in the head space.

The software initially developed would not understand what zero is and would give you a 6.2 error. So we corrected the software there, and that's no longer a problem.

And, finally, the platelet volume loss was initially 7 mls because of the use of the filter--the platelet-removing filter--which

consumes a lot of volume. And by removing that and inserting a duck-bill check-valve into the line, we could strip back a lot of the platelet concentrate. And so now our loss is minimal.

You can see each one of these is addressed by what I've just suggested for you.

Now, I'd like to talk to the alternative points; the issues related to test methods. And I think by and large they all relate to glucose and pH.

They can be measured either with dipsticks--urine dipsticks--or they can be measured with an analyzer--a pH meter for example, or a glucose oxidase assay automated analyzer.

[Slide.]

There are data in the literature--which you can see here in the study on the right--and I won't bother going through the detail of this, but just to say that--I'll refer you to the papers and to these little salient feature highlights. And what they show is that there's a lot of variability in the results. And, generally speaking, you can

find bacteria which you will not be able to detect, even out through five days.

I think the definitive study to date is one that is not actually in press, but Mark assures me that it will be soon, and that is a very extensive study looking at pH and glucose with dipsticks, also comparing it with swirling. And, generally, what Mark finds, and I'm certainly willing to have him correct me if I'm wrong--but what he finds is that basically the results are quite variable, depending on the organism.

[Slide.]

You can that bacillus sirius here, at 10^6 CFU on day two of storage, two of three were positive with glucose, with a dipstick, but they were not detected with pH or swirling.

In contrast, if you look at staph epi down at the bottom, at 10^4 CFU on day four of storage, zero of three were detected with any method--dipstick, pH, glucose analyzer, or swirling.

So this, I think, addresses the issue to a

better extent than is currently available in the literature. And this is not going to be the last time we see data like this. We understand that there at least centers that are doing side-by-side comparisons with the alternative methods.

So, in conclusion, bacteria contamination occurs with significant morbidity and mortality. I think that's unquestionable. There are two QC approved methods that are based upon longstanding and well understood principles of standard culture technology, and the preferential use of approved QC bacteria detection methods is limited to single-donor platelets because of the cost in applying it to the random donor platelet concentrate.

The reliance upon single-donor platelets may present availability problems, although, quite frankly, personally, I find this hard to understand how that could come about when we even see institutions today who transfuse blood products that are outdated--by virtue of the fact that they have nothing left.

So I don't think random donors will ever really go away. I think there will be less reliance upon them.

Cost issue for random-donor platelets can drive health care to use inferior methods of bacterial detection--and that is a fact. I mean, we see that happening now. I know of at least two institutions, personally, that are using either dipsticks or pH meters to try to address this issue with respect to bacterial contamination using alternative methodology for random-donor platelet concentrate.

And I believe that poor-and-store really is a solution to this problem. And whatever BSAC can do to reduce the latency for approval of pool-and-store, and to get to the point where we could increase the outdate to seven days, we'll actually enhance, not only the availability, but also safety.

Thank you.

CHAIRMAN SKINNER: Yes, Matt--Dr. Kuehnert?

DR. KUEHNERT: I had a question on a previous slide you had on the performance of the new system. And it was about the organism that was missed. I think it was--

MR. GIROLAMO: 24? This is zero time data--pseudomonas aerogenosa?

DR. KUEHNERT: Yes.

MR. GIROLAMO: Yes.

DR. KUEHNERT: What concerned me that it was pseudomonas. That's a bad one.

MR. GIROLAMO: Yes, it is a bad one.

DR. KUEHNERT: And it generally grows pretty quickly. So I was trying to understand what the problem was.

MR. GIROLAMO: Yes. Well, I inquired about this data and found that the unit was detected positive when we held it for 24 hours. So it's not as if there weren't bacteria in there--there were, and the bio-burden was pretty low, at 6

15 CFU per mil, but not ridiculously low, at less than 5.

So the answer to your question is: we

don't know why this occurred.

DR. KUEHNERT: Was it a mucous-producing organism? Was it something that got sticky or something? Or you don't know?

MR. GIROLAMO: I can't find an explanation for it.

DR. KUEHNERT: The other questions I had, basically asking the same questions I asked the BioMerieux representative, which is about a false positive rate--

MR. GIROLAMO: Yes, it's less a tenth of a percent. And I'll give you--the data that we're relying on here is the recent publication of Gail Rock, in which she did over 12,000 and found one false positive. And we have one more, I believe, from field experience, and it's about a similar sample size, when you consider all of the product in use. So we're saying it's less than .1. It's probably closer to .01 percent.

DR. KUEHNERT: And the final question I have is: you mentioned about the system being used internationally?

MR. GIROLAMO: The system is being validated for use in Europe. There are many institution that--you know, the European process is a little bit different. Every time you go for a new product in Europe, they have a long period of time where they actually evaluate. And they started the evaluation before we actually approved product here. So they're continuing to evaluate, and they've amassed a considerable amount of experience, and that includes the National Blood Service of the U.K.

DR. KUEHNERT: Are they comparing--or are you aware of any comparison--of day five versus day seven, in vivo?

MR. GIROLAMO: Gail Rock is the only study where we saw day seven data. I know that the National Blood Service is interested, but I'm just not sure how far along they've gotten.

CHAIRMAN SKINNER: Other questions?

Dr. Holmberg?

DR. HOLMBERG: How do you get around the aerobic and anaerobic files? You only have the one

pouch.

MR. GIROLAMO: Correct. We didn't consider the anaerobic to be a clinically significant issue. There was only one reported fatality in the literature that we were aware of at the time we started this, and that was for propreanabacter acnes. And, as it turns out, quite serendipitously, we had in our actual clinical use of the product, two occasions where propreanabacter acnes was actually detected with our system.

We wouldn't have predicted that. You know, we don't think that it actually responds to anaerobic organisms. But if we give it a little bit of thought, there may be a scientific explanation for that, or a theory that we could propose.

CHAIRMAN SKINNER: I might ask the same question Dr. Lopez asked of the previous presentation: if you can give us an estimate of the cost?

MR. GIROLAMO: Yes, it's $20 per platelet-detection system. So you're paying for

disposables here. So it's $20 for the disposable. All of the equipment is provided at no additional charge, so basically the disposable cost includes amortization of the equipment over the life of the instrument, which we are held responsible for. So, if there's any issue with respect to equipment, it just gets replaced or repaired at our expense.

CHAIRMAN SKINNER: Dr. Holmberg?

DR. HOLMBERG: So that raises the question: you are approved for leukoreduced whole blood.

MR. GIROLAMO: We're approved for leukoreduced apheresis product, or random-donor platelet concentrate--not for whole blood. Whole blood-derived.

DR. HOLMBERG: Whole blood-derived platelets.

MR. GIROLAMO: Yes.

DR. HOLMBERG: So if there was a pool of five, then we're talking $100.

MR. GIROLAMO: That's correct. That's what makes it impractical.

See, actually, from a practical experience, we want to facilitate its entry into the market, we've actually lowered the price. It really isn't that--I mean, it could go as low as $8, for example, but even that is too high.

So we're trying to encourage the utilization of random-donor platelets, for reasons unrelated to bacterial detection. They happen to relate to our other side of the business, which is leukoreduction for random donors. So--you see what I mean? We'd be shooting ourselves in the foot if we didn't make it available, but we don't make it available to the extent where it becomes actually a reasonable cost. Eight dollars for a random donor translates to, 8, 16, 24--$48 for the pooled product, if it's a six-unit pool.

CHAIRMAN SKINNER: Other questions?

[No response.]

At this point, then the committee will take a break. We will return at 3:30, and we'll hear from the blood centers and the hospitals on their experience.

[Off the record.]

CHAIRMAN SKINNER: If the committee can come back together, I'd like to begin this afternoon's presentations--or the last part of this afternoon's presentations.

BLOOD CENTER EXPERIENCE

And next up, we'll have an opportunity to hear--the next item on the agenda is the opportunity to hear about the blood centers' experience. And we're going to have the opportunity to hear from two blood centers.

First we're going to hear from the Florida blood centers, and then we're going to hear from the Puget Sound blood centers. And Mr. Timothy Malone will present first.

MR. MALONE: Thank you, and I'd like to thank the committee for the opportunity to offer our experiences from the blood center perspective.

And as many blood bankers, we're dusting off our micro books and discovering that whole field of microbiology once again.

Not to be redundant of what's already been

discussed--we know about he accreditation requirements and where they all stem, both the AABB standards and the CAP inspection checklist.

Just a brief commercial for the blood service. It's located in the Tampa Bay area on the west coast of Florida, not to be confused with Florida Blood Centers in Orlando. But Florida Blood Services collects and processes approximately 170,000 whole blood collections, 11,000 platelet pheresis donations yielding 17,000 components; over 70,000 whole blood-derived platelets were distributed in 2003, and a total of half a million blood components are manufactured annually.

We service the entire Tampa Bay Metro Area, which includes 34 hospitals. We are also considered by most to be the fourth largest transfusion service in the U.S., in that we perform compatibility in the major transfusion centers in the Tampa Bay area.

Bacterial contamination, we've learned--not to be repetitive, again--but it's the most recognized residual transfusion-transmitted

disease risk. Bacteria in platelets is defined in the literature: detected in 1 in 1,000, causes reactions in 1 in 10,000, sepsis in 1 in 100,000, and death somewhere in the neighborhood of 1 in 200,000.

We've approached this from several angels: limiting opportunities for contamination; detection of contamination; and the Holy Grail, we hope to be one day, pathogen reduction or inactivation.

Under the topic of limiting contamination, we've gone forward with good aseptic technique in phlebotomy. We, ourselves, have changed from a 2 percent providone iodine solution to now using tincture of iodine and an alcohol scrub, Chlorhexadine, although recognized as a very efficient means of scrubbing is rather cost prohibitive And, of course, the diversion of the initial blood flow, all limiting contamination.

Bacterial contamination by culture methods--we've also learned earlier today--the Pall BDS system, measured by oxygen consumption; the BactiAlert BioMerieux system by CO2

generation--both having the highest sensitivity of any of the detection methods noted; however, they do require a lag phase, and are recognized to be the most costly.

Other methods, including staining, sensitivity in the neighborhood of 1 million CFUs per mil; Gram stain, Wright stain and acridine orange; the dry chemistry dipsticks--that is FDA cleared for urine analysis, and not necessarily for platelet rich plasma, but hence we are using them asa surroggate marker, measuring glucose and pH to determine potential for bacterial contamination. And that magical swirling, which we all learned that, earlier as well, as a CAP allowance, but not AABB, and the sensitivity of 10 million CFU per mil.

Dr. LeParc visited both--Dr. LeParc, Herman LeParc is our chief medical officer. He visited both Dr. Bricker's lab and Dr. AuBuchon's lab back in late 2002; came back to me and charged me with the process of providing bacterial detection--initially of our platelet pheresis

products. At the time we were in litigation over a death of a patient that had received contaminated platelets, and he wanted us to be the first in the country, in the large scale, to be up on this process.

Our validation strategy included performance qualification, that of detection in using seeding known organisms, negative controls, positive controls, determining the CFUs per unit; considering the dilution by the plasma volume of the component, of course, and relative concentrations of 10 to 100 CFUs per unit.

Lag time variables we looked at from the time of seeding to inoculation. We looked at, pretty carefully, the volume of inoculant and its effect. Repeatability was an issue, and also, of course, personnel training and competency, as part of our performance qualification.

Operational qualifications included the use of the BactiAlert BioMirieux system, the computer platform, that of offering positive ID, the sample integrity from the storage bag to the

culture medium; the elapsed time; the temperature of the incubator itself; and the inherent messages that come across the Bacti 3-D system, which include error codes and the relative print functions and problem logs that are generated from the Bact 3-D system.

We also looked further into our operation system entry, and we decided at some point to create that as a label control mechanism for allowoing platelets to be QC released.

This is some of our initial data--not 30,000 samples, but in terms of using simply platelet phereses, inoculated with--and these got--I apologize, this slide got cropped off--but this column represents staph aureus; this column represents Candida albicans; and this column represents E. coli.

And we looked at the potential of reducing the time to detection overall by reducing initially the lag phase. We thought perhaps--or rather than a 24-hour lag, we would look at the comparison of time to detection in the bottle without a lag

phase, as compared to a 24-hour lag phase. And you can see the time to detection was readily sooner in the column that maintained the 24-hour lag phase.

And the comparative data: this is staph aureus at 10 to 20 CFU per mil.

[Slide.]

We also looked at the variable of volume, looking at from a small inoculant of 2 mls up to 16 mls, and looked at the time to detection over the volume range in triplicate. And I believe that was also a staph aureus at the same relatively low concentration.

We do not think then, from this data, that it was clinically significant to have an accurate measure of volume, so we estimate the volume in a sample pouch to be 8 to 10 mls. And we're using just an aerobic bottle.

[Slide.]This is the same data represented from the reflectants graphs that come off the Bacti 3-D system, showing the upswing of reflectants and the positivity at the hours associated. Again, staph aureus at low inoculum volumes--or

concentrations. And I believe it was a hight of 9.8 hours, to a low of 9.1 hours.

So our operations ;then included--or does include--and this is for our platelet pheresis products--we isolate and sample for daily QC cell counts, our platelet count and our WBC count by flow cytometry, both done at day zero. We then incubate the platelet pheresis product in its aliquotted, or allocated storage containers--whether it be a split product, single, double or triple--for that 24-hour lag phase.

We combine the units then, again, and test the parent bag, if you will, by sterilely connecting a sample pouch, filling that sample pouch to an approximation of 8 to 10 mls and removing that pouch and isolating the platelet pheresis while the bottle now incubates for a minimum of 12 hours.

So the inoculated culture bottle, we obtain a 12-hour negative to date report that allows us to enter what we know is BD1 into the operation's computer system that allows for then

labeling and release.

We do monitor that culture bottle through day five, and we again enter then a fiave-day result into our operation's computer system.

This is a pouch that we designed, through the help of Charter Medical, Winston-Salem, North Carolina, where we are able then to sterilely connect the platelet pheresis to one lead, and it has a Y-connector and simply a savety needle that allows us to apply the inoculum into the blood culture bottle aseptically.

[Slide.]

This is our sterile connecting device, and the process that allows us simply to fill the pouch to the base of the label for the volume of inoculant. And then we move the pouches into a laminar flow hood--a biological safety cabinet--where we then proceed to inoculate the bottles.

[Slide.]

Similar information--or similar pictorial views of the action in the laminar flow hood. We

do clean the bottle with a sterile alcohol prep pad, and then we take a second sterile alcohol prep pad, place it over the bottle top, and inoculate through that pad into the bottle to inoculate the culture.

Interestingly, when we started the process, unbeknownst to us, there are such things as non-sterile alcohol pads. And you'll see in our data, shortly, that several of our initial contaminants were thought to be from the actual cotton fiber of a non-sterile alcohol pad.

[Slide.]

More logging information. We batched the pouches after they were sterilely connected. We obtain a second blood unit identifier, if you will, and attach it to the sample pouch which then transfers to the log that identifies then, or matches the log blood unit ID to the bottle ID. The bottle IDs are unique, however you can have multiple unit numbers associated with the same bottle ID.

[Slide.]

What have been our implementation issues? Particularly that of handling positive results?

We, early on, decided Dr. LeParc would notify the physician if the unit was released. We've determined, then, subsequently to that notification, whether it is a false or a true positive by replicate growth study.

We notify the donor--we've set up a donor deferral status, and we flag the donor in an initial positive result, and if they've come up positive two times, they are permanently deferred. And we've had--one of those such folks that had donated over 280 times, and it was very obvious by the looks of their antecubital faucets that they were harboring bacteria that we just couldn't clean off. So if we do have two positives--a two-strike donor, if you will--that donor is deferred.

We set up mechanisms to ID the organism and provide sensitivity to the physician, and we do that through a local microbiology lab in town. And we've yet to--although we have a goal to develop or have a computer interface to the BactiAlert system.

So what happens when we have a posititive result on a released unit?

[Slide.]

Well, in our scenario we have three such scenarios, in that we have contract transfusion-service hospitals, which about one-half of our issued blood components go to our own transfusion services. And in that case, we have computer information that indicates the patient's name and physician, and we do manage those as panic values to the ordering or transfusing physician.

At those hospitals where we consign the blood to, we notify the lab. And on those occasions where we've been able to export or resource-share a unit of platelets, we notify the receiving blood center.

[Slide.]

Then we move forward with a root-cause analysis, evaluating the phlebotomy staff--both the phlebotomy staff and the donor. We perform root-cause analysis on both our true positives and our false positives. And, as I said, the false

postivies are determined by a lack of replicate growth.

Within the phlebotomy staff, we review their records and we do an audit on their technique, particularly their scrub technique.

On the donor side, we've brought the donor in, and Dr. LeParc obtains a thorough medical history, thorough physical exam, and we've cultured skin, urine and blood through the process.

[Slide.]

These are our stats to date, looking at one full yeaer now of bacterial detection on our platelet pheresis products--just under 11,000 total donations tested. We've had 11 positives, which is right on the recognized norm of .1 percent.

Of those, we've categorized the positives to be false positives and that of contaminants; in other words, they did not show true to be--in a replicate growth study, they did not regrow.

We had five of those, and the bugs associated; we had four bacillus species in positive at the times noted here. I should also

note that once we switched over to a sterile alcohol pad, those bacillus species stopped appearing.

We did have one Kleb pneumo that we could not repeat on replicate growth; whether it was an auto correction by the plasma, or whether or not it was a contaminant, it's hard to say.

But we did have six true positives; for staph epi, one E. coli, and one staph aureus.

Interesting here, the staph aureus was a donor that identified and, upon physical exam, informed us that she had a long-term osteomyelitis of her ankle that was supposedly cured about a year prior, however we grew the same bug that was growing in her ankle.

[Slide.]

Challenges that remained at this point, then, included now an inventory control of a three-day shelf-life product. And we're looking forward to seven day expiration, pending Bacti data.

We did begin bringing in our expired

platelet pheresis back into the center--those from our transfusion services--and we've begun re-inoculating those components, and we've not yet found--and I think we're just about 200 products re-inoculated--we have not yet found a unit that grew through day 11 that did not grow through day five.

We're grappling with the idea of hospital inventories, and whether or not to credit or not to credit returns. Currently, we do allow our hospitals to return products to us with 24 hours remaining on them, and they get full credit--which is a continuous revolving door with a three-day shelf-life.

And that issue of what we're going to do with whole blood-derived platelets, and of course to work all the bugs out--pun intended.

[Slide.]

Status of bacterial detection. Now, currently, there exists a dichotomy of safety, with two different safety profiles existing for platelet doses. In our shop we issue 70 percent of our

platelet doses as platelet pheresis that are tested by blood culture, and 30 percent of our whole blood---or our platelet doses are issued as whole blood-derived platelets, and these are currently being tested by surrogate markers for bacteria; that of pH and glucose. But there definitely exists a dichotomy in safety, and I'll show you that data.

Again, going back to Charter Medical, we have developed this platelet sampling device for a means of applying our investment in our Bacti detection system for our whole blood-derived platelets. And this system initially was designed to allow us to sterilely connect six whole blood-derived platelets here, and to pull an aliquot, then, from each of the six samples; or each of the six platelet units.

Then our plan was to seal off the syringe; take the syringe and the safety needle to apply to the blood culture bottle, remove this portion, and then we even had a pooling back associated with the set that we would--we thought the transfusion

services then would utilize to pool the platelets and they'd remain in this pool of six without physically actually pooling them, but by pooling a sample.

Dr. LeParc came back from one of these meetings, and Dr. Epstein informed him that, yeah, he thought it was a good idea, but we'd have to do about 30,000 to show that that was efficacious.

[Laughter.]

And he said not in his lifetime.

So we had another discussion about what we would move forward with.

I guess part of the concern, too, is that serial connecting device, and the potential for bacteria to flow upstream into your platelet and not be detected downstream in your syringe.

[Slide.]

So, we moved forward with a new concept, in that we would remain, or leave, a nine-inch segment of tubing at the end of the platelet production process. We take that nine-inch segment of tubing and we strip it back and mix it well at

the end of production and at the end of the one-hour rest period.

And then we've found that putting these segment materials, if you will, into sets of six, and incubating the lag phase at 37 degrees, we can greatly enhance the detection in the time in the bottle.

[Slide.]

So what we're doing the next day, then, after the 24-hour lag phase at 37 degrees, is sterilely connecting our six samples--our six segment samples that we've logged previously with a pool ID--the pool ID is now associated with the syringe. And once connected, we go into the hood and we clean the distal end of that segment. We apply, then, the Baxter Hemotype Segment Device to the end to allow for a vent, and with that, we pull that volume of six random platelet, or six whole blood-derived platelets into a syringe for testing into one bottle.

Initially, we were concerned with whether or not the segment would sustain bacterial growth,

and we looked at a lag phase, comparing 12 hours at 37, to 24 hours at 37 and 24 degrees--trying to vary that lag phase once again. And, interestingly, we saw in every exmample here that the time to detection with a lag phase of 37 degrees was much less than that of a room temperature lag.

[Slide.]

We looked at a small number of organisms; a lot of staph epi, E. coli. And then, in terms of determining the sensitivity, or trying to evaluate the sensitivity of a pool of six, we inoculated one--or we seeded one of the six with a staph epi, at a relatively inoculant. Again, 24-hour lag at 37 degrees, and we found positive detection at 7.4 hours.

It's also interesting ot note that the total tiime elapsed--the 18 plus the 12, and the 24 plus the 6 or 7, is the same total time elapsed. But we feel it's important to shorten the time to detection in the bottle, because that is the time where the platelet may be released prior to

detection.

[Slide.]

This is an example, then, further, of our ongoing validation. Our goal is to get 100 pools of six blood unit numbers, or 100 pools of six whole blood-derived platelets. We set them up in those pools of six, as I've described, but we also set them up in singlet to look at the relative sensitivity between a singlet application and that of a pool of six.

We interpreted that data, and we compared then, at day five, a pH and a glucose from a urine dipstick.

[Slide.]

And this is a summary of that data. We've done 100 pols now; a total of 594 platelets--whole blood-derived platelets. We had no growth in both the pool result or in the singlet result. However, looking at the surrogate markers--pH and glucose--we had 6.1 percent fail a pH of less than 7. We had 25 percent fail a glucose of less than 250 g/dl. And using both of those criteria, we had

a failure of 5.6 percent of our whole blood-derived platelets, using the surrogate markers.

[Slide.]

Further studies included, now, taking seeded organisms, or seeded platelets in a pool of six. We seeded one whole blood-derived platelet within that pool of six at a relatively CFU, at 15 CFU per mil. Comparing, then, a 37 degree lag to a 24 lag--and you can see in every case, with staph aureus, staph epidermis and E. coli, we were able to reduce the time, in this case, by half; the time to detection in the BioMerieux BactiAlert bottle.

And, again, we fell that's very important, because that's the time frame when the platelet can be released.

Interestingly, we looked at the pH and the glucose at day five in the singlet application, both--with all three organisms. We probably would have noted these in our dipstick methods, however the E. coli at a low inoculant maintained a pH of 7.5, and a glucose at 250 through day five.

[Slide.]

Our conclusions are that pH and glucose levels as surrogate markers are not consistently maintained in platelet storage day five, and we do recognize that we're in a Baxter PL1240 plastic, which is probably not the most breathable plastic on the market, and we are in a 500 ml collection. So that probably has a negative effect on pH and glucose as well.

The correlation of surrogate markers to actual bacterial contamination is poor. And our time to detection is reduced by half, using a 37 degree lag phase.

[Slide.]

What are the costs associated with all blood component sales? And there's been some concerns, I understand from the committee, about removing whole blood-derived platelets from the blood product inventory menu, and what that would do to the cost of the other blood components.

In our model--in our cost model, much of the cost of collections, if you will, or of providing whole blood and red blood cells, and

platelet pheresis, are loaded onto those that we can determine to be a one-to-one ratio between what we issue and what we collect. So the cost for recruitment, collections and processing and testing is associated all with the cost of the red blood cells, and/or the platelet pheresis.

However, if we're looking at the components--platelets, plasma and cryo--it's a variable ratio to whole blood collected, and it's a by-product cost. So the incremental bag cost: the cost of quality control, the cost of production and labor and inventory and distribution is different than it is for the cost load that's associated with red blood cells and platelet pheresis.

[Slide.]

What has been our testing cost to date? Well we have roughly $175,000 invested in hardware, both in the BactiAlert system and that of the laminar flow hood, and a dedicated sterile connecting device, and a dedicated sealer. We anticipate to do 80,000 tests over what we feel is the life of this equipment, which is a three-year

depreciation schedule, and that comes out to roughly 75 cents a unit.

The labor associated with both the testing of the platelet pheresis and the platelets in groups of six--keeping in mind that the cost is associated with the pool of six, or six samples spread over the cost of that process--ranging from a high of $2.99 for the pheresis, to $1.05 for the platelets.

Consumables are listed here, as well.

Our direct costs, then total--for that of the platelet pheresis--just under $14, and that of each unit of platelet in a group of six: $6.70 a unit.

[Slide.]

But the real cost needs to include the cost of increased expiration. And we looked at the same months in 2002 as in 2003, post development of bacterial detection in our platelet pheresis, and our outdate rate went from just over 5-1/2 percent to almost 13 percent. And that certainly is a big cost issue, in terms of doing this process.

What's going to happen to our platelets? Well, we're seeing, now, roughly a 15 percent outdate rate. If we add another 15 percent to that, we could envision a 30 percent outdate rate in our whole blood-derived platelets. So the need for a variance to allow for seven-day storage is very much in need.

[Slide.]

And the emergent technologies that we hop to see in the future: the immunoassay in dry media that was presented at the AABB last year; some idea of spectrophotometric analysis, perhaps, that can take the magic out of the swirl and shimmer. Concentration in mass spectrometry is probably cost prohibitive. I believe the Chiron GenProbe group is working on a molecular probe to detect bacterial wall DNA or RNA; and that Holy Grail of pathogen reduction.

And I thank you for your time.

CHAIRMAN SKINNER: Thank you for your presentation.

Committee questions?

[No response.]

It was very comprehensive. That was very good. Thank you.

Dr. Holmberg?

DR. HOLMBERG: Do you ever import platelets from other locations?

MR. MALONE: We important platelet pheresis, not whole blood-derived platelets.

DR. HOLMBERG: And do you re-test those?

MR. MALONE: No, we do not. We are assured now, certainly after March 1st, that those centers that we're importing from are doing some form of bacterial detection in their manufacturing process.

Prior to March 1st, we would only import from those centers that had developed a bacterial detection technology.

CHAIRMAN SKINNER: Colonel Sylvester.

COL. SYLVESTER: On the donor you said you lost that had donated over 200 units, have you all done any studies--was that skin bacteria, or was it--

MR. MALONE: Yes, we were able to, I believe, genotype the bacteria and found that the same bacteria growing in the bottle was the same thing that we could swab from the skin.

COL. SYLVESTER: And have you all done any work with the diversion pouch to either--

MR. MALONE: No, we have not.

COL. SYLVESTER: --prove or disprove whether or not a diversion pouch would eliminate that risk?

MR. MALONE: No, we have not. And we were fortunate not to be yet in the Baxter sample for its diversion pouch. [Laughs.]

CHAIRMAN SKINNER: Yes, Dr. Sayers.

DR. SAYERS: What has Dr. LeParc's experience been with the notification of physicians of a positive product?

MR. MALONE: Well, the--of the 11 total samples we've had positive in the pheresis pool, one unit had been released and transfused. It was one of the bacillus that turned out to be a false positive. The patient was a transplant recipient

and on megadoses of antibiotics, and the physician was not concerned.

CHAIRMAN SKINNER: Dr. Kuehnert.

DR. KUEHNERT: Well, first of all, I want to comment your blood center for collecting all these data. I think it's very important to look at--try to get a sense of some sort of evaluation here.

I had a couple of questions. First of all, you mentioned that you're also looking at seven-day culture, and you said something about how you haven't had any positives. But I just wondered if you could repeat that.

MR. MALONE: Yes. Within our own transfusion services that we provide blood to--and we have total control over those blood components--we're bringing back those expired units that expire there, and re-inoculating those bags at day five and day--well, day six. And so those cultures go out to day 11, and we've not yet had a unit positive that was, obviously, not positive through day five.

DR. KUEHNERT: And the other question I had: so you speciate--when you get a positive, you speciate--

MR. MALONE: Yes.

DR. KUEHNERT: --every organism

MR. MALONE: We take the bottle from the system, and we send the bottle to a local microbiology lab at one of our hospitals in town. And they do a Gram stain, and we get the Gram stain result back within two to three hours, so that we have an idea whether or not there's actually growth.

And once that has occurred, then we--and I believe Dr. LeParc does notify the transfusing physician of the potential for a contamination based on the Gram stain. And then they go on to identify the organism and do sensitivity as well.

DR. KUEHNERT: So this is all by phone, sort of--

MR. MALONE: Well, yes--phone, and eventually written report--yes.

DR. KUEHNERT: And as far as donor

notification, do you notify the donor for every organism, or only for certain organisms?

MR. MALONE: Just those that are determined to be true positives, but--yes, each of those six true positives we've had, we've notified the donors, and Dr. LeParc has conducted a medical exam on each of those donors.

DR. KUEHNERT: And I wondered if you have in your--it doesn't look like any of these organisms have been of, you know--been reportable to public health authorities. But do you have, in your standard operating procedures, if it were a reportable organism, to report it?

MR. MALONE: If the blood unit--if the pheresis or blood product is transfused, yes. They are reported.

DR. KUEHNERT: It's only if it's transfused.

MR. MALONE: Yes.

DR. KUEHNERT: But as far as the donor--

MR. MALONE: No. No, we haven't.

CHAIRMAN SKINNER: And I'll ask what will

be the last question for this presentation.

You indicated you had one donor that had showed up twice with a bacterial contamination, but they'd given about 280 previous donations?

MR. MALONE: Yes.

CHAIRMAN SKINNER: Did you do any kind of look-back on the recipients of those other units to find out whether there was any transmission of bacterial contamination?

MR. MALONE: No, we did not.

CHAIRMAN SKINNER: Okay.

Thank you very much for your presentation.

MR. MALONE: You're welcome.

CHAIRMAN SKINNER: At this point, now, we will move on to hear from the Puget Sound Blood Center, and Dr. Richard Counts will be presenting.

DR. COUNTS: Thank you.

We strongly agree with those who say that it's high time we did whatever we could to deal with this problem of bacterial contamination of platelets stored at room temperature, and I'm please to share our experience. So far, we do have

some concerns, as you'll see, particularly with some of the difficulties with inventory of platelets that are kind of curious. And also, with the non-specific character, and lack of sensitivity of some of the methods, particularly for screening platelets derived from whole blood.

[Slide.]

The Puget Sound Blood Center serves approximately 70 hospitals in 14 counties in western Washington. It has a large central transfusion service--like Florida Blood Services--that serves a little over 20 hospitals in the Metropolitan Seattle Area. And for the hospitals in the other counties, we send blood components to those hospitals, and they have their own in-hospital transfusion service.

In a year's time we transfuse about 170,000 units of red cells; in this last year, some 16,000 apheresis platelets, and just under 60,000 units of platelets derived from whole blood. It serves large oncology and transplant services, and so we've had, for many years, pretty substantial

need for platelets.

[Slide.]

The Blood Center rejoined the AABB after a number of years of absence--just in time to--

[Laughter.]

--find this standard applying to us. And so--[laughs]--we like challenges.

And so this has been our approach that we've taken. We have, since June of 2003, been culturing apheresis platelets, using the BactiAlert system. We hold them for 24 hours prior to sampling--as is usual, as you've been hearing. They are released for transfusion when they're required, once the sample inoculation has been done. And units that are positive--if we get--if the sample turns positive, then the unit is not used. If it has been sent out, it's recalled, and additional cultures are done to identify the organism and to determine whether this is a true positive.

There is an additional cost, and we've made an additional charge for our apheresis

platelets. Our cost for the testing of apheresis platelets is not quite as low as in Florida. It's about--around $20, a little more than $20 a unit.

For whole blood platelets, we, like Dr. AuBuchon's European colleagues, we laugh at the rather crude methods available. However, our grin is a risus sardonicus, because unlike the Europeans, we had to choose one of those methods to use. And what we've chosen to do is testing with the dipstick method. We've been doing that since March of this year--so a rather shorter experience. It's just the BactiAlert system, which you've seen.

Our current experience with the BactiAlert testing, about eight months is approximately 9,000 units tested negative. We had five true positives, with three different organisms identified; 15 false positives. Seven showed growth in the BactiAlert bottle only, and were not confirmed on repeat cultures of the unit of platelets

Eight "no organisms" were detected, and my understanding is there was some situation where there was evidently a change in the bottle--perhaps

the indicating device--that did not seem to be associated with any actual growth.

So this was about 15 units out of 9,000 discarded for a positive test in the system.

However, that is not particularly large compared, for example, to--there were almost 40, or twice as many units lost in processing related to doing the sampling. This sampling, incidentally, we do in a laminar flow hood. Now, we expect that with more experience, these losses will probably come down a bit.

[Slide.]

So far as the testing of the whole blood platelets with the dipstick, we did a study on--the top couple of rows just shows some of the experience we had with 50 units, looking--these are averages of the 50 units, on days one through six. And the average pH has stayed above 7.2, and they tended to come down a bit. And the glucose average level stayed pretty good.

There was quite a bit of variation, however--this just compared with some data that we

were kindly provided with Torumal, which is something similar.

[Slide.]

When we looked in detail to do some validation on this method, the pH was always above 7, and the glucose always above--well, using that criterion--above 250. Seven units out of the 50 failed about 14 percent rate. Those were all culture-negative.

[Slide.]

We did inoculate several units--spiked them to see whether we could detect them. We detected E. coli without much trouble, but failed, with this method, to detect staph epidermidis inoculated, in one case, at fairly high levels; 100 CFU per mil.

[Slide.]

The criteria that we have adopted for screening at this point are a pH above 6 and a measurable glucose--detectable glucose with the dipsticks.

Now, you probably can't see this very

well. The dipstick procedure for doing it is rather complicated. There is a visual inspection, but it's not necessarily just swirling. We look in general for everything.

The platelet--the tubing is stripped, the bags are mixed three times. They seal off a segment, and then take a sample with a segment splicer, and put that on the dipstick and read it at, I believe, it's 30 seconds for the glucose and then, right after that, for the pH.

We also repeat this procedure if we've had units returned from any of our regional hospitals, where they may be using this technique in their transfusion service--although I might say that most of the hospital transfusion services have preferred to finesse the whole business by getting, insofar as they can, order apheresis platelets, because of the much greater convenience. We do the culturing there, and then they avoid this whole procedure.

And for some of the smaller hospitals, they considered that would be more of a burden than the extra cost of apheresis platelets.

And we haven't had an awful lot of experience, as I said, with this so far. It's about-it's a couple of weeks here.

[Slide.]

And we are testing these whole blood platelets at our two large transfusion services. We actually have two other smaller transfusion service labs that, because of the delays in preparing emergency pools of platelets for emergency orders, we also have attempted, as far as we can, to use just apheresis platelets on those smaller laboratories. They have much less demand for platelets than the large ones which serve the big academic medical centers, the trauma centers and that sort of thing.

So we've had about 970--roughly 1,000 units--tested in that period of time. Five failed for some of the reasons noted. None were culture-positive. And one unit was returned from a regional hospital, and when we tested it, it passed. It still wasn't used, but--

[Slide.]

There has been a substantial impact--we've had a significant loss of--there's a bit of a loss of discarded units directly. The loss from positive tests is quite small. We've had increased outdates, which I'll take about here in just a moment. There's, of course, the increased cost to the hospitals and to the blood center.

I think there has been an increase in the age of platelets transfused, obviously, particularly with apheresis platelets, since we're holding them for 24 hours before we transfuse them, in order to allow the sampling. And it takes longer for emergency orders, particularly of whole blood platelets.

[Slide.]

We have, at this point, made an estimate of costs, comparing some of the costs for the apheresis platelets and the--"random apheresis platelets," RAPS, is what that stands for--and platelets derived from whole blood. And this would be an annual estimate. So far, from our--it looks like the main cost is still testing, but a close

second is the additional--our outdate rate has gone from about 7 to about 10-1/2 percent on apheresis platelets. And there's a certain QC loss, too.

So we anticipate that this would be an increase in cost of about close to a million dollars over the year for our rather large service, and about 10 percent of the annual revenue from these two components. So that will--an increase in cost.

[Slide.]

Let me talk a little bit about the effects on platelet inventory, because we have seen some pattern of shortages. This is a center that does not have blood shortages, by and large, and has not even frequently had platelet shortages--at least for the past six or eight years.

This shows an increased use of apheresis platelets. Now, this was going on at a relatively moderate level--but a continuous increase--prior to the start of culture and testing. We have the sense that it's--the pace has picked up a little bit.

And, conversely, the use of whole blood platelets has gone down.

There are couple of reasons for that, and that's not entirely related to the testing. One of our largest users of platelets, a marrow transplant center, has been doing more and more of the mini transplants, and has found ways to use less toxic conditioning regimens. And so they have succeeded in decreasing the number of platelets used--or necessary to get somebody through a stem-cell transplant, which is a good thing. But it has meant that--there have been several reasons for our decrease in platelets, and that particular hospital used, for many years, primarily platelets derived from whole blood. They're now using more apheresis platelets, also.

[Slide.]

This shows some of the effects on the outdates. Of course the outdates vary a bit, although, as I mentioned, if we compare the eight months from June of 2003 to February of 2004 with the eight months of the previous year, when we

weren't doing testing, the outdate rate is up to about 10-1/2 percent, and it was about 7.2 percent for the previous year. And that's a significant change.

[Slide.]

There's probably been a bit of an increase in outdates of whole blood platelets, too. Partly, this is because when we've had shortages of apheresis platelets and demand for that, we can't produce many more on short notice because it's hard to get additional donors--which I'll mention in a minute. But we can produce more platelets from whole blood on short notice, because we can easily ramp that up. And so, in doing that, I think we've done that some times, some weeks, and then have found that there wasn't a sustained demand for that. And so it's just complicated inventory management.

[Slide.]

And these are--the dot bars are those issued, and this is over a period of about the last year--and again shows an increase in those issued.

And the yellow bars at the bottom are outdates, and they've both gone up.

[Slide.]

And, with whole blood platelets, similar to the earlier things.

[Slide.]

Now, there's an interesting pattern. In 2003--in February of 2003--we see a pattern of--the blue bars--or at least whatever color they are; the top ones--are our inventory of platelets in our system, and the yellow ones are the platelets issues, by day of the week, starting with Sunday.

And you can see there's a dip in the inventories in the middle of the week. There's a pretty consistent use of platelets during the wee, with Sunday being a bit lower than the others. But the others are fairly consistent. Although we have usually managed, during that period of time, so that we didn't really get problems with shortages.

[Slide.]

This is an accentuation of that problem. This is February of 2004--this year--since we've

been testing. And you can see that seems to have been made a bit worse. The use of apheresis platelets has gone up a bit, from an average of about 42 to 45 a day, to a little over 60 a day.

Sunday is still low, and then the top--the taller bars are the inventory. And you can see, on Wednesdays--Tuesdays and Wednesdays, we get very close.

Now, what that implies, obviously, is that our collections don't follow the same pattern as the use. And so what you might be saying at this point is: "Stop whining. Just collect more donors--apheresis platelets--on Thursday, Friday and Saturday," and that would take care of it.

One of the reasons that we're so much shorter on Wednesdays, of course, is that we don't have the extra day of storage time to keep us--tide us over the weekend.

And eventually we will do that. We've increased our apheresis platelet collections about 15 percent in the last year. But it isn't that easy to get people in on, particularly, Fridays and

Saturdays, and even on Mondays sometimes, to take the extra time to donate apheresis platelets. Curiously enough, we don't have much trouble on Tuesday, Wednesday and Thursday getting a lot of donors, which is why we end up with a high inventory on Sundays, when we don't need it--so that the storage time is a problem.

And so when we think about changes that are needed, there are a couple of defects we feel, with the present methods that are associated, for example, with culturing apheresis platelets, one is, of course, the time it takes for culture; the time it takes for the incubation. And this is a good method. Of course, we also hope that if platelets are going to grow, they'll grow faster in the bottle than they will in the unit of platelets. But the biggest problem at the moment is the loss of the use of the platelets for another day at least.

For the whole blood platelets, we think that the systems that are presently available and feasible are pretty costly for a non-specific

system that's relatively insensitive. And we also have the concern that it is tending--for some of these logistical reasons that I mentioned--to strongly discourage further the use of platelets from whole blood, which--now, there are people who think, well, that's not a bad thing; apheresis platelets are good platelets, and there should be no real need for whole blood platelets.

Well, actually, we don't think that. We, in our system--as you could see--at the moment have a problem supplying the platelets needed for our system without using whole blood platelets. In addition, as has been discussed, we have, by getting platelets from whole blood, we not only make use of a resource that's available and that functions well, but also allows some of the fixed costs of recruitment, collection and that sort of thing, in our case, to be spread over more than one component.

So that if we have to completely the abandon the use of whole blood platelets, the patient's costs of platelets will go up because our

costs of providing apheresis platelets are somewhat higher than the cost of providing platelets derived from whole blood. And, in addition, the cost of red cells and other components, in our system at least, will go up as well.

And, finally, we think that this would lead to a terrible loss of the donors' gifts of platelets, which we would simply have to throw away, and not make use of a resource that ought to be utilized, particularly at a time when we keep hearing--nationally--of shortages of all of these components.

So, what is to be done?

[Slide.]

Our suggestions are pretty similar to the others that have been made today: work out some scheme--and we hope that the FDA will be able to successfully come up with some criteria for licensing pooled whole blood platelets, and for doing the studies that would allow that data to be collected; be able to pool whole blood platelets and increase the shelf life--seven days, nine days,

10 days, whatever can be done would help a great deal on all of these things.

And, in addition, I think, obviously we're very concerned that better tests still need to be developed.

Thank you

CHAIRMAN SKINNER: Thank you for your presentation.

Questions from the committee?

DR. LINDEN: Thank you very much for the very helpful presentation.

At your center, how long do the other infectious disease tests--the serology, nucleic tests--take? And can you tell us exactly how long it is to get an answer for the bacterial detection for the apheresis platelets, and therefore how much time, exactly, this adds?

DR. COUNTS: How much time--ahh.

Actually, the other tests take about 12 to 14 hours to do, but some of the units we're testing in a way that is actually going to take almost 24 hours to do those tests, too.

So, to hold the platelets to do the culturing, the additional time takes anywhere from--I would say not very long--four to six hours up to, perhaps, 12 hours.

It's a good point: there are other reasons to delay the availability.

DR. LINDEN: Oh--I'm sorry--so it adds 12 hours? Is that--

DR. COUNTS: Probably, on the average.

DR. KUEHNERT: I just had questions along the lines of what I've asked before.

You're identifying all your organisms after there's an indication that there's a positive indicator on BactiAlert. And that's done at your center? Or you send it out? Or--

DR. COUNTS: It's done at the University of Washington microbiology lab.

DR. KUEHNERT: So then you have the report sent back to you--

DR. COUNTS: Right.

DR. KUEHNERT: And if there's a need for recipient notification, you have--

DR. COUNTS: Right.
DR. KUEHNERT: --a reporting procedure in place for that?
DR. COUNTS: Yes.

DR. KUEHNERT: How do you handle the--
DR. COUNTS: I think we have had one--of the five positives, I think we have had one where it became positive after it was sent out, and we contacted--our medical director contacts the physician. And in that particular case, there was no evidence that the patient had any problem having received those.
The others, I believe we caught before any of them were released.

DR. KUEHNERT: And what about donor notification?
DR. COUNTS: We do try to get the donor back and see if we can find a cause for the contamination.

DR. KUEHNERT: I--umm--
DR. COUNTS: And I can't tell you right now what the details of that--of what we found in

each case. But, I mean, we've got that information. I just don't have it with me.

CHAIRMAN SKINNER: Dr. Holmberg?

DR. HOLMBERG: I'll ask you the same question I asked previously.

Do you import or export any of your platelets--apheresis or whole blood-derived?

DR. COUNTS: Not to speak of. We--ahh--have not imported any significant amount, and we really haven't exported many either.

DR. HOLMBERG: If you exported, would you--how do you inform whoever is receiving it that it's been bacterial tested?

DR. COUNTS: Umm--well, that's an interesting question, because the--only a few places we have sent any to, I think they know that we're doing that, because--but we would either tell them or they would ask, I presume. But we haven't had a systematic way to doing that.

CHAIRMAN SKINNER: Dr. Penner?

MR. PENNER: I'd like to get those extra platelets you've got.

[Laughter.]

DR. COUNTS: Well, we had an interesting--there's an interesting reason why we don't export--or haven't, until--in that we licensed our apheresis platelets, and then, in a triumph of long-range planning, as soon as we got them licensed, we changed the machine that we were using.

And so it's taken us another--

[Laughter.]

--while to get the license up to date. And so--and that's just happened. So now we're potentially available.

MR. PENNER: Rich, you've got a huge transplant operation going on in your shop there.

DR. COUNTS: Yeah.

MR. PENNER: What percentage of platelets are really going in that direction?

DR. COUNTS: Well, I think at one time it was probably about 50 to 60 percent. But, as I say, I believe that's decreased somewhat in recent years because they have managed to find ways to do

the transplants with needing less platelet support.

Ten years ago, they needed an average of--and these were platelets from whole blood--about 130 donations of platelets to get somebody through a transplant. Now they're doing quite a few of them with maybe one or two doses of platelets. So that's been a substantial decrease.

So I suspect it's probably a third or less now, compared to--even though the volume of patients is large.

CHAIRMAN SKINNER: Dr. Sayers?

DR. SAYERS: Thanks. Just a few comments--and the one has to do with mention of donor notification that was brought up a minute or two ago.

Donation is becoming increasingly perilous. And it's not perilous because of the risk of the procedure, but because of the quality of the information that individuals are given, which quite often flies in the face of their own sense of well-being, good health.

Take this as an example. We're struggling

now with what to tell the individual whose platelets--whole blood-derived platelets--were found at a hospital to have failed pH or swirling.

You know, that individual is not going to take kindly the information that his or her platelets don't swirl--

[Laughter.]

--and we don't have answers to that yet, but we do have the responsibility to let donors know what happens to their donation, and whether it's transfused or not.

And the other comment has to do with: I'd really like to endorse what Dr. Counts said about the value of whole blood-derived platelets. This product has been undervalued for a long period of time. And when I look at our experience in Dallas-Fort Worth, we would not be able to meet the community's requirements if the community was to decide to go 100 percent in the apheresis platelet direction.

No amount of aggressive recruiting on our part is going to ensure that the community's

transfusion-dependent patients who require platelets are going to be able to get them from apheresis donors. So I just wanted to endorse what Dr. Counts had to say about the whole blood--the essential whole blood-derived product.

CHAIRMAN SKINNER: Other questions from the committee?

[No response.]

Thank you very much for your presentation.

[Applause.]

HOSPITAL EXPERIENCE

CHAIRMAN SKINNER: The last section that we're going to discuss today is we're going to hear from the hospitals about their experience. And the first presenter in this section will be Dr. Robert J. Bowman, with the University of Minnesota Medical School.

MR. BOWMAN: Thank you for the opportunity to present our perspective to the committee.

I'm going to give you our experience with bacterial testing of platelet concentrates, particularly the impact on our operations; and some

about the economics of this.

There have been a number of questions about this today, and I'm sensitive to the fact that I sort of feel like I'm at the end of pipeline--sort of literally and financially. I mean, we do pay for all of these things, and we do pay for all of the testing that's done at the blood center.

But I can't start a talk like this without talking about leadership first. This is not done alone, and these are the people who I need to recognize.

[Slide.]

You can't see the lady's picture there, but Nancy Ward is our technical supervisor, and implemented the testing that I'm going to tell you about. And the other people supported me as well. When I go back to tell them what I've done, I will show them this slide, and I hope they will appreciate that.

[Slide.]

I also want to give you a quick overview

of what Fairview University Medical Center is. It's formerly University of Minnesota Hospitals. We were acquired by the Fairview System some years ago. But it's the same institution.

It's about nearly 1,000 staffed beds; about 36,000 admissions each year; 23 or 24 thousand surgical cases, with a substantial number of adult organ transplants, and pediatric transplants; also, probably 225 or so blood or marrow transplants in the year 2002.

[Slide.]

To give you a feel for the transfusion activity, we transfuse leukoreduced red cells about 18,500--nearly 20,000 a year, roughly. Platelet equivalents--now, this is apheresis times five, plus whole blood platelets times one--about 54,000 equivalents are transfused each year, and they are all leukoreduced--including the whole blood platelets. Those are each individually filtered--about 11,000 frozen plasma, and 42,000 cryo.

[Slide.]

Now, another perspective I want to give you is--this shows platelet usage strategy at Fairview University Medical Center over a number of years. And--is there a pointer? Well, I don't see a pointer.

You can see at the end of the chart, there are three curves shown there. The dark blue is the total platelet equivalents transfused since 1990. The magenta--or whatever color that is--shows--that shows apheresis platelet equivalents.

Oh, thank you, Roger.

That shows apheresis platelet equivalents back in 1990. And there were about--you can see, I don't know, 45,000 or so platelet equivalents that were transfused--apheresis products. And then the yellow is whole blood platelets.

A conscious and thoughtful decision was made back in about 1992--12, 14 years ago now, to specifically favor whole blood platelets, or platelets derived from whole blood, over apheresis platelets. The judgement was made that they are certainly equivalent functionally, but also from a

risk point of view, it was a reasonable trade-off for the cost-benefit. And that was driven largely by financial concerns. Okay?

So that decision was made back then. And that decision has essentially stuck. You can see the apheresis platelets came way down, the whole blood platelets came way up--and stayed there.

Now, you can see apheresis platelets have increased more recently. That's at our suppliers' option. That's not at our request. So when those are substituted for whole blood platelets--for whatever reason--we buy them at the whole blood platelets price. All right? So that's at our suppliers' option.

So we have a propensity to choose whole blood platelets.

I also want to tell you that we're not immune to observing transfusions reactions due to bacteria contaminated blood components.

[Slide.]

And this shows the fatalities--we had one back in--and I think this is a fairly complete

list. My colleague has compiled this list, and he's got a pretty good memory for this sort of thing. So these are identified as reactions.

We had two fatalities: one in '89--that was a red cell, and was due to Yersinia entericolitica; the other was '99, a platelet pool, and was due to Serratia.

And then are a series of non-fatal reactions that are actually more recent, and that's kind of--I don't know, I can't give you a solid reason for that, but I suspect it is because we essentially began transfusing leukoreduced platelets--all products were leukoreduced at about by 2000. And I think that previously, reactions that might be secondary to white cell contamination of platelet concentrates, for example, now don't happen as often. So we may be picking these up. But, again, that's not a--I don't feel that's a robust answer. That's my best guess.

[Slide.]

Well, when this new standard was published, a number of challenges--and probably

more than this. We needed to determine what test we should use, and we cared about how much it would cost. And we cared about whether it would change our practice; for example, were we going to have to go to all apheresis platelets versus whole blood platelets? And there were probably a whole bunch of other issues as well that I just didn't list.

Let me give you an idea of the timeline that we had.

[Slide.]

Back in July of '03, we began to define our approach. You might say that we knew about it before that. Well, we did, but then we got serious about it and said we need to face this. By August, we were looking at initial investigations. We gave a heads up to our management, telling them money was going to be needed. We were looking at demonstrations of the various technologies that we could use.

By September of '03, we had a specific outline. We were pretty clear what we were--or how we were going to make our decision, and that

included, you know, getting information; "consultations"--that means calling up your friends and saying, "What are you going to do?"

[Laughter.]

Technology assessment: we did do a technology assessment. I'm not going to go through a lot of that with you, but we made a little chart and looked at dipsticks and culture and the Pall system and that sort of thing, and we wanted to look at the cost impact as well.

And then we specifically sent people to AABB--it was a good excuse to send them; tell management "You need to go because this is important. There's an issue here." And I attended the annual meeting with specific instructions to go and get information and learn.

And let me give you an editorial comment: that, given the standard, I think AABB has done a good job of giving guidance around this issue. At least that's my perspective, from the hospitals' point of view.

By December we had a final decision on our

technology. We made up our validation plans and implementation plans, and by March 1st we implemented the testing.

[Slide.]

Early on--very early on in this we decided this was going to guide our approach to our actions.

First, we said, we will meet the standard. We're going to meet the standard. We're going to meet it on time, and we're going to do it with an accepted test.

Further, we're going to collaborate with our supplier--that's Red Cross in St. Paul, Minnesota. We want to know what they're doing, and we want to talk with them and so we make sure that we're working together with them. We are highly dependent on them. They're our supplier.

Thirdly, we thought it was prudent to be a late adopter. We did not want to lead the field in this. We want to see what other people are doing, and wait for someone to do something very clever, and then we want to copy them. And that's a

specific strategy, and that remains our strategy.

[Laughter.]

Well, we thought that: look, this is a new standard. There's new technology being applied, and it's probably going to change. And we don't want to invest too heavily to start--and so--either, in our operations, or in equipment, or space or anything else. So we felt, as well, that we would try to minimize the operational and the economic impact on us.

Well, there are implications to our approach.

The first was: we intended to maintain the current apheresis-whole blood platelet mix, and that's mostly whole blood platelets--mostly whole blood platelets.

We were going to keep testing simple, and we were going to monitor the technology. And that remains our plan.

We were going to observe our supplier's efforts in testing, and their improvements in collection technique--that sort of thing. We

wanted to follow that so we knew what was going on there.

And then we also wanted to make sure we monitored regulatory policy on pre-storage of platelets derived from whole blood. That has already been discussed here.

[Slide.]

Well, what was the economic impact to us? Early on we needed to take a look at this.

Well, it was--how bad is it?--it's $1.5 million over the expected expenses for us. And I'll show you more detail about this. So $1.5 million. Well, is that a lot? A little? I understand this is a governmental meeting. It may not seem like a lot. But it seemed like a lot to us--

[Laughter.]

--because that was 42 percent more than we were currently paying for platelet concentrates. All right? 42 percent more.

So the question is: are there options? So we did begin to look at some options, as well.

And we did a little economic impact study; a simple little model study.

[Slide.]

And these are the assumptions underlying it. We assume we're going to be using 1,000 apheresis platelet concentrates; about 47,000 whole blood platelet concentrates--and they are all leukoreduced. We, furthermore, have an equivalency. We say five whole blood platelets are equivalent to one apheresis platelet. And, the estimated cost to test for bacteria was to be $30 per test. That's the number we had heard, back at that time. And I don't know if it's too far off--I mean, at least for the culture techniques. If it's a little bit high, that's okay. I mean, it doesn't really have much--actually, it favors my conclusions if it's high.

[Slide.]

So we did a model study. And what this chart shows, this shows our current product mix, at current prices--negotiated prices: 1,000 apheresis, 47,000; leukoreduced platelet

concentrates from whole blood-- 3.5 million, roughly.

If I take the current product mix--take all those and say, "Add bacterial tests at 30 bucks a unit,"--$30 a test--it's nearly $5 million.

So you say, "Well, we can't hardly afford that. So let's just convert to all apheresis, and then just bacterial test those." So you have to--you know, you if you do the equivalency, that's 10,5400 apheresis, plus the current negotiated price, and that costs $5 million.

Well, I mean, how can this thing be? It could be, because the apheresis components--at least to us--are a lot more expensive than whole blood platelets. They just are. They're more expensive.

So--we'd take a look at the current product mix, and we talk about bacterial testing just connected platelet pools and we can get it down to $4 million. And then--I'll talk about this later--take the current product mix and do testing on pools. I'll come back to this a little bit

later.

So, with that in mind, that sort of validated the approach that we thought we ought to take and, in fact, to continue to use whole blood platelets, and to test them ourselves.

Now, we didn't select any of those options, but we did choose to test whole blood platelets ourselves. And we did that because we knew then we wouldn't have to change the apheresis versus whole blood platelet strategy; no change in practice, no discussion about anything with medical staff.

There was no change for our supplier. We cared about that. There's an issue about adequacy of supply. They probably couldn't have turned on a dime and provided all the apheresis products. So there would have to have been a transition anyway.

And then, finally, we thought: we can test for a lot less than $30 per test. So we also decided at that point that we're going to use bacterial-tested apheresis platelets from the supplier. We aren't going to fool around with

that. We're not going to test them ourselves. Why? We don't use many. It's easier than establishing additional test criteria, and it really only adds about $30,000 per year; a thousand apheresis products time $30, $30,000. Straightforward.

[Slide.]

Again, test whole blood platelets ourselves--the process we use is to do a glucose test. We use a glucometer--it's a SureStep Flexmeter--we don't use dipsticks. We chose not to that--or the swirling. We didn't want to do the dipsticks because we thought it had a component of subjectivity to it. We get a number. It's good to get a number.

We chose eight hours as a time period. We don't test these on release. We test them--we try to batch test them, and then they're good--we say they're good for eight hours. And then you have to test them again--okay?--if you're going to use them. So that's the way we approach that.

The cutoff we chose as a result of our

validation studies was less than 520 mg/dl; units falling below the screen are not used. If they fall below the screen, they get reflex tested on another machine, mainly because we want to get a pH, because our supplier wants to know if the pH is less than 6.2. So we get a glucose, a pH--and, actually, a lactate, too. But if the pH falls below 6.2, that we report to the supplier.

And then we Gram stain. Anything failing the screen gets Gram stained and cultures, and any positive is reported to the supplier.

The estimated cost for this testing, we think, is about $3 per test. That's the direct cost, we think--about that. I haven't got a lot of faith in that, but that's our best estimate right now.

That means the total added expense--about 47,000 of these we do a year--is going to be about $150,000, but redundant testing adds another $60,000 or so; that is, some of those units are tested multiple times.

[Slide.]

That's the results. Just thought I'd show you the distribution. It's--I can't see the thing, either, here. But here's--our cutoff is down around here. And so there are a few that did, in fact fail. By and large, almost all of them pass.

This shows you--we've tested, in the month of March--this is just for a four week period that we have available--we received about 3,400 platelets; we tested about 5,200--a little bit of redundant testing going on, clearly. Those that had glucose less than 520, there were 38 of those. Those that had pH less than 6.2, there were two of those. None had a positive culture or a Gram stain.

And I have to say--I say "Gram stain"--our micro lab quit Gram staining early on. They said, "Look, you're culturing them anyway. We're not going to fool around doing a Gram stain, too." So they quit doing that--and then they told us awhile later [laughs] which is a little annoying, but it works. And they're correct.

We have not experienced shortages since

doing this--but we didn't change to all apheresis platelets.

[Slide.]

Our operations on this can be improved. This is not without some challenges. We didn't appreciate the redundant testing that was driven by that eight-hour period set for test validity. We think we could probably lower our cutoffs, so we want to look at that.

We did hire an additional FTE--and I know this: that a lot of this is still manual. I mean, we record these results on this glucose meter; record them and then we enter them into a computer, and the computer doesn't exactly prompt a person in an effective way. So we can improve some things. But we think we can improve things.

[Slide.]

What do we think is needed? Well, we need better testing that includes Gram negative and positive organisms. It needs to be automated, and it needs to be blood-center friendly.

I personally would rather have the blood

center do this. I'd like to get the product from them and have them say, "This is good for the period of time that you need to store it for your use." I'd like it to be that way. That would be highly desirable.

The test needs to be sensitive, specific, and a lot of other stuff that other people can enumerate for you.

And then, I think also--quite importantly--we need an objective assessment of pooled, stored whole blood platelets. It's important to look at that. We need to leukoreduce those things as pools, and we need to do the bacterial testing as pools on them.

Let me come back to some of the pre-storage--the economic benefit.

[Slide.]

this is the current product mix that we use--pretty close--for $3.54 million a year. That's what we would spend. If I could take and back out the leukoreduction that's done on each whole blood platelets--back it out--pool the whole

blood platelets five into a pool, leukoreduce and bacteria-test those pools and sterile-connect them, it would cost $3.5 million--all right?

I can take, and I can have what I'm getting now, and I can add bacterial testing to the thing, and I can get it cheaper. So I can get a better product cheaper. I think that's a compelling argument for a careful evaluation of this kind of a strategy. I think we have to do this.

So, in my notion, it is clearly time to consider pooling whole blood platelets before white cell reduction and bacterial testing and storage. Pool them, leukoreduce them, test them and store them.

Thank you.

CHAIRMAN SKINNER: Thank you for your presentation.

Questions from the committee? Dr. Kuehnert.

DR. KUEHNERT: Thanks for the presentation.

I wondered--just on your last message there, with the $3.5 million, which appeared to be less than what you're doing now--

MR. BOWMAN: Yeah.

DR. KUEHNERT: --less costly than what you're doing now--what type of testing are you talking about for bacterial screening?

MR. BOWMAN: Included in that was a $30 charge.

DR. KUEHNERT: Oh, it was the--okay.

MR. BOWMAN: Yeah. See, you can add it in. I mean--and by the way, if the $30 charge is a little high, and someone thinks, "Well, you're a little high on that, Bob," if you lower it, it gets better for whole blood platelets--because, you see, you apply it to so many components for us.

DR. KUEHNERT: And when you mentioned that--the plan to, after your glucose and pH screening you use a culture method, what culture method do you use?

MR. BOWMAN: Oh, we send it to our micro lab, and they use their culture method. They use

an aerobic--I think--I don't know if they're using an anaerobic bottle as well. But they're using an aerobic culture.

DR. KUEHNERT: Mm-hmm. And maybe I missed this, but did you validate your methods in some way?

MR. BOWMAN: Yes, we did. We spiked platelet concentrates. We got whole blood platelet concentrates and spiked them with bacteria. We tried to spike them at about 50 colony-forming units per mil, and then we followed pH and cultures in time. That's the way we did that.

Yes, I did not show that--those details.

DR. KUEHNERT: I have one other question about that--the validation.

I've noticed that--from the other presentations--there seem to be some variability--well, one, if I remember right--one presenter had some lack of sensitivity with Gram negatives; another one said they got them all. And I wondered, with yours, did you have any issues with Gram negative?

MR. BOWMAN: No--I tell you--our validation--there were complications in our validation--all right? Part of it is so that I can't tell you exactly what our sensitivity is, because once again, our micro lab decided to quite doing quantitative cultures for us as we were rolling along on this thing. So we knew there was growth, but then we didn't know, exactly quantitatively, what it was. And so we cannot tell you--I cannot tell you what sensitivity level we're at.

I'm presuming it's about at what people say it is: 107 CFUs per mil. I'm assuming it's something like that.

CHAIRMAN SKINNER: Other questions?

[No response.]

CHAIRMAN SKINNER: Thank you very much.

And our next presentation, we're going to hear from the American Hospital Association, Ms. Mary Beth Savary-Taylor is going to present. She's the Vice President of the Executive Branch Relations with the American Hospital Association.

MS. SAVARY-TAYLOR: Good afternoon. My name is Mary Beth Savary-Taylor, and I'm AHA's Vice President for Executive Branch Relations.

The AHA represents nearly 5,000 hospitals and health systems throughout the country, and we are pleased to be here this afternoon, and appreciate the opportunity to comment before the committee.

The AHA was asked to comment on how the new AABB standard on detecting bacteria in platelet components would affect the availability of both apheresis and whole blood-derived platelets. Because the standard is so new, we do not have sufficient evidence from our members at this point to determine, really, whether platelet shortages exist.

The AHA does strongly support maintaining a safe and adequate blood supply; and certainly supports efforts to detect the presence of bacterial contamination in platelets. We would be concerned if this new standard, as currently implemented, would result in a lack of platelets

for patients facing dire circumstances.

With this in mind, we will apprise the Advisory Committee on blood safety and availability, of platelet shortages by our members as a result of this new standard.

In closing, our goal is to make sure that we do have the safest blood supply possible. Of course, with every new blood safety measure comes addition costs that the health care system must bear. These costs come amid various financial pressures that are currently bearing down on America's hospitals throughout our country.

We applaud the committee for its recent recommendations on increased reimbursement for blood and blood products, and ask that you continue to push for adequate reimbursement for blood and blood products through an infusion of additional Federal funding--or, what Dr. Sandler repeated again and again at the last committee meeting--new money.

Thank you very much for your attention, and I would be pleased to answer any questions.

Thank you

CHAIRMAN SKINNER: Thank you for your comments.

Questions?

[No response.]

Thank you very much

MS. SAVARY-TAYLOR: Thank you very much.

CHAIRMAN SKINNER: Appreciate it.

This concludes the formal presentations for the day. It does say on the agenda there's time for committee discussion. I don't know if there are specific topics the committee would like to discuss at this point. What I would like to suggest is, given the nature of how this topic arose--the agenda for the committee--I think it's quite clear that the Assistant Secretary of Health is looking for some guidance or some feedback from us, so it's not one of those typical meetings where we may or may not come up with a recommendation in the final analysis.

Typically, we write recommendations on the afternoon of the second day, and we often start

with a black screen--which is somewhat of a painful exercise, but sometimes is the only way that we can actually do it. In other instances, there's actually been individuals around the table who have taken some ownership and helped pre-conceive some ideas to at least get the discussion rolling. Typically, that's occurred either through our chair who, you know, is not in a position to participate, or through, perhaps Dr. Epstein, who's a very good wordsmith, who isn't with us this time.

So just anticipating those two voids, I was wondering if it might make some sense for people to begin some thought about taking some role in helping to craft where the recommendations are going to go, and whether it would make sense to talk about that now--or to at least just leave it out there for you to think about overnight.

But I think it is going to take some initiative on a number of folks' parts to actually identify the components that we want to address and offer feedback on, and then--to the extent people want to volunteer--to try to draft aspects of those

to at least begin the discussion, I think that would be helpful.

On a separate note, I would say that a number of individuals--because the first topic of the day was addressing some of the CMS changes and recommendations, and there are some individuals that are actually working on some language for a recommendation for that. So that aspect of it has been addressed. There may be others that would be raised.

So, with those preliminary comments, I open it up for any thought on whether there's anything we can do at this point to prepare for our discussion tomorrow, without drawing conclusions prematurely, before we hear the rest of the presenters.

MR. WALSH: I'm just tempted to say, in a very naive way, that we focus on going after the barriers, and not challenge the standard. You know, I mean I just think that the AABB has done a good job, and they've implemented, and seem to have good response by all parties. And we ought to just

focus on the barriers, and not waste a lot of--I don't think--waste a lot of time, with all due respect to anybody that disagrees, on challenging what's been done.

CHAIRMAN SKINNER: Any other thoughts or comments at this point?

MS. MIDTHUN: Yes, I think that it would be helpful for all of us to think--again, I wouldn't say so much "barriers," but perhaps a different way of expressing it is to say: how can we collect enough information, or ways to collect enough information to really get additional scientific data that would help fill in the gaps?

CHAIRMAN SKINNER: Others that have anything that they want to share at this point?

DR. KUEHNERT: I just had a question about tomorrow's presentations. There's another--is there a set of presentations by ARC, ABC and AABB? I wondered if there's going to be any discussion of sort of the plans for collaboration, specifically, by these organizations. Specifically, I know the AABB TTD committee has had discussions about

collaboration.

I just wondered if that was going to be discussed at all?

MS. LIPTOR: Again, this is factual, so I feel that I can--

[Laughter.]

--say this. Tomorrow, Dr. Sazama is going to talk about some of the initiatives we're undertaking, particularly in terms of putting together a task force to examine some of the issues.

I will also tell you that we did put together what has been described as a survey that collected "unvalidated" [laughs] data, because it necessarily--I mean, it just doesn't have representative sampling. But we do have some information back, and Dr. Sazama, again, will be sharing that information, and we hope to use that as the basis for the task force to go ahead and look further at some of these issues; for example, some of what we're seeing with the dipstick, the glucose.

I think what was important, though, is at least we have this on the table, and we have something that we're all talking about concretely right now.

CHAIRMAN SKINNER: Well, I think at that point then, this really does conclude our discussion. I just was wanting to warm you up that someone's going to have to, you know, make the first suggestions tomorrow in the recommendation phase. So think about who's going to do that.

We reconvene tomorrow morning at 9:00 a.m. in this room.

Thank you.

[Whereupon, at 5:08 p.m., the meeting was adjourned, to reconvene on Thursday, April 8, 2004.]

- - -