DEPARTMENT OF HEALTH & HUMAN SERVICES

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

TWENTY-THIRD MEETING

VOLUME II

Thursday, April 8, 2004

9:00 a.m.

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

PARTICIPANTS

VOTING MEMBERS

Mark Brecher, M.D., Chairman
Judy Angelbeck, Ph.D.
Edward D. Gompert, M.D.
Paul Haas, Ph.D.
Christopher Healey, J.D.
Jeanne Linden, M.D.
Lola Lopes, Ph.D.
John Penner, M.D.
Merlyn Sayers, M.D., Ph.D.
Mark Skinner, J.D.
John Walsh
Wing-Yen Wong, M.D.
Karen Shoos Lipton

NON-VOTING MEMBERS

Dr. Karen Midthun
James S. Bowman, III, M.D.
Matthew Kuehnert, M.D.
LTC Ruth Sylvester

C O N T E N T S

P R O C E E D I N G S

MR. SKINNER: Good morning. Welcome back.

This morning we are going to begin our discussions hearing about the approved methods for whole blood sample diversion.

Oh, I am sorry, we need to take roll call again. Dr. Holmberg.

DR. HOLMBERG: Quick roll call.

Mark Brecher.

DR. BRECHER: Present.

DR. HOLMBERG: Larry Allen.

[No response.]

DR. HOLMBERG: Judy Angelbeck.

DR. ANGELBECK: Present.

DR. HOLMBERG: Celso Bianco. Absent.

Ed Gompert.

DR. GOMPERT: Present.

DR. HOLMBERG: Paul Haas.

DR. HAAS: Here.

DR. HOLMBERG: Christopher Healey.

MR. HEALEY: Here.

DR. HOLMBERG: Andrew Heaton.

[No response.]

DR. HOLMBERG: Jeanne Linden.

DR. LINDEN: Here.

DR. HOLMBERG: Lola Lopes.

DR. LOPES: Here.

DR. HOLMBERG: Gargi Pahuja.

[No response.]

DR. HOLMBERG: John Penner.

DR. PENNER: Here.

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.

DR. HOLMBERG: Jay Epstein is not present,

but we do have Dr. Midthun present.

Dr. Klein.

[No response.]

DR. HOLMBERG: Jim Bowman.

DR. BOWMAN: Here.

DR. HOLMBERG: Matt Kuehnert.

DR. KUEHNERT: Here.

DR. HOLMBERG: Ruth Sylvester.

LTC SYLVESTER: Here.

DR. HOLMBERG: Thank you.

MR. SKINNER: Our first presentation this morning will be Dr. Rob Dickstein, who is going to present for Pall on approved methods for whole blood sample diversion.

Approved Methods for Reduction of
Bacterial Contamination Risk
Pall – Dr. Robert Dickstein

DR. DICKSTEIN: Thank you, Jerry. Good morning.

What I would like to do for you this morning is give you a little bit of insight and background into the area of sample diversion pouch,

which in many respects, for those who were here yesterday, is a corollary to Pall's bacterial detection system, which is part of our bacterial risk management system.

Over the past several years, there have been a good deal of information and literature gathered to address the challenge of residual skin flora. If you look at the literature, you will see that even the most stringent skin disinfection techniques may not be able to ensure sterile venipuncture site because of a number of factors. Those include subcutaneous hair follicles, sebaceous glands, and skin dimpling, et cetera.

Therefore, there have been a number of studies particularly in France which have addressed this issue by looking at the potential for taking a small amount of the first blood component and removing it before you would put collection into the bag, that is, if you would remove anywhere from 10 to 15 ml of blood, it has been shown that there is a significant amount of bacterial contamination.

The best way to address this is by doing

just that, by removing these 10 to 20 ml of blood during donation. A study that was done two years ago demonstrated that you could literally remove up to 72 percent of the contamination by doing so.

For the most part, bacteria is in the form of Staph epi and a number of bacilli, to the extent that if you could accomplish this, you would literally remove or potentially remove up to 4 percent of the incidences that are now occurring.

What Pall has done is to address it in this fashion. If you look at Jesse Bates's schematic, what we have here is typical phlebotomy set whereby you are removing by passing blood into what we call a sample diversion pouch, which contains anywhere up to 42 ml of blood.

Usually, typically, what is done is 10 to 15 ml of blood are removed, clamped off, and the rest of the collection is passed through this tube into the collection set.

What is important to note--and I am going to get back to this, because I am going to try to give you a little insight into the problems that we

have addressed--is this particular area here of the sample diversion pouch.

It is interesting to note that what we do is somewhat a little bit different than other manufacturers in that we have here what we call a snap open closure, which remains closed until the blood is passed into the sample diversion pouch.

Typically, what you find is that you prepare the set, you start the donation in typical fashion. Blood automatically will pass into the sample diversion pouch, you collect anywhere from the 10 to 15 ml that you so desire, clamp off this region and allow the blood to then pass into the collection set.

What is important to note--and we will get back to this--is the picture that you see on the left, and there is where we have noticed several incidences that have occurred over the last several months, which I will get to a minute.

As you can see, what you do is you put the vacuum tube holder in place, then, you put the typical vacuum tubes in place, and you draw blood

typically within the first three to four minutes, the reason being you have no anticoagulant in that sample diversion pouch.

What is interesting to note is--and we will get back to this also in several minutes--you typically collect anywhere from four to seven tubes to run your infectious disease test, as well as your ABO-Rh testing.

Just to give you a little background, Pall has been using this type of sample diversion pouch for approximately 16 months. We first introduced it in North America in December of 2002, and to date in Canada. When I say North America specifically, we introduced it in 2002 into Canada, we have implemented and used somewhere in the range of 1.2 million over the past 16 months.

Pall received approval in the U.S. about 8, 10 months ago. We put it on the market in August of 2003. Our experience, because of our Canadian experience, demonstrated that this was typically very user-friendly. The ergonomics allowed us and allowed the user to collect this

amount of blood in the sample pouch and complete the rest of the collection in a timely fashion.

When we did introduce it, did what we normally do at Pall, we go through field trials at several sites to convince ourselves from a quality perspective that it meets our standards before we went into typical commercialization.

What we did notice when we did implement this, I will say somewhere in the range of about 6 months ago to about 20 centers, we started to get some feedback this past February from one or two centers that they were observing hemolysis. Hemolysis is, depending on how you want to define that, it would just cause hemolysis whether it be 20 mg or 400 mg per deciliter.

This certainly got our attention simply because it had been our experience in Canada not to have seen this at all in those 1.1 or 1.2 million uses of the product over the last 16 months, so what Pall typically does when they do see an issue out in the field, we send our product application specialists out there to assure ourselves and

assure the customers that the product is being used right.

In this case, one user was demonstrating significant levels of hemolysis. We went in there as we typically do. We convinced ourselves and convinced the user that yes, the product was using as instructions for use indicated.

That stymied us a little bit considering, due to our experience in Canada, we had never seen the problem of hemolysis. What we did from that perspective is we brought back samples, we took some of our retains in-house, and we completed that type of testing that was done out in the field in-house.

Again, in our hands, it demonstrated no degree of hemolysis, which stymied us a little bit simply because of what the customer had reported and what had been observed out there.

As a third step in this whole process, we decided to go back to the center and look at it from a different perspective, that is, rather than just seeing if the product was used correctly, we

brought our engineers out into the field to look at it from a mechanical point of view to see if anything was missed in our first addressing of this issue.

Again, we didn't see anything, and what we have learned from experience, as all manufacturers do, unless you do things exactly in-house as what you see out in the field, there are times you won't be able to reproduce the results.

So, what we did this time is we brought literally everything back that the user was experiencing. This goes down to the Vacutainer tubes and the different types of Vacutainer tubes out there. We had tried to do that in-house initially, but due to the variability of tubes, we weren't using exactly what was used at the specific center.

What we did is we brought back everything, we completed, we redid all the work, and, yes, lo and behold, we were able to demonstrate a degree of hemolysis. The story in this is that unless you do things exactly the same, and I mean exactly the

same as what your customers experience, you can miss something.

In this respect, to get to the heart of the matter, what we observed in bringing back these Vacutainer tubes, I guess I could say this in the true biblical sense from a laboratory perspective, all Vacutainer tubes are not created equally.

What we did find is depending on the Vacutainer tubes you found, they worked slightly differently. That doesn't mean they are not good, it means that Vacutainer tubes that have 7 ml, Vacutainer tubes that have 10 ml, can work slightly differently from the perspective of drawing vacuum into the tubes.

Age of tubes makes a difference, we certainly found out, variables like that, which were not originally considered. When we put out this product in the market, we obviously tested with a number of Vacutainer tubes, but not every one out in the market.

What this led us to do is try to determine, well, if we were seeing differences, and

hemolysis was being caused by several different tubes, what could we as the company do about it.

Obviously, the simple response would be limit the types of tubes that could be used. We didn't consider that to be user-friendly, and not the way we wanted to go as a company.

What we realized during this investigation is because of the differences being pulled by these tubes, if the blood was passing from the sample diversion pouch through a little cannula into the Vacutainer tubes, if it was passing into this cannula at too rapid a rate, this, in fact, could cause this degree of hemolysis that we were seeing.

We had not considered that again during our developmental design because of the number of tubes we looked at, we did not see this problem, so what we decided to do was, in quick fashion, prototypically, look at different designs in very modest means in changes to allow for this blood from the sample diversion pouch to pass into this cannula at a slightly reduced rate.

Literally, what we were doing was trying

to create more resistance going into this cannula. If you imagine a reservoir being the sample diversion pouch, it is just sitting there, Vacutainer tube pulls into the cannula, into the Vacutainer tubes. If it pulls at a slightly higher rate, there is a chance for hemolysis to take place.

In fact, when we did our studies and demonstrated that if you could add resistance, you could certainly cut down and remove and eliminate this degree of hemolysis, so essentially, in about a 10-day period of time, we were able to determine what the cause was, number one, what we could do to fix the problem, and what we could do long range to put the product back, to enhance the product on the market.

During the interim, we were working with FDA and Compliance, as well as Office of Blood, who I must commend, were very good in working with us and understanding the problem, and agreeing with our approach while keeping the product out on the market in all the centers except one who chose to

transition to something else in the interim, to work with us, allow the product to remain on the market while we came up with what we considered to be a small fix in the whole perspective of things.

That is essentially what we have done. We have taken literally our sample diversion pouch and added a small little piece of tubing downstream of it before it enters into the cannula to increase resistance in order to eliminate any of the problems we have seen in any of the tubes no matter whether using 7 ml, 10 ml, 3 ml, plastic, glass, et cetera.

You know hindsight is always 20/20, and it is a good lesson for all of us from the perspective of Pall that you can't always concern yourself with your product, you have to look at the ancillary products, in this case, a vacuum tube container, a tube, which could cause a problem for you.

When we went back to a number of customers, we also brought this to their attention. In the interim, what we have worked out with the agency, as some of you may know, we put an alert

out to the field to caution people as to the potential for hemolysis at a small rate that could ensue, therefore, be careful in the instructions for use for all product, be careful for use in the instructions for Vacutainer tubes, to alert them to the fact that there is potential for hemolysis.

Will, in most instances, the hemolysis upset the ability to effectively perform testing? Most likely not. I have seen very few instances since this has arisen four or five weeks ago to demonstrate that it is affecting doing your testing for infectious disease or ABO-Rh, but it is of consideration for us, as a company, to assure that the product we are putting out there meets all the goals which our users literally set for us.

Essentially, as I have stated, this is just a scenario of events leading up to where we are including on the bottom the root cause identified, as I said, the differences in tubes from vacuum pressure to size of tubes, to multiple vendors, and it is just a cautionary note for Pall, as a company, as well as everybody else, to make

sure they consider these in the future in any subsequent products we may put out.

As I said, we are looking to transition from the product now on the market in approximately 90 days. This is a relatively small enhancement for us to make. As a matter of fact, we are completing our in-house trials. We will be going to out-of-house trials very shortly in cooperation with the Office of Blood, who has given us guidance on what they would like to see before we put the product out on the market again.

As part of the whole program Paul has initiated with customers, as I stated, we have a letter out there which cautions users as to how best to use the product. We followed up with weekly telephone calls and/or our Technical Services group with the customers who are now using the product to assure that there are no problems that may ensue in the future.

We also have as part or our vigilance program, the customers sending in any information that they may have on hemolysis to assure that we

address it in a timely fashion.

In closing, I think the lesson to take home certainly from Pall is that you can never be sure no matter how many products you put out on the market, no matter how many times it is being used, that you have covered every variability.

As I stated, our Canadian perspective indicated to us that there were absolutely no problems with 1.2 million users, but as we saw in the U.S., there were problems that needed to be addressed, and I would say within a period of two weeks, those problems were addressed, a fix put in place, and ongoing from there, we are somewhere into day 20 or day 25 of our 90-day target to put the product out on the market.

As I said previously, we consider the sample diversion pouch as part of our overall program for bacterial risk management, which includes what you heard yesterday on our bacterial detection system, as well as our Leukotrap system for the collection and leukoreduction and storage of blood products.

Any questions that I can answer for you?

MR. SKINNER: Questions from the committee? DR. PENNER: Cost? The cost of the bag?

DR. DICKSTEIN: The cost of the bag. I will turn to our Product Portfolio Manager.

MS. KLUGEWICZ: [Inaudible. Not at microphone.]

DR. DICKSTEIN: Obviously, there is no additional costs that we are adding to this change. This is just a transition in the U.S. By the way, since the product works in Canada, we have no intention of changing it at this point.

DR. PENNER: You said $17 to $22 range?

MR. SKINNER: Could you come up to the mike, please. It needs to be recorded in the transcript. Also, I need you to identify yourself for the record also.

MS. KLUGEWICZ: I am Sharon Klugewicz. I am a vice president of Global Product Portfolio Management for red cells.

The pricing ranges anywhere between $17 to

$22 depending upon which systems are being used, whether it is a system for leukoreduction of red cells or a system for leukoreduction of random donor platelets.

With the sample diversion pouch system, there is an incremental cost compared to the Y sampling system.

DR. PENNER: What is that increment?

MS. KLUGEWICZ: It can range anywhere from $1.00 to $1.50.

DR. PENNER: So, that is about $1.00 to $1.50 above the cost of the bags that are routinely being used.

MS. KLUGEWICZ: Yes, that is correct.

MR. SKINNER: Other questions? Yes, Dr. Lopes.

DR. LOPES: I think you said that about 72 percent of the contaminants that might be there are flushed out in the collection of the sample.

Do you have any sense of how large an amount of blood would need to go into a diversion pouch in order to reduce the remaining contaminants

to, say, 1 percent?

DR. DICKSTEIN: I can tell you that the best study that I have seen is by Bruneau several years ago, which demonstrated--and I will try to get the answer to that--within the first 10 to 15, I think it was 13.5 exactly demonstrated in 72 percent, they did not see a significant reduction in the second 13.5 or 15 ml beyond the 72 percent of any significant value. It's the best I can do in answering that particular question.

Any other questions?

MR. SKINNER: Dr. Holmberg.

DR. HOLMBERG: Yes, Rob, I want to thank you for your candidness and openness on some of the issues in introducing this to the marketplace. I think that helps give us a frame of reference, and what I was wondering, is there any difference between the product that was introduced in the United States and that, that was introduced in Canada?

DR. DICKSTEIN: That is a good question and, if you recall, I asked when I showed you the

schematic to focus on that sample diversion pouch. The answer to your question is no, that portion of the system, which is really a separate entity, there is no difference, it is exactly the same.

That is why it came as a surprise to us when we started to see these initial hemolysis reports coming in after, as I said, 1.2 million out there being used over 16 months, it is exactly the same.

But the lesson again learned when we went back and we did further checking, we did realize that in the perspective of what Canada does, their tubes, they were using different tubes than what is typically used in the States.

They had tried several along the way, found one that worked best for them, and as it turns out, that is one set of tubes that does not cause the problem. Their pull on the vacuum is less than other tubes.

DR. HOLMBERG: The other question was you addressed the issue of hemolysis and the infectious disease testing, that, to your knowledge, it was

not a problem.

Do you know whether this created any problem in the availability of whole blood, were there centers that were resistant to releasing those products?

DR. DICKSTEIN: Well, let me qualify that. When I said there was in my mind or in my experience no problems, the one user who did have a problem felt that it would interfere with some of their testing.

DR. HOLMBERG: But how did this affect blood products that were already collected in your bags?

DR. DICKSTEIN: It did not.

MR. SKINNER: Other questions? Dr. Gompert.

DR. GOMPERT: Yes. I am not quite clear on the data from the point of view of the reduction of contamination. You say there is an approximate 70-odd percent reduction in the amount of bacteria in the blood sample or the number of ultimately contaminated units?

DR. DICKSTEIN: In the blood contaminate, in that first 10 to 15 ml.

DR. GOMPERT: Is there any data from the actual numbers of units of blood, platelets, whatever, that were not contaminated? You know, the actual end product.

DR. DICKSTEIN: Not to my knowledge. Again, these studies were focused on just determining what would be the incidence of the contamination due to skin flora.

DR. GOMPERT: Thank you.

MR. SKINNER: Dr. Brecher has some information for us.

DR. BRECHER: I just want to say something factual. One shouldn't be diverted too much by diversion. This does stop gram-positive organisms from the skin, but the majority of deaths, two-thirds are gram-negatives, and it is not anticipated that this will affect those cases.

MR. SKINNER: Thank you. Thank you for your presentation.

DR. DICKSTEIN: Thank you.

At this point, Dr. Jeffery Mirapol will present for Terumo.

Terumo - Dr. Jeffery Mirapol

DR. MIRAPOL: Thank you for the invitation to speak to this group. It is going to take us a couple minutes to get this slide show on the road, so just bear with me.

I am going to give you an overview of Terumo's development history for our sample first system. I will also give you information on how we actually brought this system to market, the nature of our studies, our strategy and process in doing field implementation, as well as, and I think some folks are aware of this, we are going to show you a video of the use of the system.

Once again, I am going to discuss our experience with our system. I am going to give you a little bit of background on development, an overview of the system, how the system is operated, how it works in people's hands, and how it was actually used by the customers and how we got the product in the hands of the customers.

The background to the development of our system really was focused on some early work that we started to do about 1999 on a way to take the samples prior to whole blood collection to ensure that blood samples were always available for testing.

One of the issues actually in blood collection is that a fair number of donors oftentimes don't give you a full unit, and you lose therefore the samples for ABO testing and HIV, et cetera, testing.

As we were doing this work, we recognized that a method that keeps the initial portion of blood that goes from the donor to the final whole blood unit would also reduce the chance of having bacteria go to that unit.

We worked with folks over at the Holland Labs, Steve Wagner and his group, Dr. Friedman, Robinette, and developed a model system whereby we challenged bacteria on an injection site, and then either using saline or whole blood, passed either the saline or whole blood through the site, and

then took out aliquots of blood subsequent to that contamination.

Those studies demonstrated that you could reduce that initial load of bacteria by about 1 log using this system, and this is an example, a drawing of the system that was used at that time.

Again, here is the bag that would hold the whole blood or saline. We spike the bacteria here, and again using this as sort of like making a phlebotomy, and then take off aliquots of either saline first and then blood into this little pouch, and then measured bacteria.

We did aliquots in increments of about 14 to 15 ml and did aliquots out to about 5 to 7 aliquots.

Subsequent to that work, the FDA and also Dr. Nemo's group had some meetings regarding what one would like to have for a design for these sorts of systems to take the initial bolus of blood from the donor.

What they wanted was a closed system. They wanted a system where the blood was diverted

from the final product by one-way flow, that they wanted enough blood for testing, and they also would hopefully reduce bacteria contamination.

The features that we developed and that we really put together to incorporate the FDA criteria included the use of what we call a CLIKTIP, which is again a big break-away cannula below the Y on the primary collection bag, and this keeps the blood from going to the collection bag, and ensures that you have a one-way flow from the phlebotomy to the pouch.

Also, it ensures that you never have any anticoagulant going from the bag back to the pouch, so your samples are always free of anticoagulant.

Also, the goal was to have a system that had a small pouch with short tubing segments again closely attached to the donor tubing. The pouch was designed to aid the user in visualizing the amount of blood that is actually filled in the pouch.

The pouch volume in our system is up to about 50 ml. Subsequent developments led to

notches at about a 35-ml volume point. Also, the pouch allows an adequate volume of blood to be diverted, so that you can get all your samples for testing and that you can also reduce again by about 1 log the bacteria associated with the skin during that collection process.

Also, we have an HR clamp, in other words, a Roberts clamp and a little twist-off lure connector below the pouch to allow you then to put on a lure adapter and holder, and then subsequent to filling the pouch, the tubing above the pouch is sealed, and this again was an FDA requirement to have a seal which was considered closed and permanent between the pouch and the actual donor line.

Subsequent to that seal, the line is opened going to the bag by breaking this large CLIKTIP, and then after adding the lure adapter and holder, you can get the samples.

This is a diagram or schematic. These are lure adapter and holder. This is the pouch. This is your phlebotomy needle, and this, of course, is

the big CLIKTIP going to the whole blood unit. You attach all these, and this is the Roberts clamp and line, and the female lure port at this point.

When you are using this, you are filling the diversion pouch up to this notch typically, although if you are a blood center that needs more than about 35 ml, if you fill the whole bag, you are going to get about 50 ml, and you have made this permanent seal with a clip or a sealer, break the CLIKTIP, allow the blood to go to the unit, and collect the samples in the tubes.

So, our system we believe has certain advantages, the samples are taken prior to the blood going to the primary bag. You always get your samples, which was the original idea of the system. Also, it aids in letting the individual doing the collection see how that collection is going, so you can see the blood flow aids in kind of ensuring you have a good blood flow, and again, as I indicated, it does capture that initial bolus of blood and may, and we believe does, help in reducing the chance of getting those kinds of

bacteria going to the unit.

We did two field studies. We did an initial trial prior to approval in April and May of 2002. We did a second field trial in October 2002. These are the number of individuals involved, and we did it at three blood centers, and the same groups were used both times.

The first field trial, 31 individuals, everybody rated it at least acceptable. The second field trial, about 30 individuals, everybody rated it at least acceptable. Most actually rated it above average or superior.

Subsequent, though, to the field trial, we made some changes to the system where we added the mark in the pouch, which allowed the user to see where the fill line was for about 35 ml. Also, we improved the pouch, so that the pouch sheet size didn't stick as much, so the pouch filled faster, and we revised the IFU to make it easier for the user.

Then, we implemented the system. Our first sales were in October of 2003, and the

initial implementation was very carefully watched. We actually did videos, a lot of training, and gathered a lot of data.

The first studies were done at five centers, about 2,900 collections, 82 phlebotomists, and everybody rated it acceptable except for a small group felt that it needed improvement, and this had to do with the break-away connector at the very end of the line where you attach the lure adapter. Some folks found it a little hard to break.

After the system was implemented, we did follow-up at two blood centers, about 3,400 collections, about 63 folks, and again we had very good response, again, a few folks still said needs improvement. It had more to do with the handling of taking the sample.

This is what the system looks like in use. This is, of course, the collection system, this is the big CLIKTIP, filling the pouch with blood to this--you can't see the notches very well here. This is the break-away connector, female connector,

that actually, we are making further changes on to allow that to be more easily used.

Right now these are users in the U.S. We have sold in the neighborhood of about 250,000, 300,000 blood bags with this diversion system, and hopefully, this works.

This shows you the use of the system. The phlebotomist makes the phlebotomy. You can see the blood is going to the pouch, fills very quickly. You can see the female lure down here on the Roberts clamp. That is kept closed. The pouch is completed, putting on a grommet, sealing the grommet.

It is hard to see where she is breaking the big CLIKTIP, but you will see blood going to the line, which is off here, it goes. This is the line going to the blood bag. You can see the notches here. This is filled to probably about 40 ml.

Now she is adding the lure adapter and holder, so she just broke that female lure out of the lure adapter and holder. If I recall

correctly, this is the group that uses 5 tubes, puts them on the holder, opens the Roberts clamp. Of course, remember that this lure adapter has a valve, so even if you take tubes out, you are not going to get any blood coming out of that system.

You can see how quickly the tubes fill. This is real life use at a real live blood center.

LTC SYLVESTER: Is this in Canada?

DR. MIRAPOL: No, no, there is Terumo. We don't have any business in Canada. This is the U.S.

As I say, we have sold about 250,000, 300,000 units in the U.S. since October 2003. You can see she is collecting--I think this may be the last tube--she closes that Roberts clamp, which really isn't necessary.

This is the end of the video, but obviously, she has completed the whole process in under two minutes. That is the process.

I would like to thank the members of my staff and, of course, the folks at the Red Cross, as well as our customers and our field staff, who

have implemented this process.

Any questions?

MR. SKINNER: Thank you.

Are there questions?

[No response.]

MR. SKINNER: The video answered all the questions.

DR. MIRAPOL: Is that it? I am disappointed.

MR. SKINNER: Dr. Kuehnert.

DR. KUEHNERT: I won't disappoint you.

I have a question that just occurred to me. Have there been any studies done on possible interference between the existence of gross contamination by skin flora in any of the other testing for viral pathogens?

DR. MIRAPOL: I am not exactly sure what you are asking, but during the field studies, the centers we work with did do infectious disease testing of samples taken, and there were no problems. We also measured flow rates and hemolysis, et cetera, and saw no problems

whatsoever.

We have had no complaints whatsoever with this system in the wide range of centers that have actually implemented including Red Cross and non-Red Cross centers.

DR. KUEHNERT: What I was asking was if you had, you know, presumably this bag, it might include skin plug and associated skin flora, has there been any testing done to see if it would interfere with HIV or hepatitis testing.

DR. MIRAPOL: I see your point. I guess based on the fact that we have never had any reports, and as I said, the early field trials did look at infectious, you know, methods of testing, et cetera, and never saw any differences, you know, I guess that is the only way I can answer it.

Of course, the other point is this is a Terumo bag, a Terumo needle, so we don't have a skin plug.

Any other questions?

MR. SKINNER: Dr. Linden.

DR. LINDEN: My question is really for

Steve Wagner, who had his hand up last time around.

Do you have data on really the question that was asked the last time on the effect of diversion on actual frequency of contamination of the units themselves?

MR. WAGNER: Hi. Steve Wagner from the Red Cross.

There is about two or three different papers in the literature. To answer your question, it was probably best done by a study by DeKirk [ph], which looked at sample diversion, and found a significant reduction of Staph epidermidis, but not other organisms in a field trial.

I think the extent of reduction, as I recall, was about a factor of 5 or so reduction in the percentage of units that had Staph epidermidis contamination.

I agree with Dr. Brecher in the assessment that the skin organisms often are not involved in fatalities. They are involved, though, in septic reactions. It is my own thought that this method complements well some of the weaknesses in the

current culturing methodologies where people take samples at one day, because that methodology is likely to miss a significant fraction of slow-growing organisms, many of which are Staph epidermidis.

Some studies early by Dr. Blackman in the Canadian Red Cross showed that about 50 percent of the units that were actually contaminated were not picked up on day 1, and the ones that were not picked up on day 1 typically had Staph organisms.

I agree they don't cause fatalities as often as some of the other organisms, but they do cause fevers and complications for patients. Since sample diversion is not a costly maneuver and it can prevent people from having fevers and rigors and such, I think it is a good complement with culture.

Thank you.

DR. MIRAPOL: If I could add one more point, again, as I indicated, the original intent of the system that we were developing was really to help collect the samples first to ensure that you

got your samples in.

We have anecdotal evidence, we don't have good numbers on this, but it is helping reduce the number of re-sticks at the blood centers.

MR. SKINNER: Thank you.

Other comments or questions?

[No response.]

MR. SKINNER: Our third speaker in this session will be from Baxter. Dr. Steve Binion will present for Baxter.

Baxter - Dr. Steven Bunion

DR. BINION: Good morning. Thank you, Dr. Holmberg, for the invitation to speak here this morning. I am not going to discuss or debate the relative merits of the diversion of initial blood collection. I think that topic has already been addressed.

Also, in similar fashion, you have seen certainly through Jeff's video a demonstration of how the system works. I am going to focus on Baxter's product as approved here in the U.S. and just discuss some of the issues that were

encountered with the recent introduction of our sample first technology.

One quick look at the relevant portion of the blood pack unit that we are discussing. As you see, the venipuncture needle here, the use of the sample for a system which was approved in the U.S. in January 2003 really went into limited distribution Q3, actually Q4, 2003, and is currently approved, but not on the market in the U.S., and we will discuss that in a moment.

Basically, immediately prior to venipuncture, the phlebotomist, to use the system properly, closes the white Roberts clamp. The blue clamp on the segment of the tubing leading to the sample first pouch is open, and at that point again immediately prior to phlebotomy, the operator should open the break-away cannula, which is just immediately before the sample first pouch, so the initial volume of blood flows into the pouch.

It is prevented from going to the primary container, and likewise, anticoagulant is prevented from entering the sample first pouch prior to

phlebotomy by the appropriate sequencing of the clamping and the cannula breakage here.

Once the sample first pouch is filled, this clamp is closed, the white Roberts clamp is open, so that the blood draw can continue into the primary container. This portion of the tubing is sealed off and the pouch is then available for sample collection.

As I indicated, this technology or this system was approved in the U.S., January 2003. This sample first pouch subassembly has been in use on millions of Baxter BPUs since 1999 in Europe and used very successfully there.

However, I do recall January 30th quite well, 4:00 p.m. that afternoon, Chicago time, I received a phone call from the director of CBER's Office of Compliance and Biologics Quality inquiring as to reports or a report from a single center involving possible dilution of infectious disease testing samples, discussed this situation with CBER, looked into it, and later that evening, the entire inventory of the sample first products

under Baxter control were placed on voluntary corporate hold.

The events that played out over the next week or so were working with customers and FDA to provide basically a transition for customers, there were 14 customers who up to that point had received the sample first system, not all of whom were using it at the time, but nonetheless, all 14 customers who had received the product were contacted.

There was an important customer safety letter that was sent out to them based on significant advice and interaction between Baxter and CBER, and basically requiring--I know the slide says "requesting," but requiring inspection of current and retained infectious disease testing samples by all customers who had used the product and still had samples on hand.

Also, we sent technical teams into each of the customer sites to provide additional training and also as a means to simply get a hands-on look at what was going on in those centers.

The week of February 8th, additional

letter again after consultation with CBER was sent out to customers and also at that point, there were communications between Baxter and ABC, BCA members, I believe also direct contact with AABB at that point.

Really, the activities in the week following the report of the diluted sample were simply focused on quickly and safely transitioning the sample first customers to other blood pack units.

I think the focus for Baxter, in collaboration and consultation with CBER, was to effect this transition as quickly as possible, but without interrupting the whole blood collection activities of the customers involved.

As I said, the sample first inventory had already been put on hold. The follow-on decision was to halt the production of that design that I showed you earlier pending the redesign.

There were also discussions with AABB Standards Committee representatives regarding the potential strain on customer compliance with the

5.1-5.1 standard during this transition period, and naturally, daily communication with customers, as well as CBER.

The initial report of this situation triggered extensive investigation within Baxter. Some aspects of that investigation are still ongoing. But the ultimate conclusion was that, number one, sample dilution could with that product design occur if the sample pouch cannula was inadvertently incorrectly, improperly broken, and/or if the clamping sequence was compromised during use or handling of the blood pack unit.

We found no evidence of any manufacturing defect or a product failure mode other than inadvertent, inappropriate breakage of the cannula and/or compromise of the clamping sequence for the product that could generate this failure mode.

This led us to the conclusion that based on the customer experience in the field, a more user-friendly design is required, and that is the focus for the redesigned product.

The critical priorities for the redesign,

number one, based on certainly feedback from customers and, at least at this point, the acknowledged acceptability and desirability, if you will, for this approach to complement other methods for reducing the potential for bacterial contamination.

We are focusing on a rapid introduction of a redesigned blood pack unit system, and clearly, the goal, well, the obvious requirement is incorporating a more user-friendly design which should significantly further limit, if not absolutely prevent, the potential for anticoagulant to inadvertently enter the sample pouch.

Although there was extensive training and work with customers when the current design was introduced, obviously, there will be a renewed focus on customer training and educational activities associated with the use of this new method of obtaining donor testing samples.

Questions?

MR. SKINNER: Thank you.

Questions for Dr. Binion? Dr. Lopes.

DR. LOPES: Was the U.S. version of the product less user-friendly than the European version, or did you have the same sort of issues arise when you introduced the product in Europe?

DR. BINION: That is an excellent question. At this point, any hard data regarding the experiences during the introduction of this same technology in Europe are unfortunately, the matter of anecdote and/or loss to individual or institutional memory.

Basically, with distribution of over 4 million units of this same design in Europe last year, there were no reports of anything similar to this at all, and the lack of incidents in Europe is certainly consistent over the past several years, and as I said, the technology was initially introduced approximately 1999 time frame in Europe.

MR. SKINNER: Dr. Linden.

DR. LINDEN: So, right now then you are selling bags that don't have any diversion pouches?

DR. BINION: Correct.

DR. LINDEN: Okay. Have you considered at

all setting up arrangements with any other type of manufacturer to use somebody else's--

DR. BINION: That is entirely up to the customers. That is the customers' choice obviously. The only reason that the slide indicated transitioning customers to Baxter blood pack units was if that was what the customers desired.

I mean clearly, the obvious choice, as you have heard, there are other systems on the market, customers ultimately make that choice at this point.

DR. LINDEN: So, basically, this is not intrinsic to the bag. Basically, the bag and the pouch systems are entirely independent and can be used a la carte, as it were.

DR. BINION: No, I don't think that is what I said. Is that your question?

DR. LINDEN: I guess it is. The pouches and the bags are separate, they are not intrinsic?

DR. BINION: No, as I think was demonstrated in the presentation by Dr. Dickstein,

as well as Dr. Mirapol, and similarly for the Baxter system, the sample diversion systems are integral to each of the manufacturers' BPU designs.

DR. LINDEN: Right. That was my understanding, which is why I was asking the question I was. So, therefore, if you are using Baxter bags, you are not using the diversion pouches.

DR. BINION: Yes, I am sorry, I misunderstood the question. What I was indicating was that customers, yes, if folks are using the Baxter bags right now, BPUs in the market, it is a post-donation sampling technology, which was what was available prior to the introduction of this.

What I was indicating was that if customers wished to use one of the BPUs from the other manufacturers, that is up to them.

DR. LINDEN: Right, but that would mean using different bags.

DR. BINION: Right, right.

DR. LINDEN: I thought you meant they could use a different--

DR. BINION: No, I am sorry, I apologize.

DR. LINDEN: --sampling system in conjunction with your bags.

DR. BINION: No.

DR. LINDEN: I thought that is what you were saying.

But my question is have you considered, since it seems like you have a large challenge before you to adapt your system to work with basically a competitor to use their system incorporated into your bags.

DR. BINION: I think the answer to that is no.

DR. LINDEN: Okay.

DR. BINION: Actually, we are working very closely with CBER to very quickly effect the reintroduction of a design, which probably will incorporate a repositioned break-away cannula that will virtually eliminate the possibility of these situations occurring.

Actually, from the design standpoint, it is a relatively minor modification to the existing

BPU system, so we do expect to very rapidly validate and work with CBER to reintroduce the Baxter sample first system.

MR. SKINNER: Dr. Holmberg.

DR. HOLMBERG: Yes. I will make the same statement that I made with Pall. I want to thank you for being very open with some of the problems that you faced in introducing this to the marketplace.

The question that I have for you is you mentioned that these samples were retested. Were there any units that were lost?

DR. BINION: I believe that there were voluntary withdrawals of a limited number of whole blood collections from one or more of the blood centers involved. We were not involved, nor, to my knowledge, was there any sort of FDA or FDA-mandated or perhaps even recommended action, but there were individual actions taken by the blood centers based on their assessment of their situations.

I think the situation with regards to the

samples was certainly once, following the report January 30th of possible sample dilution, then, the customers who were currently using the product were directed to reinspect or inspect, because, in fact, not all customers, as it turned out, had inspection procedures in place that focused on this type of occurrence.

In the situation where compromised samples were identified, I am sure that there were collections that were interdicted.

DR. HOLMBERG: And how many centers did you roll this out to?

DR. BINION: There were 14 customers in the U.S. who received the sample first product, but there were very widely varying usage patterns.

DR. HOLMBERG: Thank you.

MR. SKINNER: Thank you for your presentation.

Next, we will hear from Allan Ross with the American Red Cross Biomedical Services.

American Red Cross - Mr. Allan Ross

MR. ROSS: Mr. Chairman and members of the

committee, thank you for the opportunity of sharing our experience on limiting and detecting bacteria in platelet products.

My purpose of the presentation today is to review how the Red Cross is meeting the AABB standard, our implementation challenges after five weeks of experience, our early results of testing for bacteria in single donor platelets, and the impact on platelet inventory and availability.

We made a number of decisions early on. Certainly, we are going to test all platelet collections by apheresis. We are going to implement chlorhexidine improved arm scrub, and sample first technology was important in our strategy.

We decided to put the automated detection systems in 35 locations for single donor platelets. We made a decision not to test whole blood derived platelets. Now, that was a decision made with a survey of our hospital customers where over 90 percent of them said they wanted to do it themselves considering the estimated costs that

they would experience.

We also wanted to continue to monitor customer preferences in new technology and the options of pooled platelets.

Our rationale for testing 100 percent of single donor platelets was to meet the AABB standard and, of course, increase the safety of single donor platelets utilizing the automated systems available for use, standardizing single donor platelet inventory, and really, we had a great deal of demand in the system for single donor platelets.

We currently manufacture about 500,000 single donor platelets annually and about 900,000 whole blood derived random platelets.

Our rationale for not testing whole blood derived random platelets, operationally, it is a huge challenge, but the biggest reason from the customer's point of view was the cost they are going to experience, which was at least 40 percent increase.

We also had a problem in our early trials

of attempting to culture whole blood derived platelets of having a negative impact on the available platelets in the containers that would challenge us in meeting our quality control requirements for the number of platelets in each one of these individual containers, so that we could meet the 90 percent rule whereby our platelet counts where 90 percent of our platelets would meet the count minimums.

We made a decision on automated testing systems. We looked at one with high sensitivity, a proven track record, and clinical setting, ease of use and high degree of automation, and our cost was about $22.

Our original collection bag was sampled before splits were made for single donor platelets. We made a decision based on a medical office recommendation to do aerobic bottle only. We inoculate after a 24-hour hold at 20 to 24 degrees centigrade. We incubate 12 hours before we label and release our products, and then we continue to incubate through the expiration date of those

products.

Suspect positive results, we dispose of the platelet product in inventory or recall if the product is released. We notify the physician if the product was previously transfused. We dispose and withdraw all co-components. In other words, if there were red cells and/or plasma products made from that particular collection, those are also withdrawn and disposed of.

We identify organisms if product was transfused, however, I think we are really looking at going through further identification for all positives that are identified.

We place the donor under a surveillance system, so if we get two hits on them, then, we will further evaluate that particular donor.

We made an attempt to be in constant communication with our hospitals on our decision processes, send the first letter out in November 03. We told them it was going to be about a $25 increase in cost, the shelf life was going to be reduced by 0.5 to 1 days.

We have told them about our plans for notification of positive culture results, and we also communicated that we would be limiting bacteria in random donor platelets, not necessarily testing.

The second letter was in December. We confirmed a $22 price increase, communicated no plans to test for whole blood derived random donor platelets, that would be the hospital responsibility.

I send a third letter out in March where we indicated discontinuation of sample first to limit bacteria in whole blood derived random donor platelets due to hemolysis in tubes, and extensive arm scrubs would be continued.

If a hospital reported a positive culture on Gram stain, the products were presumed contaminated, other components from donations discarded, and a deviation was filed with the agency.

If a hospital reported a pH less than 6.2, this indicated to us that the product failed to

meet our release criteria, and the product was potentially contaminated, others components from donations were discarded, and we filed a deviation with the agency.

If a hospital reported pH 6.2 to 7.0, this does meet our release criteria, no products or reporting action taken by us, and the hospital is encouraged to use Gram stain or referred to the AABB bulletins on further actions.

Implementation challenges. There are supply challenges, start-up costs, standard operating procedures, staff training, apheresis staff and laboratory, and then a space for equipment in 35 locations. With some of the volumes that we have on platelet production, and the automated instruments taking up a lot of bench space, benchtop space, it was a challenge, and we had to do quite a bit of remodeling to accommodate this.

Sample First technology. It was a short time frame as far as availability of volumes of bags that we use, logistics of conversion to new

bag sets from two different vendors, collection staff training, problems with dilution of testing samples from anticoagulant, problems with hemolysis.

We were very concerned about test tubes and the interference with the infectious disease testing. We even went to quantitative-free hemoglobin analysis to ensure that we were not testing samples that did not meet the package insert.

Challenges with implementation of chlorhexidine arm scrubs to be used with donors who are hypersensitive to iodine. The acceptable storage temperature in their package insert is 20 to 25 degrees centigrade. That is a very, very narrow temperature range. When you are doing 800 to 1,000 blood drive operations a day in all kinds of environments, it is very difficult to meet that standard of 20 to 25 degrees storage temperature, so we end up throwing away all unused chlorhexidine products that aren't used in that blood drive because we can't guarantee they have been

maintained in that 20 to 25 degrees period. We have also lost some products due to using arm scrubs that are outside of the temperature range. That has been about 250 donations.

Impact on safety. To date, the Red Cross experience approximately 39,000 single donor platelets tested. We have had 27 initial positive results, 4 reproducible true positives, there is still quite a bit of testing underway, 2 Staphylococcus, 2 Streptococcus, 6 contaminated product interdicted to date.

I am sorry we don't have more detail, but these data are very fresh for us, only in the past 6 week, or 5 to 6 weeks. We will have much more in the coming months.

This is an example of the weekly impact on our supply. Our average total inventory 4 weeks prior to testing was 3,067, 3 weeks after it was 3,308. What is interesting is what has happened to release inventory has gone down, in other words, the available inventory. The work-in-progress inventory has gone up by 38 percent.

So, while we have more products in the pipeline, if you will, they are not available for transfusion. Our overall production has been pretty much the same. Customer shipments have been increased somewhat.

Our outdates, interestingly enough, have gone down by 28 percent. That is kind of counter to what other folks have experienced. I attribute it to two factors or several factors. Number one, we did see, for the month, an increase in demand, overall demand, for products.

We also think that customers are using older platelet products now, where in the past they used to shift back to always requesting fresher products, and that always has increased outdates in the past.

This is just an example where we implemented. You can see the previous outdate rates and then they have dropped off, but they are coming back up a bit, so I expect to see this normalized and very little change overall as we go down this path with maybe outdate rates stabilizing

in the 5 to 6 percent range.

The availability conclusions. What we have experienced, we used to have a shortage between Tuesday and Thursday due to synchronization of production and demand. Now, we have seen that extended out all the way through Friday where we are challenged on the those days.

We have plenty of products really Saturday, Sunday, and Monday, and usually on Tuesday. Where we always seem to have fewer is on the latter part of the week, and that is mainly because collections are not as great on the weekends, primarily on Sunday.

As I mentioned before, we have much more work-in-progress inventory. Our outdates are down, I said before because customers are using whatever is available, and some regions have shifted to 100 percent single donor platelets to avoid conversion to sample first for whole blood collections.

In summary, our implementation with challenging decisions have been reversed due to unanticipated problems with supplies. Safety, I

believe has been positively impacted, we are very supportive of this standard and utilizing this technology. We are only one month post-implementation, and we really look forward to being able to implement the sample first diversion pouches.

The manufacturers have been very cooperative in working with us. We look forward to putting those back into use.

Questions?

MR. SKINNER: Questions? Dr. Lopes.

DR. LOPES: I have two questions for you. For the donors who have bacteria in their blood, are these people who are on their way to being sick, or is this chronic?

The second question is when hospitals do their testing themselves on random donor platelets, are the using just swirling, or are they trying to culture something at that point?

MR. ROSS: The hospitals are using a variety of methodologies, and I think we have talked about that over the last 24 hours. Many of

them are using testing methodologies, many are using Gram stains. Some are doing pH and glucose. Some are using combinations of things, as Dr. Bowman mentioned what they were doing at the University of Minnesota, and I think that is reflective pretty much of what is going on across the country.

DR. LOPES: The other question was about donors who are found to have--

MR. ROSS: Well, not being a physician, I would not hazard a guess on that. Perhaps Dr. Brecher could offer a comment factually.

DR. BRECHER: No comment.

DR. KUEHNERT: I just wanted to clarify on this question because I am confused about what you had said in the slide presentation that relates to this question.

You said they get medically evaluated if the donor is culture-positive.

MR. ROSS: Twice.

DR. KUEHNERT: Twice, but you don't know what the organism is?

MR. ROSS: Yes, we will know what the organism is, yes.

DR. KUEHNERT: But you are only identifying the organism if the product is transfused.

MR. ROSS: We are re-evaluating that process right now.

DR. KUEHNERT: Okay. I will let others speak and then ask a couple more questions.

MR. SKINNER: Dr. Penner.

DR. PENNER: A similar question. You are allowing that donor to come back again even though you found him to be positive the first time, so the follow-up on that situation is--

MR. ROSS: This is similar to what organizations are doing right now, because it has been shown that 70 percent or thereabouts of these positives are contaminations from the skin plug.

DR. PENNER: But you don't identify that at the time, all you are identifying is positive, you don't culture?

MR. ROSS: We are re-evaluating at this

time.

DR. PENNER: I see. Okay. Otherwise, these people are drifting out there, and we don't know what is going on.

MR. ROSS: Right.

DR. PENNER: One other question that is a little different. How do you equate the single donor versus random donor units?

MR. ROSS: How do we equate?

DR. PENNER: Equate them, yes. How many single donor units or how many units cover a single donor now that we have got all of these manipulations?

MR. ROSS: If you are talking about how many randoms equivalent to a single donor platelet?

DR. PENNER: Yes.

MR. ROSS: That is not our decision. That is the clinical services and the physician determination. If you talked to Dr. Ed Snyder at Yale, he is using 3 to 4 randoms as equivalent to a single donor platelet. There is other places using 5 to 6. We have even some others that we know are

using 10.

DR. PENNER: So, you haven't evaluated the numbers at this point. It used to a 6-pack equaled single donor, then, there is some question of maybe a 5-pack, and a lot depends on the numbers, but I would think that you would have some information as to what the platelet numbers are in your randoms as compared to a single donor.

MR. ROSS: Well, we think 5 to 6 is equivalent to a single donor platelet, however, in clinical practice, there have been many physicians that have seen a corrected count increase just with 3 to 4, and that is really what they are looking for.

DR. PENNER: Well, the problem comes up when the physician is ordering platelets, he has no idea what he is ordering now, and frequently, they will order 6 or 10, or something of this sort, and then someone has to decide we have got single donor units, how do they equate, and there is a translational effect there that probably needs some attention.

MR. ROSS: Our recommendation is 5 to 6 whole blood derived randoms are equivalent to a single donor platelet.

MR. SKINNER: Dr. Sayers.

DR. SAYERS: Allan, there is 27 initial positives.

MR. ROSS: Thirty-seven.

DR. SAYERS: Those 27 initial positives, do you know when during the incubation, those positives were identified?

MR. ROSS: I don't have that data.

DR. SAYERS: I am just wondering how all of us manage notification of physicians when the product is found to be positive after transfusion.

MR. ROSS: I am told that we are seeing these positives at 12 to 40 hours. That is the time period.

MR. SKINNER: Dr. Linden.

DR. LINDEN: A couple of really logistic questions. You mentioned co-components of red cells in plasma although you are only doing pheresis platelets, so you are using technology

that allows collections of platelets concomitantly with plasma and red cells by pheresis?

MR. ROSS: Using trema [ph] technology, we have the ability to collect apheresis platelets and red cells in plasma.

DR. LINDEN: That is what I assumed. I just wanted to clarify that.

You mentioned that some of your centers had changed procedures solely to avoid the--

MR. ROSS: Yes. We have a number of centers that were only manufacturing 500 to 3,000 whole blood derived random donor platelets out of 150- 200,000, and so why implement a second bag technology into their processes when they can convert to single donor platelets, and avoid implementing sample first.

DR. LINDEN: Right, and even though you are not using that presently, you anticipate going back to that, and that was the reason for that, or that you started and then discontinued because of the problems.

MR. ROSS: I doubt that we will see

regions that were only making small amounts of whole blood derived platelets go back to making them. It doesn't make a lot of sense. If they need them, they can import them from one of our other centers.

DR. LINDEN: Right, and because of the problems then with the hospitals needing to do their own testing with the exception of the cost issues, okay.

You mentioned that if the positives come up--I know this was sort of asked before--you are putting the donors on surveillance, but allowing them to come back and donate, you are not notifying the donors and not putting them on any sort of donor deferral registry.

MR. ROSS: That seems to be the standard practice within all blood collection agencies at this time.

DR. LINDEN: So, your assumption is if they are harboring bacteria in their antecubital fossa because of extensive scarring, that they will come back, and second time they will come up

positive a second time.

MR. ROSS: Yes.

DR. LINDEN: Like the donor with the 280 donations and the extensive scarring that we heard about yesterday.

MR. ROSS: Yes.

Jerry, I know you are always going to ask do we import platelets, and, yes, we import between 10- and 20,000 single donor platelets annually. We have gone through a certification process where we have written certification from blood collection agencies that send us products that, yes, indeed, they are implementing the standards and have done so.

We have one supplier who is not, indicated that they are doing testing, and in that case, we have developed procedures to do testing with that particular supplier.

DR. LINDEN: Just following up on the question about the surveillance, if the test comes up, since you are identifying, if it is a skin contaminant, I see your point, but what if the

identification comes up as something more serious like a gram-negative rod, for example, would your strategy be any different?

MR. ROSS: Oh, absolutely. I think we would probably defer that individual and refer them to their physician for further follow-up. That is really a medical office decision.

DR. LINDEN: But are you identifying the organisms then?

MR. ROSS: We are definitely going to be doing that, I believe, in the future.

DR. LINDEN: In the future, but you are not doing that presently?

MR. ROSS: Not currently.

DR. LINDEN: Okay. So, presently, you would not then be doing anything to identify gram-negative--

MR. ROSS: If we have a second positive, we do identify.

DR. LINDEN: Okay. But the first time, if it's a gram-negative rod, you are not going to know that.

MR. ROSS: That's correct.

DR. LINDEN: Okay. Thank you.

MR. SKINNER: Dr. Kuehnert.

DR. KUEHNERT: Just a couple of questions to clarify. You had on your slide on your positives, you had 4 true positives, and then you said 6 contaminated products interdicted.

So, was there more than one product for some of those 4 true positives?

MR. ROSS: Yes.

DR. KUEHNERT: Were they splits?

MR. ROSS: I don't have that data.

DR. KUEHNERT: I think it is very important, you know, you mentioned being able to trace back and also interdict other products, and I think that is important.

You also mentioned as far as random donor platelets, if the hospital tests and finds a positive, then, those components are traced back, and you said discarded. Will they be cultured or they just going to get thrown away?

MR. ROSS: I don't think we have the

answer to that.

DR. KUEHNERT: Okay. Just give it some thought.

The other question I had about it is you had about testing, you had these pH thresholds, but you didn't mention about glucose. It is just any positive test by the hospital results in a traceback, or just--

MR. ROSS: Our release criteria is not based on glucose for regular platelet release. It is based on pH and counts.

DR. KUEHNERT: So, if they do something other than pH, then, basically, any test result they get doesn't result in a response.

MR. ROSS: If they notify us that they have a product with a decreased glucose, we would ask them to do a pH.

DR. KUEHNERT: My final question along this vein is that you also said hospital encouraged to use Gram stain and referred to AABB information, so you are not necessarily encouraging them to culture if they get a positive result, but

just to do something consistent with AABB standards.

MR. ROSS: Yes.

DR. KUEHNERT: My other questions were about your testing using--you say you use the aerobic bottle only, so that is one bottle, right?

MR. ROSS: Correct.

DR. KUEHNERT: Do you know how many ml that is that you are using?

MR. ROSS: I think it is 4.

DR. KUEHNERT: And you said that you are going to continue the incubation through the expiration date, which I guess currently is 5 days.

MR. ROSS: Five days.

DR. KUEHNERT: And I have just heard different things about what is in the package insert, and I don't know if we need to discuss this now, but I am not sure if anyone is following the package insert, but I am not sure if this is consistent with it or not, but I don't know if anyone can answer that.

DR. HOLMBERG: I don't know whether you

are asking the question whether there is one bottle or two bottles. Is that the question?

DR. KUEHNERT: No, I got that answered. It is one aerobic bottle that they are using, but I was asking for how long it is incubated for and what the package insert recommends. I know for the package insert for bottles, they recommend an aerobic and anaerobic, but as far as the length of time of incubation, I have heard 5 versus 7 days, and I wasn't sure what the recommended time was and whether this was consistent with the package insert.

MR. ROSS: I believe the package insert states to incubate until the product outdate.

DR. KUEHNERT: Thanks.

DR. GOMPERT: Could you focus on the supply issue, shortage issue? You have one month of data, and it looks like from a 3-day supply issue overall, you have now got a 4-day.

Do you anticipate this changing or getting worse, or are you doing anything around changing things around the supply issue?

MR. ROSS: Well, we all know that platelet utilization is cyclical, and the variations from one day to the next are tremendous, so we are constantly up against a challenge on a supply. We have the ability to move product from one side of the country to another, and we do that on a daily basis.

I believe our statistics on our fill rates for platelet orders are in the range of 95 to 97 percent, and I believe that has continued through the past 5 weeks without an impact.

What we have seen with more products in work-in-progress is that our inventory is tighter. We don't have the cushion that we used to have in the past.

DR. GOMPERT: Are you going to focus on that and do anything about it?

MR. ROSS: Well, we have been attempting to focus on increasing platelet collections for probably 50 years, and we have made great strides in increasing production. Four years ago, we were manufacturing about 275,000 single donor platelets,

and we are now manufacturing over 500,000 per year, so, yes, we are constantly addressing this.

Each one of our regions has a target of production of 40 percent of their single donor platelet production to be on Saturday, Sunday, and Monday, so that we can try and balance the inventory and make up for the shortages or the tightness that we see on Tuesday through Friday.

MR. SKINNER: Dr. Holmberg.

DR. HOLMBERG: I need a clarification on how many units, and I don't know if you have this information, how many units were lost because of the hemolysis or the dilution or even units that were returned back from the hospitals in which you had to pull the other products.

MR. ROSS: I don't have that data. For the anticoagulant dilution, it was very small. For the hemolysis issue, it was a bit larger. The implementation of quantitative free hemoglobin analysis helped us salvage a lot.

When you look at the qualitative analysis, where it is really a colorimetric comparator chart

on hemoglobin comparison, it gets pretty gray, and working with the agency, we lowered what would be the cutoff normally and then implemented quantitative hemoglobin determinations, and that helped salvage most of the units, so the losses were very small.

DR. HOLMBERG: Just another quick question. What percentage of your platelet inventory is now apheresis?

MR. ROSS: That is about 75 percent.

DR. HOLMBERG: Okay. Thank you.

MR. SKINNER: Dr. Sayers.

DR. SAYERS: Allan, I am looking at ways to promote availability here, and if you look at that supply impact table of yours, something like 9 to 14 percent of the apheresis products are outdated, so the question is do you think that if there was an extension of platelet dating, that outdate rate could be reduced?

MR. ROSS: Absolutely, no question.

MR. SKINNER: Dr. Holmberg.

DR. HOLMBERG: Just another quick

question, hopefully, it is a quick question.

The hospitals that you serve, do they either go random, whole blood derived platelets, or apheresis, or do they take a mixture?

MR. ROSS: Out of the 2,500 hospitals that we serve, we probably have 4 to 6 that are whole blood derived predominant, and we have quite a few that are single donor platelet only. So, I can't give you absolute numbers, but we know that we have customers that have preference for whole blood derived platelets. You heard from Dr. Bowman yesterday was one, there are several others, but it is really a mix, I would say.

DR. HOLMBERG: Do you have any idea from the hospitals, the ones that have a mix, do they have different criteria for what patient receives what product?

MR. ROSS: I don't know that.

DR. PENNER: I might be able to add that I think a lot depends on cost factors for many of these hospitals, at least from the ones that I have surveyed. It comes down to the additional cost of

the single donor as opposed to the randoms, and many of them preferring the randoms because they can get by with a reduced cost and do dipsticking if need be.

MR. SKINNER: Ms. Lipton.

MS. LIPTON: I was just going to comment that Dr. Sazama is going to be presenting some data from a survey, and I realized in going through the survey, there were some things we were not going to present, but they may be interesting to the committee in terms of what people are planning to do about donor deferrals. We were just trying to get a sense of what is happening.

I don't think we are going to have time to put it together in time for her presentation, but maybe, with your indulgence, maybe over lunch we could put a few of these into slides, so that you could see, and you can see what hospitals are planning to do.

We have questions about what people are planning to do with the co-components, deferrals, and then we also have some data on hospitals and

whether they have switched from whole blood derived to pheresis platelets or the other way around.

So, that might help put some parameters around this discussion.

MR. SKINNER: Thank you very much.

MR. ROSS: Thank you.

Next, on the agenda, we are going to hear from the America's Blood Centers. Presenting for them will be Mike Fitzpatrick.

America's Blood Centers

G. Michael Fitzpatrick, Ph.D.

DR. FITZPATRICK: Good morning. I want to thank you for the opportunity to present to the committee.

In the interest of full disclosure, I need to let the committee know that in the past, I served as a consultant to the Navy and the Department of Defense for frozen platelet license applications to the FDA. I also serve on two scientific advisory boards for companies that are developing lyophilized products. One is Hemocellular Therapeutics, the other is AdLife. I

receive no compensation other than perdiem and travel for those, whatever they get from my comments.

I am employed by America's Blood Centers, and so I hope you are all aware of that. You have both a written statement and copies of the presentation. I would like to just highlight a few things in the written statement as we go through the presentation.

The first part is just to remind you that ABC serves a heterogeneous group of 75 nonprofit community blood centers. From that, we provided 7 million donations in 2003, operate in 45 states and Hema-Quebec in Quebec, Canada is one of our members.

We will skip the first part about transfusion. I think we all recognize the risks of bacterial contamination and the fact that testing is warranted.

The third paragraph, however, a number of interventions have been attempted to reduce this risk including pH, testing glucose levels, changing

the arm scrub, swirling, culturing and inactivation, but it is only recently and through the emphasis of AABB Standards Committee and the Transfusion/Transmitted Disease Committee that we have a method that allows us to, within 48 hours of sampling, be able to interdict units that have large bacterial loads or a bacterial load that can be detected.

The implementation of the standard requires methods to reduce the chance both of bacterial contamination and identify the contaminated units. The implementation could prevent between 67 and 333 deaths per year based on Dr. Mark Brecher's presentations and estimates.

Just as a reminder, similar actions were taken last year by the blood collection community to reduce the risk of transfusion of West Nile virus very successfully, interdicting about 1,000 potentially infective units.

I just want to remind the committee that the ABC members are implementing bacterial testing with the same diligence and dedication that was

applied to the implementation of West Nile virus testing, and we hope the impact on patient safety will be as successful.

We surveyed our members rather quickly in order to prepare the data for the committee. We have tried to provide as up-to-date results as possible, so the results you are going to see are as of Tuesday.

Fifty-four of our 76 centers have responded to the survey distributed to determine the impact of implementation. We tried to ascertain their methods used to comply with the new standard. These centers that have replied so far collect about 80 percent of the American blood centers blood supply.

Thirty-nine or about three-quarters of the centers produce whole blood platelets, and 85 percent produce single donor apheresis platelets. About 70 percent of those produce double apheresis platelets, and a third produce triples.

All but 5 centers are currently testing apheresis platelets for bacterial contamination.

One center does not make apheresis platelets, another center plans to implement testing next month, and area hospitals are doing the testing for the other two centers.

There is a recap of that.

As you can see, 92 percent of the reporting centers have implemented.

The methods being used to test apheresis platelet for bacterial contamination from the reporting centers, as you can see, 78 percent are using the Bac-T Alert system. Pall accounts for another 20 percent, zero percent are doing Gram stains, and 2 percent are using a dipstick.

As far as whole blood platelets go, our centers that are producing whole blood platelets, as you can see, some have implemented testing, 39 percent have implemented testing, 6 percent plan to implement, and the other 30 percent, their hospitals will be doing the testing.

The methods being used, predominantly the dipstick. Again, no one is doing the Gram stain, Pall and Bac-T Alert systems account for the other

38 percent of the whole blood testing.

That dipstick does include, those results include the plans of the hospitals that would be doing the testing where you saw that hospitals would be doing the tests.

So, what is happening to our distribution policies and the shelf life of platelets after the implementation of testing? This is the days to expiration at distribution on the bottom here from our centers for whole blood and apheresis platelets.

You can see it is sort of across the board between 3 and 4 days at distribution left on the shelf life of the platelet when it is being distributed, most of it in the 4 to 3.3 day range area.

The time it takes from collection to do the bacterial testing varies from center to center based on the method that they are using, and when we surveyed them to try and look at the impact of doing the testing and the sampling on their procedures and their distribution system, the

shortest time frame is a center that is doing the Bac-T Alert system, and as you can see by the comment, is sampling at 12 hours, but has validated that process and has notified FDA for a variance to use the system in that manner.

The rest of the centers are sampling at 24. We have some centers taking as long as 40 hours, 48, and 54, and this center is using dipsticks to test apheresis platelets at distribution.

So, you see that of the 54 respondents, we have a variety of methods being used to implement it, and the impact on the time at each center varies based on their processes.

Outdates. A number of our centers began testing last year. We felt that 30 days worth of outdate data was not significant enough or valid enough to report to the committee, so we took those centers out of the survey, and are only providing information on outdates for centers that began testing prior to February 2004 and have a minimum of three months of experience with testing.

You heard from two of those centers yesterday, Puget Sound and Florida Blood Services both are ABC members. You can see here that of the 12 centers that qualify with those caveats, there were no changes in outdates at 7, increases at 5 ranging from 3 to 7 percent with an average of 5.2. You will recall from yesterday, you heard one center that had about a 3 percent increase, the other about a 7 percent, so you heard from both ends of our range yesterday.

I provided some anecdotal comments received on the survey, not because they are statistically significant and not because they are a valid random sampling of the members, but because of the short time frames since implementation, we felt that it is important that the committee know the impact on the centers and what they are perceiving as the impact on them even though it isn't what you would consider a statistically valid sampling of 54 centers. These are just anecdotal comments.

One of the questions raised by Dr.

Holmberg has been the impact on whole blood platelets and what is the impact. In 30 days, we don't really have good numbers to provide you a statistical impact, but you can see here 4 centers reported they stopped making them.

Another says it is producing two-thirds less, another one about 25 percent less, and that hospitals are preferentially ordering single donor apheresis platelets in order to avoid testing, so their distribution of whole blood platelets is down.

However, some other centers reported very little change. Hospitals were not willing to change their use of random platelets for apheresis, probably an economic factor, and don't want to be involved in platelet testing at their facilities, so that center was doing whole blood testing for the hospitals.

Most of this center's hospitals had already converted to single donor apheresis.

This center, the hospitals have employed the dipstick method and have seen no change in

their whole blood platelet ordering or distribution pattern.

So, what is happening at the hospitals? Again, just anecdotal information, some hospitals are reporting numerous false positives, the blood center is culturing those that don't pass, it is a very subjective test, and creating unnecessary cultures.

It will be nice to quantify that over time, so that we can see the effectiveness of the testing.

Another hospital that agreed to implement a process to test random donor platelets. Fifty percent of their customers haven't been able to achieve that goal, so now they are refusing to accept them. They will implement whole blood testing, but only when an improved cost effective method is available.

What has been the impact of the centers? Again, over time we will be able to quantify this better. The two presentations you heard yesterday from Puget Sound and Florida Blood Services, I

think gave you a good feel for the impact on the center, but they are seeing a need for increased staffing, increased costs, changing blood bags and implementing new processes is a big undertaking, have to add staff, they are moving more products, they had to increase their deliveries, purchase additional incubators in order to be able to quarantine the products appropriately, changing their release procedures, and changing the times that they do things.

Again, as you heard yesterday, it is not a simple process, it's a doable process.

But is testing the ultimate solution? There are other things in the works, and while we all agree that bacterial contamination is a risk, and fatalities occur from it, we need to go beyond just testing and beyond just this system of testing, and I think Dr. Holmberg, when he charged the committee at the beginning and Mark Skinner has reinforced that we are not here to debate whether or not we should be implementing the standard, we are not here to debate whether we should be doing

testing or not, but is there something that can be done to make this a more cost effective, reliable, faster, efficient method of preventing bacterial infection in patients.

There are some things going on. There are alternate storage solutions. There are investigators looking into storage solutions that can be used for refrigerated temperatures. Freezing or lyophilizing platelets would allow extra time for testing to be done before release and could help with inventory issues if there are inventory problems.

Inactivation methods have taken a turn for the worse with the results of some studies that have been in process, but I don't think we should abandon inactivation methods if there are reasonable, safe methods that can be developed.

We know of manufacturers that are looking at filtration techniques to remove bacterial or viral or other transfusion-transmitted disease agents. Simple, quick things that we heard about yesterday are pre-pooling. If we can get approval

and find a way to collaborate with FDA on studies that are smaller to allow sites and collection agencies to pre-pool platelets, test one product instead of six, you saw a very excellent example of how cost effective that could be, how it could impact on availability, and is being done in other countries.

So, I think that is one of the more time-sensitive things that we could do if we can collaborate with FDA and a more reasonable number of samples to approve that method.

The other is extension of the shelf life to 7 days, and again you discussed that yesterday, and you heard from Allan Ross of the impact that that would have on outdating. Most likely it would reduce outdating.

So, in conclusion, we encourage this committee to recognize this is only the first step in the journey to eliminate the risk of bacterial transmission from blood transfusion, and it is a significant and important step.

We need additional research to develop

simpler, quicker methods. We need to improve the storage media and techniques that inhibit or inactivate bacterial growth and allow time to defection, and we need to do all this without impacting availability.

With that, I will conclude and thank you for this opportunity.

MR. SKINNER: Thank you, Mike.

Questions? Dr. Linden.

DR. LINDEN: Thank you, Mike, for the very timely and helpful information.

On the outdate information on the pheresis platelets, this is very interesting and helpful. Do you have any data on the increased time to release that was caused by the testing for the bacteria, the culturing, or did you ask only about the outdating per se?

DR. FITZPATRICK: We asked about time to release and time to distribution. The results of that were relatively hard to interpret, and we are going back to validate some of that information.

It appears that the additional sampling

and testing using the Bac-T Alert system is not extending the time in process beyond what was already the time in process because of infectious disease testing at most sites, but again that is just the impression from these surveys, and we still have to validate and clarify some responses.

DR. LINDEN: Thank you.

Also, I am curious about the one center that isn't accounted for. Do you have one that isn't going to do anything at all, or was there an error in the numbers?

DR. FITZPATRICK: It must be an error in the number, no, everyone had responded.

DR. LINDEN: Okay, because you had five centers.

DR. FITZPATRICK: We had five, right.

DR. LINDEN: That weren't testing, and there is one that doesn't make apheresis platelets, one that is going to be doing it next month, two that are sending it out elsewhere, so I am just curious about the fifth one.

DR. FITZPATRICK: I am sorry, there are

two that don't produce.

DR. LINDEN: Okay. Lastly, the 4 percent of your centers, which I guess is maybe three, that are using pH and glucose, are they using quantitative testing on pH and glucose meters as opposed to something like dipsticks, and are they planning to convert to one of the culture methods, and are they very small centers? Can you tell me more about those sites?

DR. FITZPATRICK: Those are all good questions, and that is actually what we are going back to validate and clarify. We didn't get a response from all the centers on the method being used, so we are going back and asking what method they are using, is it an adjunct to other testing and how they are going about it, so I can't honestly answer that right now because we don't have that information.

MR. SKINNER: Dr. Holmberg.

DR. HOLMBERG: Mike, thank you for giving us that wealth of data. What percentage of your sites are doing apheresis, has there been a shift

in the apheresis, do you have an idea of percentage?

DR. FITZPATRICK: Total out of the 75 centers, for those that produce platelets, which is about 80 percent, probably about 80 percent are doing single donor apheresis. That may be closer to 100 percent, I would have to go back and check.

DR. HOLMBERG: I have on more question as Allan Ross preempted my question. I would like to ask you the same question.

In your facilities that import and export, are there any statements that go along with these imports and exports that say that these products have been tested?

DR. FITZPATRICK: As you an imagine, with 75 members, there are a number of import agreements between members, and the members have negotiated and discussed that amongst themselves, and they don't involve us at the association level as to the details of those agreements, so that was not something we asked in the survey, and we could certainly do that in the future.

DR. HOLMBERG: I thank you again. I think that there is an importance of continuing on with the survey to monitor. Thank you.

MR. SKINNER: One more question. Do you have any information or the data on the cost or the impact on the centers from implementing?

DR. FITZPATRICK: That varies significantly from center to center. We did ask about increased cost. I didn't report it because the responses we got again require clarification and some validation.

Most centers have reported an increasing cost. The association has a group purchasing contract with BioMerieux for the Bac-T Alert system, so the centers using the Bac-T Alert system have pretty much a homogeneous cost.

The range of cost that we saw reported was between about $5.00 per unit to a high of I think of about $23 per unit, but again that requires some clarification and validation.

MR. SKINNER: Any other questions?

[No response.]

MR. SKINNER: Thank you.

At this point, the committee will take a break, if we could try to return around ten after 11:00. Thank you.

[Break.]

MR. SKINNER: Our next presentation, we are going to hear again from the American Association of Blood Banks. Dr. Kathleen Sazama is going to present again.

American Association of Blood Banks

Kathleen Sazama, M.D., J.D.

DR. SAZAMA: Thank you. It's a pleasure for me to be able to present some data to you. I know that is an important aspect of your meeting.

So, I want to say just a little bit about what AABB has done in the last few days. The AABB has, with the support of and at the initiative of the Scientific Section Coordinating Committee, which is one of the standing groups of the AABB, led by the current chair of that group, Dr. Connie Westhoff, and assisted by Tony Kasina and Dr. Dan Waxman, developed a survey.

The AABB national office staff, which included Karen Shoos Lipton, Gene Auter, Mark Pierce, and Liz Parrett, further refined the survey, and it was distributed on March 30th. It was distributed to over 1,100 institutional AABB member contacts, which does not include approximately 200 additional ones where the e-mail bounced back, so there was a reason why it didn't go through.

Within 24 hours after this distribution, we had received over 200 responses to the survey. The specifics about the survey are it was on line, it was estimated that any person knowing the answers to all the questions could complete the survey in less than 10 minutes.

The survey was divided into four parts, each containing approximately 20 questions. The first part, intended for facilities that transfuse platelets only, referred to as "transfusion services."

The second was for facilities that both receive and manufacture platelets and then

transfuse them, and the third, for facilities that just manufacture and transfuse. These are going to be shown together subsequently and will be referred to as "hospital blood banks."

The fourth were for facilities that only manufacture platelets and distribute them to their customers for transfusion.

From the preliminary results we have received so far, we have combined Section 2 and 3, and these are hospitals that are independent or a blood center that also manufactures platelets or manufactures some and receives some from external suppliers, so just so you understand how the data are depicted going forward.

There were a number of questions asked, and we are going to focus on only a few. I caution you this is very preliminary, again based on the initial responses, but we thought it would be important to have at least this much information.

One of the questions was have you experienced platelet shortages as a result of bacterial contamination testing since March 15th,

2004. This was asked of the transfusion services and the hospital blood bank facilities.

Here is how they answered. I call your attention to the fact that 54 percent of the respondents indicated that there was no increase in platelet shortages, which should be somewhat reassuring.

There were 26 percent, 16 respondents, that said yes, they had experienced shortages, but they couldn't necessarily link it to the fact that bacterial contamination testing had started, so only those, the 16 percent said that yes, they had had shortages and they believed it to be due to the initiation of testing for bacterial contamination is the group that I think would be reflective of those that might be having a problem.

I would also note that there were over 200 responses to these questions, and that number will change slightly as we go forward. Not every institution answered all the questions, and so forth.

Okay. That was the transfusion services.

You will notice that the hospital blood bank N is much smaller. This is 34. So, we will always keep that in mind, but you will see a much higher percentage, 70 percent said there was no shortage, and this number is around 12 percent, probably no different because of the small numbers that actually had experienced some sort of increase in platelet shortages.

How about the percent increase in platelet shortage? The question was considering your usual inventory of platelets, what is the percentage of the shortage.

Since most facilities answering the previous question stated they were not experiencing a platelet shortage, we looked to this question to confirm those answers, so what we saw from the transfusion services is that 59 percent of them said it wasn't applicable, they weren't having shortages, but among those that were having, which ended up being a N of 94, you can see that 61 percent said less than 10 percent increase in shortages, and 31 percent said between 10 and 25

percent. Together, that is 92 percent.

So, there were some, five facilities that had between 25 and 50 percent increase in platelet shortages, and four facilities that expressed a greater than 50 percent increase in platelet shortages. So, clearly, there appear to be some facilities that are having difficulties.

The hospital blood bank response, again, I call your attention to the small N. Seventy percent again said there wasn't a problem, so they didn't answer this question. So, of the 10 that did answer, 60 percent said again that they had less than 10 percent of a shortage, and 30 percent said between 10 and 25, and only one facility had between 25 and 50 percent shortages, and none reported a greater than 50 percent shortage. This may reflect, of course, that these are facilities that can manufacture their own.

Another question on the survey had to do with what is the dating on your freshest platelet in hours. The transfusion services normed around 48 to 72 hours. Now, what is not shown in here is

different, but this is the average, 51 percent said that they are getting their platelets at 48 to 72 hours.

Notice that some of them, 6 responders, 3 percent, said they are getting them at 96 to 120 hours. This is almost with no time left, but again, as I say, we don't know whether that is their standard practice, and 1 percent, or 3 of them, said they are getting them in under 24 hours, so that there are some who are getting them from their supplier very quickly. This doesn't also break out whether they are getting apheresis or whole blood derived platelets.

The hospital blood bank response again was a little sooner, about 70 percent were by the 48 to 72 hours, but half of those were within 24 to 48 hours, so again, there is practically an even distribution around that time frame.

Another question had to do with is there an increase in platelet outdating as a result of bacterial contamination testing, and, if so, what is the increase in the percentage of outdating.

The transfusion services again, 63 percent said there has been no problem. Of those that answered yes, which ends up to be a N of 35, there is an increasing number of them saying that greater than 7 percent have been outdating from them.

Notice also that 22 percent, or 51 responders, had some other answer, and, of course, this bears further scrutiny to see how that would impact the numbers, but again, we do see certainly there appears to be some hospitals that are experiencing increases in platelet outdating greater than 7 percent.

How about the hospital blood bank response? Again, these are people who are creating their own or importing, as well as transfusing. There is an N of 10 who responded that they did see a change in the outdating, and more of these were shifted toward the greater than 7 percent.

How about platelets available for distribution?

The question was since implementing a method of bacterial detection on platelets, has

your facility been able to meet platelet supply and ease of your transfusion service centers.

Fortunately, there were 43 blood centers that responded to the survey including the American Red Cross, which is counted as only one respondent, so you have already seen those data separately, but factor that in that that one represents a number of facilities.

The blood centers basically said have you had a problem--sorry--since implementing, has your facility been able to meet platelet supply. The no answer means they were not able to meet; the yes answer means they could meet the supply requirements.

So, if 79 percent of the 43 responders said they were able to meet the requests for their transfusion services without difficulty, and only 3 of the 43 indicated that they were having difficulties.

The other answers are also of interest on that slide, and we certainly will look further into what those responses meant. In some cases, the

answer other was there was a problem, but it didn't have anything to do with bacterial testing.

Another question that was on the survey is what percentage of need for platelets has your facility not been able to meet. To ensure there wasn't an unmet need, we asked all of these blood center respondents to tell us if they were aware of any unmet needs.

You will see again 67 percent, or 28, said there wasn't a problem, so they couldn't answer the question, but of the 14 who said that there was, 64 percent of them said that that unmet need represented less than 10 percent of all the requests that they had, however, 2 facilities, or 35 percent of those who answered said that they--that number is wrong, sorry, 3.5 percent--said that they had a greater than 50 percent. Sorry about that statistic, that's not correct.

So, that is the last slide I am going to talk to you about from the survey. Again, I think you can appreciate that these responses came in and

it took a very facile team at the national office to be able to provide us with that much data.

But we thought you might be interested in what has been happening with assessments. In the month of March, there were 85 AABB assessments conducted, 5 at blood centers, 29 at hospital blood banks, and 51 at transfusion services.

You will notice that there was only one non-conformance written with respect to bacterial contamination, representing about 1 percent, and that facility happened to be a non-U.S. blood center, so one of our international or not on the continent U.S. blood centers.

I am going to take the opportunity since I have the podium to share a little bit now about the experience at my facility.

Those of you who know M.D. Anderson Cancer Center probably know that we serve a large population of cancer patients who frequently have disease that is otherwise not treatable. That creates a unique kind of situation for us and a unique demand. So, let me just share with you a

little bit about M.D. Anderson.

I apologize, these still have AABB logo on them because we just couldn't figure out how to swap between, but this is M.D. Anderson.

We transfuse between 250 and 400 whole blood derived platelets a day, 95,000 a year. We transfuse between 10 and 15 apheresis platelets a day, or about 5,000 a year, and we transfuse our platelets at under 30 hours of age.

Now, those of you who are in this business think about that. So, when the bacterial contamination standard arose, it presented a unique challenge for us.

At our facility, we collect about 40,000 units of whole blood, and we produce about 35,000 units of whole blood derived platelets per year. That is our own production to try to meet that demand. We collect about 4,500 apheresis platelets a year, so you can see that we also import platelets, about 60,000 whole blood derived platelets, and preempt the question, yes, we do have an agreement with our suppliers that they are

either providing the testing or expect us to do it, and we respond, whichever it is.

Let me just say what we have done. Beginning in about May of 2003, we began planning and evaluating how we were going to meet the standard. We had been having discussions ahead of that time, but we hadn't really sat down in a planning meeting before.

In October, we initiated whole blood collection with diversion, since the bulk of our platelets are whole blood derived, that clearly was an area that we were concerned about. Of course, we were among the facilities, we were using the Baxter system, and obviously, we now no longer are using the diversion system because they have withdrawn the bags.

I will tell you that this has created some difficulties for us. We were not experiencing any problems, and we participated in the retro review of any difficulties, and were able to show that we did not experience any difficulties either with hemolysis or with anticoagulant dilution of

samples.

I want to give credit where credit is due. Baxter spent an enormous effort with us to be sure that our techs were trained properly and were using the system as it was intended to be used. It may be that we just had too small an N to see the hemolysis problem, so I can't comment on that.

In February of 04, we changed our arm prep to delete no green soap. We still principally use iodine, but we do use chlorhexidine for iodine-sensitive donors.

In January and February, we reviewed the swirling CD, figuring it was worth the effort at least to know what that was supposed to look like, and then on February 25th, we began culture of apheresis donors collection, and I will explain that in a minute, using an automated culture system that was in use in our microbiology laboratory.

On March 1st, we began using dipstick of whole blood platelet pools, and we are culturing samples of whole blood platelet pools. I call your attention to the fact that we are dipsticking

pools, and we have validation around that to support the fact that we are doing pools.

When you issue as many platelets per day as we do, there was no way we could meet patient need if we had to slow down and dipstick every single separate whole blood concentrate. We just can't meet patient need by doing that, and we have tried. We have looked at all kinds of variables to try to do that.

So, here are the data. Our criteria for a positive dipstick is pH less than 6.5, glucose less than 1,000. If the glucose is between 500 and 1,000, it is evaluated by one of the transfusion medicine physicians.

We use urine dipsticks and we read them with an automated reader. We do not depend upon visual detection of this. We have tested 1,690 pools. This is through Monday of this week, 10,789 individual. All results have been negative. Of those, we have tested 40 pools, which represents 300 individuals, and all of those results have been negative.

The criteria for positive is growth within 30 hours, and we hold them for 7 days.

With our apheresis platelet, we take the culture from the donor. There just is no other feasible way for us to do this culturing, and we recognize that in so doing, just as with using dipstick, we are increasing the probability of finding a positive, that is, we expect to have a higher number of false positives.

However, put that on the risk-benefit, and clearly, that is safer. If you are having a higher number of false positives, chances are you are catching all the true positives, as well.

We culture for a minimum of 12 hours. By that, I mean everything we collect today will be transfused by noon tomorrow. It will be fully tested by all methods that are currently required to meet the standard in the way I am describing, but we issue and transfuse those platelets at noon tomorrow.

So, we keep the culture only until they are issued. If the platelet unit is returned, we

issue again with a dipstick result. We don't hold the cultures for these. We are only verifying our dipstick for the pools with the culture method that I have talked about.

We have had 3 culture-positive signals from our automated microlab. One of those was negative on Gram stain and 2 were gram-positive cocci, so far preliminarily thought to be Staph, 1 of which had been transfused two hours earlier.

We do contact the physician. We have not done any follow-up with this donor as yet. We are still in discussion about what we want to do, and I am very pleased to hear what is being done in the other large facilities.

That is how we are trying to meet the standard, and I would welcome any suggestions from any of the professionals in the audience about how we could do this better. Believe me, we have thought about it, and we just can't figure out a better way with the time frames that are required.

Our clinicians believe, and it is pretty hard to argue with them based on our patient

population that fresh platelets are necessary. So, this is what we have done to try to meet that need.

Now, switching back to one other subject I want to share with you, AABB is constituting, as we speak, a task force on bacterial contamination. The members are going to be experts from blood banks and hospitals working with both apheresis and whole blood derived platelets.

This will be modeled very much after the task force for West Nile virus that has been in place for the last year or so, and we expect that representatives from similar organizations will also be participating in this task force as we go forward.

We expect the task force to, first, review data from the survey, and make recommendations, of course, about any further guidance that needs to be issued, recommend any further data collection, and we realize that because this was done in a very short time period, that the survey can be improved, and we certainly want to hear from the task force about other data, and perhaps this group can also

suggest if there are other data that should be collected.

I haven't given you the whole survey, so it is pretty hard for you to address that, but we think that we can get the recommendations, provide feedback about implementation and efficacy of methods in identifying bacterially contaminated units.

You have heard that there are a variety of methods that are being used, and the standard allows for that, and to continue monitoring platelet availability as one of the primary concerns of this meeting.

The task force should begin meeting in a very short period of time. Steve Kleinman has agreed to chair that task force, and the invitations are going or have gone out, and we expect that that group will start working very, very promptly.

With regard to availability, in previous presentations before BPAC and in communications with FDA, AABB has advocated that FDA take key

steps to improve platelet availability. I have additional data if anyone is interested about that, but we believe now it is more than ever it is critical that the FDA move forward by increasing storage time for pooled platelets, by extending the outdated platelets to 7 days, that the FDA should think creatively and act expeditiously to meet these needs for improved patient safety.

In conclusion, based on the data that you have seen, we believe that the answer to these safety measures is to continue to increase the supply, to make certain that we collect from the safest donors possible, but I think based on the data that you have seen, and will be hearing today, that AABB's bacterial contamination standard improves patient care and has the potential to save lives.

Thank you.

MR. SKINNER: Thank you.

Are there committee questions? Dr. Penner.

DR. PENNER: Just a quick question. On

the dipstick for all of your combined samples, you are testing only those that are positive, or are you testing all of them?

DR. SAZAMA: We are testing all pools.

DR. PENNER: All pools. So, you are culturing all pools.

DR. SAZAMA: We are culturing only a sample of the pools. We previously validated the method and now we are continuing to survey to see if that method still continues to have the same level of safety that we believe it has.

Right now we just couldn't implement a single unit test and get our platelets out the door, we just couldn't do it.

DR. PENNER: But do you know what the false negatives are for your dipstick?

DR. SAZAMA: We have none so far.

DR. PENNER: But you haven't tested all of them?

DR. SAZAMA: We haven't cultured all that were currently in production, that's right, we are only culturing a sample.

DR. PENNER: So, we are not sure whether there is a false negative situation.

DR. SAZAMA: Correct.

DR. PENNER: It is that you are missing--

MR. SKINNER: The numbers are too small, that's right, the numbers are too small for us to be able to tell you that.

MR. SKINNER: Dr. Angelbeck.

DR. ANGELBECK: With your M.D. Anderson hat on, Kathleen, pooling, pre-storage pooling for platelets, since your institution relies so heavily on the whole blood derived platelets to meet your pretty extraordinary demands, do you think that is essential to the continuing viability of the whole blood derived platelets?

DR. SAZAMA: Not for us, I have to be honest, not for M.D. Anderson. I mean we basically pool them as soon as we can, but they are transfused within two or three hours after that, so, you know, for us personally, and that is why I wanted to give you the unique kind of perspective that I personally come from, but I am also strongly

in favor of the data that you have heard, because our facility is so unique, it wouldn't make a difference to us.

Maybe 1 or 2 percent of our pools might be held for the next day, but that would be the only benefit.

DR. ANGELBECK: Thank you.

MR. SKINNER: Dr. Lopes.

DR. LOPES: I need your AABB hat.

DR. SAZAMA: Okay.

DR. LOPES: In facilities that do have some amount of outdating, is it common that the oldest units must be used first, or do physicians who prefer younger cells, can they jump in and get the younger ones and leave the older ones to perhaps get outdated?

DR. SAZAMA: Yes and yes.

MR. SKINNER: I had one question. The overall survey data that you are doing, will you be tracking outcomes in terms of adverse events, is that data coming back to AABB, so that there is an evaluation of whether--

DR. SAZAMA: Interesting. That is an interesting point that--Mark, it is not on the survey at the moment, but I wouldn't be surprised if the task wouldn't be looking for that.

MS. LIPTON: What do you mean by an adverse event?

MR. SKINNER: Well, I mean in terms of just bacterial contamination, I mean we are doing all of this because it's one of the leading causes of transfusion-related problems, and are you going to be tracking to see what the events were before and after in terms of just aggregate data to see that this actually is going to have a net effect on--

MS. LIPTON: I think you could, but I think we all have to recognize that this is so underreported, and we participated in the BaCon study, in fact, we were the organization that helped the CDC get that study done, and it really is a recognition issue on the other end in terms of what they are monitoring the patients for.

So, we have found that that was--I think

it would be almost impossible to really understand. I think this is something you should ask Mark, but I think from our perspective, it would be very difficult to understand what the difference was.

MR. SKINNER: Mark.

DR. BRECHER: I agree, Karen. I think the only chance we have of getting some meaningful data is to look at those institutions that have had a high level of surveillance for many years, such as Johns Hopkins or University Hospitals of Cleveland, where the clinicians have been keyed in for years, and track their rates and see if there is a difference.

MR. SKINNER: Dr. Kuehnert.

DR. KUEHNERT: I just wanted to follow up on that. I agree with those sentiments. I think if we had a national surveillance for adverse events related to transfusion in the United States, we could do this, but since we don't, it would be difficult to do retrospectively.

I wanted to ask a couple of questions. Thanks for the presentation and for wearing both

hats. I wanted to ask you a question under the M.D. Anderson hat. You had 3 positives I think under the apheresis culturing, and you said 2 were positive by Gram stain and 1 was Gram stain-negative.

Does that mean that you don't know the organism identity of that one that was Gram stain-negative or just that it was Gram stain-negative?

DR. SAZAMA: I should clarify that. Since I put the slide together, the cultures have also been done, and the culture is negative for that one, as well, so it looks as though it is a false positive signal.

The other two have been cultured, but I don't have the speciation for them.

DR. KUEHNERT: So, you just know that it's a Staph.

DR. SAZAMA: Right, I do.

DR. KUEHNERT: Do you know if that person--you said you don't have all the follow-up, but do you know at least did they have a

transfusion reaction?

DR. SAZAMA: None, didn't turn a hair. The patient did just fine.

DR. KUEHNERT: And they were intubated, I mean at the time they were--

DR. SAZAMA: As far as I know, they were not intubated. Most of our platelets go to our hematologic malignancies or our bone marrow transplants, as you might expect, and my understanding was that this was a hematologic malignancy in chemotherapy, who was on--had already been put on antibiotic coverage by the protocol the patient was under, but had no change in symptoms whatsoever, which shouldn't be surprising.

We know this. With the reported rates of contamination that we have been transfusing for the last 50 years, you know, we know that very few of these patients have symptoms, and there must be both an organism and a dose threshold, you know, an organism type and a dose threshold that triggers that, but I am happy to relate to you that the clinicians were on top of it, and the patient did

just fine.

DR. PENNER: But they are almost all heavily loaded with antibiotics.

DR. SAZAMA: They are, our patients are absolutely.

DR. KUEHNERT: I think that is an important consideration for gram-positives. For gram-negatives, of course, with endotoxin, the antibiotic issue is not going to be as relevant, but certainly with the gram-positives it is.

Thanks.

MR. SKINNER: Dr. Sayers.

DR. SAYERS: Kathleen, keep your M.D. Anderson garb on.

DR. SAZAMA: Okay.

DR. SAYERS: Do your physicians then regard youthful platelets as more important than individual tested whole blood derived platelets, individually tested for the presence of bacteria?

DR. SAZAMA: Without speaking for them, that is the impression that I have. We have clearly talked about this issue at our transfusion

committees, and indicated how we intended to approach the problem at least to begin with, and if we can get better methods, we certainly will use them, and the indication was that it was an immutable requirement that the platelets be as young as possible.

DR. SAYERS: So, how do you think then that attitude would influence the news that platelet storage to 7 days was permissible?

DR. SAZAMA: I don't think there would be an objection to it. It just doesn't apply.

LTC SYLVESTER: On your culturing of your donors, are you collecting it via diversion pouch, or are you collecting it independently?

DR. SAZAMA: We are collecting at the time of original phlebotomy. Since many of our platelets are collected with a two-arm procedure, we just collect it at the same time we get our CBC.

MR. SKINNER: Further questions?

[No response.]

MR. SKINNER: Thank you very much.

Our next presentation, we are very pleased

to have with us today, Dirk de Korte. He is the head of Laboratory for Blood Transfusion Technology at Sanquin Blood Supply Foundation Research in The Netherlands, and he is going to speak with us about the Dutch experience with reduction of bacterial contamination. Welcome.

The Dutch Experience with Reduction of Bacterial Contamination of Platelet Products

Dr. Dirk de Korte

Dr. de KORTE: First, I would like to thank Dr. Holmberg for the invitation. It was no so far for me to travel to here because at the moment, I am doing a sabbatical at Bonfees [ph] Blood Center in Denver, so it was very close.

The second remark I want to make is that my opinions are my personal opinions, and not expressed as an official Sanquin opinion.

I searched some facts about blood transfusion in The Netherlands. In the Netherlands, we have a central organization in four regional blood centers covering the whole country, in total, about 750,000 whole blood collections are

performed, in total, about 60,000 platelet concentrates are prepared mainly buffy coat, I come back to that.

In my talk, first, I want to have a short introduction, can be really short because most of the things are already covered by other speakers I think. I will talk shortly about the difficult principle very often mentioned here, then, I will show the screening residuals for the last two years, the first instance about with extended whole blood collection, secondly, with the extended whole blood collection including diversion, and, third, the effects of the changed disinfection which was introduced in the last quarter of 2002.

Then, I will talk about prolonged storage time of platelets. I will mention some validation aspects, and finally, I will try to share the implementation lessons, some of the implementation lessons we had, and some recommendations.

The background everyone in the audience should know, that the platelet concentrates are recognized as the main risk for transfusion of

bacteria, so the transfer of bacterial transfusion to the patient.

In the Netherlands, of in Europe, screening is relatively popular in scandinavian countries, 60 to 100 percent are using bacterial screening. In Belgium, it is already six year, 100 percent mandatory. In the Netherlands, it was mandatory since November 2001 with some centers, in fact, most of the centers started before, and some centers even three or four years before.

In other European countries, usually, there is 1 to 2 percent quality control requirements, but some individual centers have much higher rates, and lots of blood centers have 100 percent screening, but so far in no other European countries there are obligations, it is still under discussion.

The focus of this presentation is therefore on the Netherlands. The Netherlands, we started in I think 1991 with a committee, the actual risk for bacterial contamination of blood products, and that resulted in advice to the health

authorities to introduce bacterial screening for thrombocyte concentrates and using for 7 days with the Bac-T Alert, and that is from BioMerieux. Sometimes I am struggling with the English pronouncement, but I am glad to hear that here, most of the people are struggling with the pronouncement of this company, because I heard things like BioMerieux, and so on. If you are interested, I can try with you.

So, we decided to use negative to date as a release criteria and indirectly, there is enormous increase of quality control for related products, because every platelet concentrates represent 5 red cells and 5 plasma products.

At the same time, we advise the health authorities to implement assist for haemovigilance. The advice was accepted by our Ministry of Health, and that was at that moment Ellsborth [ph], and she was as former blood center director, so maybe it helped.

We implemented in November 2001, the screening for bacteria contamination, and it

already more times cited the perfect shouldn't be the enemy of the good, so I think our ministry did a good job with introducing the screening.

In the Netherlands, 93 percent of the platelet concentrates are buffy coat derived. Apheresis is mainly used only for donations for refractory patients. One hundred percent screening for bacterial contamination is implemented with release as negative to date.

We are using the Bac-T Alert, and we are using both aerobic and anaerobic bottles, both inoculated with 5 to 10 ml, and the mean value I checked with the blood centers is 7.5 ml.

The sampling for the buffy coat platelet concentrates has to be performed within two hours after preparation, but in our system, this means that it is 18 to 24 hours after whole blood collection, so it is assuredly an incubation time of a time to grow for the bacteria.

Sampling for apheresis products has to be performed within 12 hours after collection, so that varies from immediately to 12 hours.

Preparation of platelet concentrates, there are two methods based on whole blood derived platelet concentrates, first, the so-called PRP or platelet-rich plasma methods. It is mainly in North America, a single platelet concentrate from whole blood units, but as discussed many times in the last 34 hours, there is a strong direction into pre-storage pooling.

The buffy coat method is mainly in Europe, 1990 roughly, '91, '98, was single buffy coats and pooling upon transfusion, and since 1995 until now, it is the pools buffy coat methods. Recently, a part of Canada also introduced the buffy coat methods.

Then, of course, you have the platelet apheresis methods to prepare platelet concentrates.

Very shortly, the platelet plasma methods, you start with a unit of whole blood, give it the soft spin, then, you end up with two products, platelet-rich plasma and red blood cells. The platelet-rich plasma is given additional hard spin, giving you again two products, plasma and platelet

pellets bitten [?]. The platelet bitten is resuspended in about 60 to 70 ml of plasma, and it gives you a single platelet concentrate.

So, just before transfusion, 4 to 6, sometimes 10, I heard, units are combined to give you a platelet concentrate. Platelet concentrate roughly contains 300 ml plasma and 300 to 400 times centridine [?] platelets.

The whole blood unit is given a hard spin, resulting in 3 different products – plasma, red blood cells, and the interface buffy coat, which contains more than 90 percent of the platelets and also more than 70 percent of the white blood cells.

This buffy coat contains also some plasma, it is given a soft spin, and that results in a single platelet concentrate and a waste of buffy coat.

Just before transfusion, 4 to 6 of these units are combined and giving you platelet concentrate containing about 300 ml plasma and 250 to 350 times 10 9.

Also, to recall why the single buffy coat

method and also the PRP methods was introduced was mainly for the optimal use of the valuable gift of the donor, so to make complete use of the unit, making all products which are possible, and not to throw away valuable platelets.

Later on, especially with the introduction of all the infection tests, and so on, it gives you an additional advantage that the cost of the screening is shared by three products, and not only by one or two products.

The pooled buffy coat method, the initial step is exactly the same, the whole blood unit is given a hard spin, but now 4 to 5 of the buffy coats and 1 unit of plasma or possibly also additive solution are combined to give you buffy coat pool with a low hematocrit about 20 percent, and that is buffy coat which is given a second soft spin, and that results in two products, a platelet concentrate, which can be stored for 5 to 7 days, and a waste of rest buffy coat.

This product contains about 300 ml of plasma or a mixture of additive solution and

plasma, and 300 to 400 times 10^9 platelets. So, there are some differences in the PRP and the buffy coat platelet concentrate, I will not mention them all, but, first, the initial amount of white blood cells in the final product is different, the PRP has much higher amounts of white blood cells, 5 to 25 percent whole blood value, and the buffy coat products have less than 0.5 percent of the whole blood value, but in the area of leukodepletion, this is not really a difference because usually, leuko use platelets are used.

The initial platelet activation is also a little bit different. The PRP methods probably due to the hard spin and contact with the plastic of the bag, the initial platelet activation is higher than in the buffy coat products, but during storage, the difference is no longer existing, and in five days, the amount, the degree of activation is similar for the products.

The platelet yield is a little bit higher for the PRP method compared to a single buffy coat platelet concentrate, but the pooling of the buffy

coats overcame this difference in yield, so now the platelet yield is similar or even higher because you can, with the leukodepletion, you can allow a little bit higher whole blood leukocyte contamination, and that will yield in even higher platelet yields.

The plasma yield is with the buffy coat method, a little bit higher compared to the PRP methods, and, of course, if you use an additive solution, then, you will go even to 375 ml of more plasma yields.

The pooling is post-storage for the PRP methods and for the single buffy coat platelet concentrate, before the pool, it is pre-storage effect, it is pooling during preparation, but that is similar to pre-storage.

The in vitro characteristics during storage are very acceptable for up to 7 or 8 days, and among others, we published that in Vox Sang 1994. The pooling process has no effect on the availability of the platelets, even positive effects because the production is faster and easier

than with the single buffy coat procedure.

There is no delay due to bacterial testing because of the negative to date principle and also because of the sampling less than 2 hours after preparation. An additional remark was made by some of the centers that it has some effect on availability of apheresis platelet concentrates because these are often directed donations, which I don't know the details of this difference.

When I come to the results of the screening, first, I want to say something about the diversion. One of the blood centers on an experimental basis was allowed to introduce the diversion pouch for the whole blood collections, and different from the U.S., all centers in the Netherlands are using diversion pouch for apheresis collections.

The diversion of the first flow, as already mentioned several times, also our study was referenced several times. We did a study of the effects upon the bacterial contamination of whole blood units after diversion of the first 10 ml.

The studies of Breneau and the study of Wagner did only show that the first amount of collected volume contains more bacteria than the later volume, but our study, we tested really if the remaining whole blood units had a lower contamination or not.

As was already mentioned several times is that the skin plug was taking through scars, and so on, taking bacteria, which is very important as a cause for the contamination, because if you look carefully to the bacteria and whole blood units in platelets, it is up to 90 percent of 85 percent skin flora.

So, the residuals of the whole blood diversion study, in total, we tested 7,000 units of whole blood. We sampled the unit after diversion of the first 10 ml, so it's a minimal amount, but that was because we are only able to do that with a Vacutainer, so then the maximal amount was 9.6 ml.

Then, we tested the whole unit, we sampled the whole unit, and tested it for Bac-T Alert both with anaerobic and aerobic bottles. The degree of contamination was 0.21 percent, and the 95 percent

confidence interval was 0.12 to 0.35, and that is important because we are hearing here a lot of numbers, which is all about 2 or 3 or 4, and that doesn't mean too much in statistical terms, because the confidence interval of that number, the values is very broad.

The base level of contamination in whole blood units was tested before in another study, and that was 0.36 percent, so there is a significant decrease. It's in the margin, if you look to the p-value, but as already mentioned by Steve Wagner, we found much more significant degrees of one, that was the encephalococcus coagulase-negative population that had a much larger degree, less relevant propioni and becter [?] and rods are more or less the same level.

However, this was only in whole blood cell. The open question remains if the diversion during blood collection really has an effect on the contamination of the platelet concentrates from a pool of buffy coats, and there was a need for a special collection configuration, and that was used

in the study from the blood center in the region southeast of the Netherlands.

This is more or less similar to the systems by Pall and Baxter and Terumo, and through Fregini's [ph] system in which after the needle sample bag was included, and a diverse volume could be used for test purposes by just clicking on the Vacutainers.

Another aspect in the screening is that we changed the method of disinfection during the last quarter of 2002, we implemented nationwide double swab disinfection method with isopropyl alcohol, because various papers indicated that double swab method, especially with enough time in between to dry, so 30 second spacing was more effective than single application of disinfectants, and then it didn't make too much difference between the different disinfectants if you used chlorhexidine, alcohol, or isopropyl alcohol, or iodine. The difference was much less different than the difference by double swab methods.

In the Netherlands, the arguments are

contra-iodide one. People didn't want to be dirty from the iodide, and so on, so we introduced isopropyl alcohol as a disinfectant.

Before the change, most of the centers used the single swab methods, but some also used the double swab. Most of the centers used the single swab, the chlorhexidine, 0.5 percent chlorhexidine and 70 percent alcohol.

In the Netherlands, we have two and a half year experience with some centers up to six years with 100 percent screening of platelet concentrates, and I will show you, first, the residuals before versus after change in the disinfection. Then, I will show you the residuals of the collections with diversion including the effect of the disinfection change, then, the residuals for apheresis units including the effect of disinfection change, and then I will do some overall comparisons.

So, the standard collection of whole blood experience, January 2002 to October 2003, I left out the first two months because to allow the

centers with starting up and so on, and also there are some problems in reporting the results, so I started with data from January 2002.

In total, with the old disinfection, more than 42,000 units were tested. That reflects, don't forget, more than 200,000 whole blood units, and with the new standardized double swab technique, more than 46,000 units were tested.

Overall, the initial positive rate was 0.96 for the old disinfection and 0.82 for the new disinfection. Then, the confirmed positives, I have to explain that what we call confirmed positive is just that we have a positive culture from the bottle from the Bac Alert, so that is not confirmed positive that the product is resampled and tested, which I will come back with also later, which confirmed positive, you can see that most of the samples were confirmed positive.

However, you see a remarkable difference between the numbers in which no culture from the positive bottle could be obtained. From the old disinfection, it was 6.3 percent and with the new

disinfection, it rise to 9 percent of the positives. You will see the change, the same effect in other slides.

Here, I show the results for the collection of whole blood with the diversion pouch. In total, with the old disinfection, nearly 4.5 thousand units were tested in with the new disinfection methods, similar amount.

Again, this represents more than 20,000 whole blood collections for both arms. Initially, positive in the Bac Alert culture were 0.5 percent of the units with old disinfection and 0.36 with the new disinfection.

However, again, here, you see at the moment that the number of positives, initial positives is going lower, then, also, the number of bottles, and this is not possible to derive a subculture from the positive bottle is increasing.

Then, the data for the apheresis platelet concentrates with the diversion pouch, as I said. This represents, of course, a much lower number than here in the States because we have only 7

percent of collections collected as apheresis, so the total number tested was about 3,000 for the old disinfection and about 3,700 for the new disinfection methods.

The percentage initial positive was 0.22 for the old, and 0.32 for the new one, again you see here a slight difference between the number of no subculture from the positive bottle from 14 to 70 percent, but here you are talking really about very low numbers.

So, the comparisons, the effect of the diversion was found to be highly significant for platelet concentrate with the old disinfection, it reduces from 0.96, to 0.50, the p-value of 0.004, and with the new disinfection method, it's decreased from 0.82 to 0.36, with a p-value of 0.001.

The double-swab disinfection showed a changed disinfection methods, was found to be also significant for the standard collections. The reduction from 0.96 to 0.82, p-value of 0.03, which there was no significant effect for already

diverged collections, or with apheresis. But that's also lower numbers, so the statistics is less reliable.

As a last comparison, I checked if the apheresis versus pools with the cultured PC was still different. It was large--highly significant, the value. Before the introduction of diversion and double-swab, but after the introduction of diversion and of whole blood collection and double-swab method for disinfection, the final contamination in the apheresis versus the pooled [inaudible] platelet concentrate was not longer--different, with a value of .32 versus .036.

With respect to cell cultures from post [inaudible] bottles, the differentiation was significantly different after diversion--as described for whole blood diversion study. You have relatively less coagulase negative staphylococci, and you have more propioni and chorinobacter bacteria.

There was an increase of the percentage with failure to grow in sub-culture after diversion

and changed disinfection. And the percentage of dangerous bugs, the rapid growers, decreased more than the overall percentage, but not significantly, because then you are talking about 9 in 500 going to zero in 20. So if you really would compare that, you need at least 200 positive ones.

Then--in the Netherlands we have, every time, again a discussion about negative to date, versus current time. In practice, that appears to have similar results, if we have current time periods for two days after starting the culture, we would have prevented 90 percent of platelet concentrates with the fast-growing bacteria to be released. And if we look to the real data from our scaling system, then for more than 90 percent of signal it's fast growing bacteria, the product was still in the blood center upon the positive signal. So it could be prevented from entering the transfusion cycle.

The products with a positive signal after release are mainly slow growing, like propioni species and--rods.

A short remark about the related products. Related products, we found for the red cell concentrates, that about 709 percent still was in the blood center stock, and that the 30 percent which has to be recalled was, in 75 percent of the cases, successful. So, overall, you were able to prevent 92 percent of the related red cells from being transfused. And all the 92 percent were also cultured, and then we found that in the red cells we had in 45 percent of the cases, we had positive culture; for platelet concentrate we had also a positive culture and the related red cell product, and it was always, then, the same microorganism.

However, something was remarkable. If you look to the differentiation in the red cell concentrates, then you see that in 143 cases of coagulase-negative staphylococci--in the platelet concentrate, we only found this to be positive in the red cell concentrate, and 20 cases in 123 cases was negative, more or less a similar ratio for the bacillus species. But for the propioni species, we found the opposite; that is, that from 134 cases

with propioni in the platelet concentrates, we were able to find 110 positives in the red cell concentrate, and 24 times negative in the red cell concentrate.

So, theoretically, you would expect that 20 percent of the red cell concentrates would be contaminated, because you had five red cell concentrates for Buffy-coat platelet concentrate. In practice, it was less than 10 percent, and we found that mainly the slow growers survived in the red cells; the coagulase-negative staphylococci had much lower probability to survive and to result in a positive culture.

Based on the results of the screening and ongoing insight in platelet qualities, there are some changes starting in June this year. All collections should be performed with the system, including diversion pouch. So, as I said, all apheresis products are already including the diversion pouch, and for the whole blood collection we have to change 100 percent diversion pouch.

And since January 2004, there's official

authorization for a shelf life of seven days for Buffy-coat platelet concentrate in plasma.

That brings me to the subject of prolonged storage of platelet concentrates. For prolonged storage, the main concern is bacterial contamination, and this is minimized by the screening, and so far is validated with respect to in vitro quality of platelets, prolonged storage in combination with culture was allowed in the Netherlands, also in Sweden in Norway, but it should be supported by in vivo data and, as also mentioned by the speaker before me, not all physicians believe that seven days-old platelets are as effective as fresh platelets. So you need to prove the efficacy.

In vitro quality is really no problem. There are multiple studies showing it in the various conditions. Day seven to eight is maximally--20 percent worse, compared to day five, providing the use of the right containers and off-loading the containers.

Seven days is also possible with the use

of additive solutions and variable amounts of plasma cross-over--and it's described for 10 to 40 percent in vitro. So this is only improved to compared to 1986, due to the availability of better containers.

And just as a remark, also, for pre-storage pools, PRP, it's shown already long before that there's very acceptable in vitro quality after seven days in our publication, in [inaudible] 1995.

However, we had to prove in a clinical study that the platelet concentrates, after longer storage were--had a good efficacy, so then the blood bank--blood center northwest, and the free university, academic hospital, performed a clinical study in which they determined the corrected count increments, and the count increments one hour after the infusion. This was in a group with hemato-oncological patients, having no serious bleedings. The platelet concentrates were in plasma from five pooled Buffy-coat; storage was for two to seven days. And this study was recently

published in Transfusion this year.

Based on this publication, seven days is now authorized in the Netherlands, with both transfusion services,

Just, very short, this study, on the x-axis is shown the days of storage, and on the y-axis is shown the count increment--or the corrected count increment. The black numbers in the margin indicating the number of transfusions given. And you can see here that there is very low differences between the values for day five to seven. So there is really a decrease during the first days, but at the end there is not too much--at least no significant difference between five or seven days.

So both in vitro and in vivo data support that platelet concentrates, for the Netherlands, specifically, Buffy-coat derived, in plasma, can be stored for seven days and still have a good quality, and can be used for patient care to overcome logistical problems. And it has now an official authorization in the Netherlands.

The extension of shelf life from five to seven days, the outdating will greatly reduce. The first experience so far has at least a 10 percent reduction. One of the centers in the Netherlands had experience for about three years with the seven-day storage, and then also there was found 15 percent reduction in outdating.

So there is a big financial benefit from extension of shelf life and that itself pays already for the screening, and you don't look to reduced patient care and so on.

Some validation aspects about seriotivity or false positives, and about sensitivity or false negatives.

First, about the false positives. In the Netherlands we are using an integrated sampling pouch, or sterilely connected sampling pouch, which has already a needle or an adaptor to fit to the culture bottle. And we are using it in a laminar flow.

So there are different types of false positives. There is very often spoken about false

positives here, but there are different types. So you have first an accidental contamination by processing. That is called a false positive but, in fact, the system recognized correctly a bug in the bottle. We know that from using aseptic procedures that results in a very low number of accidentally contaminated bottles.

We checked in our facilities that zero out of 2,000 procedures were positive. So that means lower than 0.05, and probably its closer to 1 in 10,000, than 1 in 2,000.

Then you have a negative confirmation culture. That is, we found that in 36 our of 474 positively flagged bottles, that mean that the bug is not growing under standard culture conditions, or it's a system failure. And my personal belief is that it's mainly not growing under standard culture conditions because system failure is fairly rare. And we use for our confirmation cultures, we use sheep agar plates, and probably some of the bugs are not growing there. And it's supported by--this opinion is supported by the fact that you

see, under different conditions, different amounts of positive--of negative confirmation cultures.

Then you have a temporary positives. Upon re-culture of platelet concentrates which are flagged positive, only 20 to 50 percent, depending on the center a little bit, only 20 to 50 percent is again positive in a BactiAlert positive. However, it is a limited number which is studied--about 100 to 150 platelet concentrates, you are able to have back in the center and to do re-culture after it was flagged positive.

So that means that you have, indeed, a kind of self-sterilization that reduce the number of bugs in the platelet concentrate, in contrast to the culture.

Then you have false negatives. That means, first, the bug is not recognized by the culture system. However, if you look in literature--for example the Study of Mark Brecher--it's indicating that all the bugs thought to be relevant are picked up. So it's very low chance that the system--the bug is not recognized by the culture system.

Then, the system is not sensitive enough. Well, also, extensive studies showed that the sensitivity is 1 to 10 colony forming units per bottle. And if you inoculate 7.5 ml, that means that 0.2 to 1 colony forming units per ml of platelet concentrates will give you already a positive signal.

That we are on the lower limits of sensitivity is indicated by the fact that only for four percent of the positive bottles were positive, so that means that you are really on the lower limit of sensitivity.

The next argument is: too early sampling. From quality control data in the outdated products, we know that the frequency of contamination is much lower, indicating that you have more false positives rather than false negatives.

In conclusion, with the validation aspects, sensitivity is relatively low, but it is not in the classical meaning that you have a false positive, but there are other reasons to have false positives, because the bugs are not always

surviving in the actual products; only a fraction of the positives would have caused clinical problems; and the products changed during testing, so it is not simply to repeat, like for a virus test, and you just repeat the sample within this--with the bacteria. It's not possible to do this so easy.

Sensitivity is very high with this chosen approach, especially with the two bottles, but can we afford to go lower, because we don't know if we go back to, for example, one bottle, how much would we miss? We know that about two-thirds of the positives is coming from the anaerobic bottle, so from that most is--a large is propioni, this is relatively not harmful bacteria, usually, it is believed, but we found also that you pick up a lot of the fast-growing bacteria earlier in the anaerobic bottles than in the aerobic bottle.

What we learned from the implementation a lot, I would think. But things I will mention is that motivation of all involved people; having good relations with the clinic, because that makes it

acceptable for the clinic to have a results negative to date which is not common for them. Normally, you have positive or negative; acceptance in the clinic, also of positive signal in the culture which already transfused; and also it made it also acceptable that we give the message, related to red cell concentrate, might be positive, but it will have a low possibility because of the fact that you have five red cells per concentrate.

It is also important to train the involved personnel in microbiology to know what is causing accidental contamination. And what we also learned was standardization, standardization, standardization. That was also to be very important.

Some recommendations: for all platelet concentrate, I will say use an as sensitive detection method as possible, and use a negative to date release.

For whole blood-derived platelets, you will be not surprised: changed to Buffy-coat platelet concentrates. And I will be glad to have

another sabbatical here to introduce Buffy-coat in the U.S.--or at introduce pre-storage pooling of PRP platelet concentrates.

In case of the transfused product, with clinical symptoms, use the fact that the blood center is ahead. I heard yesterday already, the blood center in Florida was doing that. So help with the determination of possible resistence to allow a better treatment of the patients.

And also introduce a system of hemovigilance to monitor the effects, because that is one of the main problems in the Netherlands, the system of hemovigilance is just this year starting to be introduce, and so it is very hard to get real hard data from the clinic about the prevalence of bacterial contamination. We only know that before introduction of the screening, we had several incidents reported, but there is no duty to report, and there is underestimation of that; and that after introduction of the screening we had no reports of sepsis or fatalities.

Final conclusion is that, based on the

experience so far, implementation of a system for bacterial screening is found to be very successful; easy monitoring of possible improvements like the diversion pouch and the changing disinfection; allowing shelf-life prolongation; reduction of clinical cases--also not supported by hard data--and we found that there was a quick adaption in the clinic.

But a combination of diversion and improved disinfection, we found that the risk for bacterial contamination for Buffy-coat preparation became similar to apheresis platelet concentrates.

So this is an important argument in favor for whole blood-derived platelets.

Thank you.

CHAIRMAN SKINNER: Are there questions?

Dr. Penner.

DR. PENNER: I enjoyed your presentation. It was very thorough, and I believe you're a step ahead.

I do have a question, though, about the five to seven-day change in platelet storage, and

that is: from what I can see, the functional activity of the platelets is a judgmental, or a subjective view, and you don't really have any solid data to say whether these platelets are just floating around and dead, or whether they're actually doing something.

MR. de KORTE: That is true. It's usually--it was a requirement to show that the corrected count increments was okay, and it is very hard to have a study with actually stopping bleeding and so on. So it was therefore also the post-transfusion surveillance is obliged to collect data about that.

DR. PENNER: Do you have any in vitro data as to the quality--functional quality of the platelet in various testing devices?

MR. de KORTE: Yes. But what you see is that you have a decrease, mainly during the first two to four days, and then five and seven is not too much different. But you if you--you can look to mitochondrial activity, you can look to adhesion, you can look at aggregation and so on.

But most of that, you--it's unknown the real relation with in vivo is unknown. So it's also giving you limited information.

DR. PENNER: So you're saying in vitro--the in vitro data, there's not--there didn't seem to be a change in the five to seven day--

MR. de KORTE: Yes.

DR. PENNER: --or even four day--

MR. de KORTE: Yes.

DR. PENNER: --or that you can't see any qualitative difference in the platelet function.

MR. de KORTE: No--not too much.

CHAIRMAN SKINNER: Yes, Dr. Kuehnert.

DR. KUEHNERT: Thank you for coming to present this experience.

I just had a couple of questions, just concerning the methods concerning bacterial culture. You hold for seven days, and I just wondered if there was any comparisons that you made before you made that decision about holding the culture for seven days, versus five days; also the use of aerobic and anaerobic culture bottles; and

also the seven--and-a-half mls, versus, say, a smaller amount.

I just wondered if you had any experience with any other combinations.

MR. de KORTE: Well, with respect to the volume, we decided to use the volume which we started our studies. And packets for instruction in the States, it's mentioned 4 ml. But I think there is hardly no difference between 4 and 7.5 ml. The main difference is between the fact that you have two bottles, and so that you have twice the possibility to hit the bug.

And therefore we decided to use the anaerobic and the aerobic bottle, also to hit real anaerobic bacteria. But most of the bacteria, you can see it also from the studies from Mark Brecher, that most of the bacteria grow very well in both the anaerobic and the aerobic. So you will really double the possibility to pick up a bug.

And we decided, from the starting of the screening, to culture for seven days because we planned to increase the storage time for platelets.

So you have to keep in mind that the culture is always ahead of the situation in the bag. So, with seven days, you are really very safe.

DR. KUEHNERT: My other question was about--you had some data on the effect of diversion bags. And it looked like, for some apheresis collections, you didn't have a diversion bag, and it looked like the contamination rates were much higher for that situation.

Did I misread that, or--MR. de KORTE: Yes. We--all apheresis units were collected with the diversion pouch.

DR. KUEHNERT: Okay.

MR. de KORTE: But only--what you see is that after the introduction of the new disinfection, the actual contamination increased a little bit for apheresis units, but that is probably due to the lower numbers, because you are really talking about 22 or 16 on a total of 3,000; and before you have-- then have significance, and you have the seasonal variation and all that kind of things. That's very hard to discriminate.

DR. KUEHNERT: And my final question is: how do you handle donor notification? And given that you've now implemented hemovigilance over all, are you using the data for national surveillance for public health as well?

MR. de KORTE: with respect to donor notification, we decided only to notify a donor in case of very specific bacteria which were known to have a chronic bacteremia. So, like--I look it up, because I expected this question--it was staphylococcus aureus, and Yersinia and listeria. So that is specifically mentioned in the guideline that, in that case, you have to notify the donor and to check. But otherwise, it's up to the medical director of the blood center if, maybe for some other bug also the donor will be notified. But not normally.

DR. KUEHNERT: Thanks.

CHAIRMAN SKINNER: Dr. Holmberg has couple final questions, and then the committee will break for lunch early.

DR. HOLMBERG: I guess I just need a

refresher on your Buffy-coat preparation.

Are these units leukoreduced to start with?

MR. de KORTE: Yes.

DR. HOLMBERG: Okay. And then, when you do the hard spin, it appeared that you put either saline or additive solution. Is it routine to put the additive solution? And what are you using?

MR. de KORTE: Yes, it's--30 percent of the production is additive solution, and 70 percent is plasma. And especially because only the plasma is authorized for seven days, there is no a trend to go to plasma for all units back.

DR. HOLMBERG: Can you tell us what that additive solution is?

MR. de KORTE: The additive solution, as far as I know, is Pass-2 from Baxter.

CHAIRMAN SKINNER: Well, we're checking on one thing on the presentation from the CDC. My concern was it's a new subject matter that we'll be shifting to, and we're a little bit behind, and it will probably take more than the 20 minutes that's

allotted, because it's not yet loaded.

Just to give you a brief indication--my plan would be, this afternoon, when we do get to committee discussion, will be to work through the questions that Dr. Holmberg proposed yesterday, and then to see if there's a resolution that's coming out of those--just to give people a sense of how I plan to structure the committee discussion.

And I am aware that there are potentially three resolutions coming out of the CMS presentation yesterday morning. So there is quite a bit of work ahead of the committee this afternoon.

[Comment off mike.]

Okay. So we do need to take the CDC presentation now because of flight schedules. So we will actually probably be a little bit late going to lunch. I apologize for that.

Presenting for the CDC is going to be Dr. Arjun Srinivasan. Did I get that correct? Thank you. He's going to present on some of the public health relevance, on surveillance and other aspects

related to bacterial contamination

Public Health Relevance of Platelet Screening

DR. SRINIVASAN: Thank you very much. I appreciate you're letting me go ahead and present now. I'm full cognizant I am the only thing standing between you and lunch, so I will make my remarks very targeted.

I'd like to thank you for the opportunity to come and talk a little bit about some of the public health relevance for the new standard of platelet bacterial screening. I'd like to talk a little bit about some of the public health perspective on the need for bacterial screening, and then to focus my talk on the public considerations.

And there are four key areas that I'd like to focus on: issues with organism identification; shared data collection and analysis; the use of these results; the impact of screening on platelet supply, and then close by talking about talking about some of the potential next steps from a public health point of view.

Now I think that the very reason that we are here is a testament to the dedication that people in the blood banking community have had for so long in providing a safe blood supply. We've worked hard on the viral pathogens, and we've reduced the incidence of transfusion-related viral pathogens to the point that bacterial pathogens, and transmission of bacterial diseases has no become a very real concern for us.

So, in many ways, the very fact that we're here is a testament to our success.

Now, though we've long thought that bacterial contamination is a significant issue, there had never been a serious, rigorous, prospective multi-center evaluation of associated adverse events, prior to the BaCon study. And I'd like to talk a little bit about this study, because I think it provides a little bit of background in some of the foundations of the new standard.

Now, the goal of the BaCon study--and many people in this room, of course, were involved in that study--was to prospectively evaluate the

incidence of septic transfusion reactions cause by contaminated blood products. And I emphasize "septic transfusion reactions," because I think it's important to really understand the scope of the BaCon study.

If you consider the universe of contaminated products as an iceberg, the BaCon study was really targeted at the very tip of that iceberg: at fatal reactions and septic reactions. I think we'd all agree that there a number of febrile and other reactions that can occur from contaminated blood products, but the BaCon study was not designed to pick those up. It addressed the fatal and septic reactions.

[Slide.]

The design was really kind of a model of its kind. It was a huge collaborative effort involving a number of groups that worked extremely well together: the American Association of Blood Banks, the American Red Cross, the Department of Defense, CDC, and a number of hospitals and transfusion centers, who all had to work together

to make the study happen.

[Slide.]

Because this was a study of clinical sepsis, the entry criteria for patients to be enrolled were signs and symptoms of sepsis within four hours of a blood product transfusion: fever; rigors or shaking chills; changes in the heart rate--tachycardia; or rise or drop of systolic blood pressure--standard criteria for septic reactions.

[Slide.]

Now, in addition to meeting these clinical screening criteria, in order to be enrolled in the study, a number of specific microbiologic criteria had to also be met. First of all, there had to be a culture-positive blood product involved. The recipient blood culture had to grow the same organism that was recovered from the product. And, finally, the additional step was taken that the organism pair from the product and the recipient had to be identical by pulsed-field gel electropheresis by molecular analysis.

So, I think, very strict entry criteria here; very tight criteria.

[Slide.]

They ended up with 34 septic reactions during the two-year study period. The products--there was no surprise to what they saw there--29 of the 34 reactions were in platelets; 19 in single-donor platelets; 10 in pooled platelets; only five in red blood cells.

The recipients were, I think, a reflection of the population who get transfusions. Three-fourths of them were patients who had underlying malignancies. And in this series, one in three actually had a fatal outcome.

Now, I think some of the most important findings from the BaCon study with respect to the public health implications and the foundations for screening come from the microbiology.

[Slide.]

We know, from previous studies, that Gram-positive organisms--if you're simply screening--account for the vast majority of

contaminated blood products. However, if you look at the findings from the BaCon study--if you take out a subset of septic and fatal reactions, Gram-negative bacteria actually account for a very healthy minority of those: 41 percent--almost half of the reactions in the BaCon study--were due to Gram-negative organisms. So--an interesting an important finding.

[Slide.]

Furthermore, keeping on this theme, if you look at outcomes in patients with Gram-negative infections, mortality was significantly higher. 83 percent of the fatalities were associated with the Gram-negative organisms, compared to 17 percent for Gram-positive--highly statistically significant.

Furthermore, when endotoxin testing was done, fairly high levels of endotoxin were found in many of the units that were contaminated with Gram-negative organisms.

If you take the results from the BaCon study and you extrapolate to septic reaction rates and fatality rates in the United States, what you

get is an estimate of about 10 septic reactions per million platelet units transfused for single-donor platelets and pooled platelets; and about two fatalities per million transfusions of those units.

Now, it's important to note that many people have pointed out: these numbers are likely a substantial underestimate. Because the entry criteria for the BaCon study were very, very strict, may people argue that these numbers, though important, likely underestimate the true scope of the problem.

So, it was an important study, but, of course there were some limitations to the study. What BaCon did do, I think, is prospectively describe for us reaction rates and etiologic pathogens for documented septic reactions. What BaCon did not do is give us any information on other non-septic reactions due to contaminated products, nor did it estimate the incidence of bacterial contamination of products.

[Slide.]

However, I think BaCon does have some very

important implications for screening, particularly the microbiologic findings.

As we know, the Gram-negative contaminants are more likely to be related to donor bacteremia, and less likely to be related to skin contamination. Therefore, the screening certainly lend credence and support to the issue of the screening standard.

Furthermore, I think the findings of the endotoxin contamination also support the screening standard, because endotoxin will greatly complicate therapy--even rapid initiation of antibiotic therapy will not be effective if there's a very high level of endotoxin in the transfused unit.

So, as Dr. Holmberg has mentioned, the question before us is not really whether to screen platelets, but how to accomplish this goal.

The data indicate that screening will save lives, however we also know--and we're hearing here over these couple of days--that implementation of the screening standard is going to raise some important challenges; and that's also true for the

public heath.

I'd like to focus on four issues for public health considerations of platelet screening--as I've mentioned: identification of organisms; shared data collection; the use of results for quality assurance and improvement; and the issues with platelet supply.

First of all, organism identification.

[Slide.]

Certainly, identification is going to require a significant investment in both resources and time on behalf of the blood centers. There will need to be purchase of microbiology equipment, staff training and staff certification. So these are centers that already faced with tight budgets, with enormous demands on their resources. Why do I think it's important that we allocate the additional resources to identify organisms?

Well, I think that organism identification can have some very important benefits for the health of recipients, donors and the overall community.

First of all, with respect to the recipient, in cases where the units get transfused, knowing the organism certainly can help the treating clinician chose the most appropriate therapy. Now, certainly, in many of these cases the recipient will develop a positive blood culture. However, knowing what that culture is likely to show, in advance, gives the clinician a very important head start.

Furthermore, we're talking about patients in cases where they may be on some kinds of antibiotic therapy that may inhibit the cultures, or at least delay those culture results.

[Slide.]

with respect to donor health, certainly the blood banking community has already set the standard for donor notifications. It's long been felt that results that had important implications for donor health--such as the viral pathogens--need to be shared with donors. And I think bacterial screening is certainly no exception to this rule.

Now, in most cases, donors with bacterial

bloodstream infections will probably be excluded from donation because they'll have symptoms. However, as we implement the standard, I think we're going to find that there are important cases when asymptomatic bacteria may have consequences for the donor.

I'd like to present to you a very short case as an illustration of that, and this was shared with me by Dr. Stevens and Dr. Leitman at the National Institutes of Health. The had a patient last year who had received platelets and subsequently development a bloodstream infection with streptococcus agalacteae--or Group B streptococcus. And, indeed, the unit that they received was found to be contaminated.

Now, in discussions with their infectious disease colleagues, they learned that bacteremia with this organism has been associated with cases of colon cancer. They called back the donor; they notified him and encouraged him to undergo screening for colon cancer and, in fact, he underwent a sigmoidoscopy that revealed a tumor

that was removed.

So that's one example of how the results of screening may have implications--and important ones--for donor health.

[Slide.]

Community health. I think findings of unexpected clusters of organisms--if we know what organisms we're dealing with--may lead to some very important discoveries. And there's a could of examples that I'd like to share with you here.

The first is an experience from Denmark. This was an unusual cluster of two cases of Serratia marcescens bloodstream infections related to transfusions. Now, because the organism was so unusual, it prompted an investigation--especially because the cases were clustered in time. They did a national survey, and found that .73 percent of all the units that they screened were contaminated with Serratia--a phenomenally high contamination rate for this organism--which, of course, prompted a further investigation.

Well, the investigators found that all of

the contaminated units had been collected in bags that were produced from a single batch made by one company. When they went to the manufacturing plan to do an on-site investigation they did cultures, and found that places in the fact were, in fact, contaminated with Serratia that matched the isolates that had been found in the bags.

Because of this intervention, and because of this investigation, they were able to correct the problem and stop any more contaminated bags from being produced and released--a very important public health intervention.

The second case is a little more recent, hits a little closer to home, and is a little bit stranger.

This was the case of a healthy donor who was a very regular blood donor in his community; had given nearly monthly over the last few years, many apheresis sessions. And platelets obtain during one apheresis session were transfused into two patients in this case. Patient One developed septic shock during the transfusion, requiring

initiation of life support; and Patient Two developed septic shock an hour after the transfusion and, unfortunately, later died.

Blood cultures from both of these patients grew Salmonella enterica--again, a very unusual pathogen. Because of the organism that was identified, an investigation was initiated. The donor was called and asked to come in for blood cultures and, lo and behold, cultures of this asymptomatic donor in fact grew Salmonella enterica.

Now, on further questioning, it was found that the donor actually had a pet snake that was colonized with Salmonella enterica, and it was thought that in handling his pet snake he became repeatedly exposed to Salmonella, and was asymptomatically bacteremic. And so the Salmonella was able to get into the blood supply.

Now, given how often this person donated, the investigation that was prompted by knowing the organism probably prevented transmission to many other patients, in addition to having some

important implications for this particular donor.

Now, I think these types of outbreaks are extremely rare--at least, I think that very people own pet snakes contaminated with Salmonella. But I think the cases illustrate how important the consequences can be. And bacterial screening, if we identify the organism, provides us a very powerful method to find and stop such events.

[Slide.]

Shared data collection and analysis. I think we've already learned that bacterial screening is going to generate an enormous amount of data--especially if we take the step of identifying organisms. Again, keeping track of all of this information will require an investment in resources. So why do I think that we should make that investment?

Well, I think that knowing how often units are contaminated, and what they're contaminated with, and keeping track of that information can help us with quality assurance, and can help us with surveillance for unusual outbreaks.

First of all, using microbiology for quality assurance.

[Slide.]

Data collection that's done over time with help us establish baseline, or expected rates of contamination. And if we know what the expected or baseline rates are, changes in contamination rates can help prompt investigation into collection and processing practices, to make sure that there aren't breaches that explain the increase in the rate.

[Slide.]

Furthermore, if we actually know the identity of the organism, we can even better refine those types of investigations of increased rates. For example, increases in skin flora might prompt a review of collection practices, while increases in some of the Gram-negative organisms might prompt investigations into processing and storage issues--like they did in Denmark.

[Slide.]

Likewise, I think bacterial screening and

keeping track of the results also provides us an opportunity to link results from maybe different areas, or results collected over short periods of time, which may help uncover outbreaks.

[Slide.]

Finally, issues with supply. I think some very important questions have been raised--and some legitimate concerns--about the utility of some of the non-culture methods for screening. We certainly want to protect the blood supply, but we also want to have an adequate blood supply.

Now, we always err on the side of caution, but if we have too many false-positive results, some people have legitimate concerns that this may have very serious implications on platelet supply.

So I think the standard represents a very important step forward. However, there are certainly some unanswered questions.

[Slide.]

How should we compile and track results? How can we best use the results for quality assurance? How sensitive and specific are

non-culture methods? And what impact might false-positive results on supply?

Now, as we think about how we're going to try and address these issues, it's important to address them, I think, in a collaborative manner. And it's important to build on past experiences where we've tried to answer some of these questions.

And I think we're lucky in that we don't have to go back very far to find a directly applicable example of how the public health and blood banking community can work together to address an important issue for public health.

And I point to the example of West Nile virus.

[Slide.]

Soon after the identification of transmitted associated West Nile virus, the blood banking community and public health worked together to implement screening for West Nile virus. The AABB convened a task force that met regularly to address issues with data monitoring and to

coordinate nationwide data monitoring.

This is truly an example of a public health success--and a rapid one. Soon after implementation of the standard, nearly a thousand units of presumed infected blood had been detected and removed. Now, given the fact that many of these units could have resulted in multiple products, many, many people have already benefitted from this intervention, and continue to benefit from it.

So I think collaboration is certainly key. The West Nile Virus Task Force, and the BaCon study, I think, were excellent examples of how the blood banking community and public health can work together to address very important issues for the public health. And I think bacterial screening provides yet another opportunity for collaboration in this area.

There are a number of issues, I think, that we in the public health are very interested in working on, and working in a collaborative manner. For example, how can we establish procedures to

collect information in a standard format? How can we work together to put together projects to demonstrate the use and value of screening as part of quality assurance? How can we have projects to prospectively evaluate the performance of these screening methods, and the impacts on supply?

[Slide.]

So, in conclusion, bacterial screening of platelets is certainly an important step forward. And, like any step forward, it does raise some important questions. And, as we have in the past, I think it's going to be crucial that blood banking community and public health work together to try and address these questions.

And I'd be happy to try to answer any questions that you may have, or any comments from the committee.

Thank you.

CHAIRMAN SKINNER: Thank you for your presentation. Are there questions from the committee?

Dr. Linden?

DR. LINDEN: Thank you very much for the interesting presentation. As a public health person I certainly appreciate the issues that you've raised.

I have two questions. One is: in regard to the identification of organisms, which I agree with your points about why this would be a very valuable thing to do, but as we heard earlier, that is really not the standard of practice at the present time. So, while you gave some interesting examples, they really are probably extremely unusual events.

Does CDC have a list, specifically, of organisms for which you would recommend donor notification as an implication for donor health?

DR. SRINIVASAN: There's not a list that I'm aware of at this point in time. Matt Kuehnert may want to comment on this, as well. But I think that's, again, an area where, if it's felt that such a list would be useful, that's again an area, I think, where we can work together to try and come up with some of those standards and some of those

types of lists.

But, so far as I know, one does not exist right now.

DR. KUEHNERT: I think that's something that could be, you know, discussed in a task force sort of setting--although I would say it probably would start with those that are nationally notifiable, and then expand from there.

But I certainly wouldn't want to imply that every single organism necessarily needs to be reported. But I think that should be the starting point.

DR. LINDEN: Yes, I mean, I suspect that number's actually pretty small, and pretty infrequent--based on, you know, the organisms that are going to be seen.

DR. SRINIVASAN: I think that's probably true.

DR. LINDEN: My second question is: I was somewhat surprised by what you said early on that implied the CDC is suggesting that the blood centers start up their own microbiology

laboratories, as opposed to sending positive cultures to established microbiology laboratories that would have a lot of expertise in identifying and potentially speciating organisms.

DR. SRINIVASAN: No, and I--

DR. LINDEN: Did I misunderstand that? Or--

DR. SRINIVASAN: No--and I apologize if I created a policy. No.

[Laughter.]

The point to make was that if you were going to implement that in-house, there would be, of course, a significant investment in having all those resources in place; and, of course, the issue of sending out--there are some costs associated with that.

But, no, we don't recommend that individual centers bring in-house all of the equipment if there is send-out capability to get those done. And I a apologize if that was unclear.

CHAIRMAN SKINNER: Other questions?

Dr. Sayer?

DR. SAYERS: Thanks.

I don't think we're very far from having to include in the donor consent the warning that the donor's active donation may render him or her an object of curiosity to the CDC.

[Laughter.]

So, you know, against that background, I'm wondering if you're recommending that the identification of a bacteria by specie, in an asymptomatic but bacteremic donor should become a notifiable illness.

DR. SRINIVASAN: Well, I think it depends. I think it depends on the organism. And I think, as Dr. Kuehnert, you're suggesting, that there are already organisms that would require that.

Whether we make that--I think that's a topic for discussion. I don't think we would want to say a coagulase-negative staph in a blood culture from a donated unit is a notifiable disease. But I think that we need to work together to decide what would be things that we want to have

on that type of list.

CHAIRMAN SKINNER: Other questions?

Thank you very much for your presentation.

DR. SRINIVASAN: Thank you for letting me present now. Thank you.

CHAIRMAN SKINNER: It's just after one o'clock. I'd like the committee to try to return as close to two as possible. I realized that's a short lunch, but that will help us get out of here on time.

Thank you.

[Off the record.]

A F T E R N O O N P R O C E E D I N G S

CHAIRMAN SKINNER: Back on the record.

I actually believe there's a quorum in the room. Some of the audience, I know, will be trickling back in.

I know we have an extremely tight schedule this afternoon. I know a number of committee members are going to have to start leaving around four o'clock. And so it's important that we move through the agenda as quickly as possible so that we have a quorum to actually make committee recommendations later this afternoon.

So I have asked the speakers--I don't want to do a disservice to their presentations and their travel, but to avoid repeating information that's already been imparted for the committee, and to move as quickly as possible through their presentations.

The first presentation this afternoon is to pick up the one item that we did not have this morning, which is Dr. Richard Davey, from the New York Blood Center, had some brief comments that he

wanted to make.

Public Comment

New York Blood Center

DR. DAVEY: Thank you, Mr. Chairman, and thanks to the committee.

Again, I would like to just very briefly summarize the experience of New York Blood Center, in terms of our experience with bacterial detection implementation.

The New York Blood Centers, as you may know, is the largest independent Blood Center in the country. We're a member of ABC. We draw and transfuse about 500,000 units of red cells every year; 50,000 single-donor platelets; and about 50,000 platelets derived from whole blood--which would be about 10,000 pools. So we're about 85 percent--our customers are about 85 percent converted, or acceptant of single-donor platelets in the New York area. We serve about 200 hospitals.

Shortly after I arrived at the New York Blood Center about two-and-a-half years ago, we had

a cluster--an unfortunate cluster of events with contamination with--I hope it wasn't related, these events--involving both single-donor platelets and random platelets, which involved significant patient morbidity and mortality. So it certainly got our attention. And, along with this committee and others, we decided to move aggressively to do what we can to address this problem.

[Slide.]

Again, just as others--you've heard from other blood centers and other organizations--we had a number of operational considerations to deal with: whether to select Pall or BioMerieux--if I pronounce it right. We had to go through a lot of validation, obviously; a lot of SOP writing; clearly a lot of training and competency testing. We had to decide whether we were going to test the primary bag or split products. We decided to go with the primary bag--as most others. We had staffing issues in two laboratories that were getting up to speed.

The FDA and the New York State Department

of Health were very helpful to us in terms of getting through the regulatory and licensing arrangements. My thanks to Dr. Linden and her colleagues from the State.

We did have medical considerations--we have a medical director's council that evaluated the medical considerations that were involved in this implementation. We decided to incubate--we use the BioMerieux system--we selected that. And after--24 hours after collection, we take a sample--aerobic sample only--and we held that sample in an incubator for 24 hours before we decided to release products.

So we had to, as a medical group, decide what criteria we should have in place for emergency release of platelets before the 24-hour incubation period was completed. That would be in times of severe shortage, or in special needs for specific platelets for our hospital customers.

We also dealt with issues of donor management--you've heard what others have done. Our decision was that with positive cultures,

donors would be notified, but we would put into place, as much as we could, a little bit of art of medicine. We were very cognizant of the fact that certain organisms are more worrisome than others; Gram-negatives versus common skin contaminants. In talking to donors, we wanted very much to know what their health status had been since donating the platelets; had they developed a fever or any other signs of a bacterial sepsis situation? And, obviously, if there was a significant organism that might produce more severe complications--both in donor and recipient--we wanted to make sure those donors got proper medical care.

If a donor was feeling well, it was a skin contaminant, we would not do any further work, but that particular donor was flagged fora second hit if that should occur.

[Slide.]

We had significant problems with inventory management; with product availability to our customers; distribution of product. We did deal with what we should do with important products and,

indeed, we assured that we were--we assured our customers that all important products to the New York area were from other organizations that did conduct appropriate testing. And we did a lot of work with our hospitals to let them know what was coming.

[Slide.]

We did select the BioMerieux system. As I said, we decided to test the primary bag; the aerobic bottle only. I think you've heard most of the reasons why others have selected that also.

And we did make testing available for our hospital customers--if they so wished, we would do the testing for them.

We went live on October 12th last year. Our licenses--this was right after New York State granted the licenses to our two facilities that do the testing, and we proceeded to test all single-donor platelets--I'll talk about randoms in a minute.

[Slide.]

As Rich Counts mentioned yesterday--and

others--one of our real challenges is the weekly variation in supply, versus the demand from our customers. And the fact that now our outdating was more compressed, we felt we lost a half a day from where we were before. This accentuated this weekly fluctuation. And we've really concentrated on increasing Sunday collections.

[Slide.]

Our results to date are as follows--this is about three weeks ago. We've tested over 20,000 single-donor products. We have released three products under emergency or administrative release, and they have been for HLA-matched platelets at hospitals that have specifically requested to be available as soon as possible.

We have detected five true positives--or .02 percent of the products tested; one in a little over 4,100, true positives. The three organisms that I'm aware of are all strep organisms; Strep Group C, Strep mitis, Strep A--no bad actors we detected at this point.

We've had five false-positives, which are

bottle positives, product negatives--again, with a one in a little over 4,000, false positive rate.

[Slide.]

in terms of inventory management: we've been--one advantage of this whole opportunity for the New York Blood Center is it's really focused us on being very precise in managing our inventory. Hopefully, we were doing that before, but we're even more attentive to this right now. And we really feel we've only lost about a half a day in inventory. Of course, in a five-day product, that's still a significant change.

[Slide.]

We've worked very hard on cooperation between our hospitals, between our different regions, in transferring product. We've engaged in a lot more deliveries to our hospitals. We've gone to encouraging them in having more product on demand, rather than having standing orders. And this has been worked out pretty well. Our hospitals have been quite happy with the arrangement so far, even though they have

experience up-tick in outdating.

[Slide.]

Just a little bit about our weekly variation. If you look at--let's call it "distribution by day," but I think it correlates with "transfusion by day."

You can see that most of our distributions are, obviously, mid-week, toward the end of the week, with the weekends being variance from average, quite a bit below our average--of your average through the week. You can see the positive variance and the negative variance, in terms of distribution of our product.

[Slide.]

Now this would result--if we could even this out, this would result in what we'd like to see is a real change in collections by day. If we look at the median collections by day, what we would need to do to kind of even this out is increase our Sunday collections by about 26 percent, our Monday collections by 19 percent; a little bit more on Thursday, Friday and

Saturday--and in mid-week--look at that--Tuesday and Wednesday, we would have to really decrease our collections, right in the middle of the week, by significant percentages--30 and 37 percent.

We're working on this as hard as we can. And this--because what we're seeing now is we have enough platelets, but we're outdating platelets on the weekend, and running out mid-week. We're actually outdating about 14 percent of our platelets, but yet we occasionally have to import on mid-week--Tuesday and Wednesday. This isn't good. We need to smooth this out, but it's been accentuated--this problem's been accentuated by the shortened period that we have platelets available for distribution.

[Slide.]

We're working very hard on a Sunday campaign; encouraging our donors to come in on Sunday and donate. And it's working--but we still have a ways to go.

[Slide.]

So my last slide is that our weekly

variation does continue. We're finding we're short on Tuesdays and Wednesdays; outdating on Friday and Saturdays.

In terms of RDPs, we do distribute--as I mentioned--about 60,000 RDPs; again, about a five-to-one ratio of SDPs to RDPs in our organization. We accept any whole blood-derived platelet that our customers find positive by dipstick or any other method--we will accept back at the blood center. And we will culture that particular unit. All associated products, we do quarantine at that point also.

We now have had about 37 whole blood-derived platelets sent for culture. None have been positive so far. We're finding that the quarantining and subsequent release of the associated products is painful and time-consuming. We'd like to get around that. We're re-evaluating, if we continue to get all negative cultures on these RDPs, whether we need to go ahead and continue to quarantine all these associated products.

We're assisting our hospitals with their RDPs. We're going to be giving our major hospitals that use this particular product pH meters, so that they can get a bit more objective. They're using dipstick--get away from a dipstick to use a pH meter to perhaps get a little bit more objective. But this obviously isn't the ultimate solution to this problem.

So, in conclusion, at the New York Blood Center, we've had an experience that's now gone back several months. We're working through this with our customers. We feel that it's going well. But we ask the committee to support studies designed to permit both pre-storage pooling of RDPs, and extension of platelet storage to seven days. We think that both of these steps will be very useful in working through inventory matters, and allowing platelets to be available for our customers.

Thank you.

CHAIRMAN SKINNER: Richard, thank you very much for your comments. We appreciate it.

Karen mentioned this morning that she had a couple more slides she was able to put together over lunch that they were going to present to fill in a couple holes. And if we could take those quickly at this time, as well, please.

DR. SAZAMA: I was just asked if these are factual slides. And these are factual slides.

[Laughter.]

CHAIRMAN SKINNER: Thank you. That's now in the transcript.

DR. SAZAMA: We just had three more questions that we thought we'd share, quickly.

The question was, have you changed your request for platelets--this was from the transfusion folks, or the hospital blood banks--from whole blood-derived to apheresis platelets as a result of receiving or being offered untested whole blood-derived platelets in response to the orders?

That's a little bit convoluted. Everybody with me on that questions? Meaning--has the hospital changed.

[Slide.]

And the responses are, combining again both the hospital blood banks and the transfusion services, the response was that they would test; instead of rejecting the order, they would test, themselves. That was the response for 123. We didn't do the percentages here; that 78 of the responders said they would change to apheresis only, to get the cultured ones; and 28 had other responses.

So, again, there's a fairly sizable minority there that would say they'd rather have apheresis that were already tested.

[Slide.]

The blood centers response, when asked, you know: what happens if--have you been a position where you can't distribute the whole blood platelets--which was kind of the reciprocal of the question--11 of them answered "yes"--11 out of 34, about a third; 20 answered "no," that they would not--they have not found it a problem.

So, again, about a third are finding that

their facilities are saying if you can't give me tested, then give me apheresis.

[Slide.]

In response to a question about handling co-components, the question is: "If you get a positive or unacceptable test result, will you withdraw co-components?" And we combined the results here--actually, there are two categories--I mentioned earlier today--of the hospital blood banks. And so they're all listed together here. One group is those that import; the second group is self-sufficient, and the other is transfusion services.

And the answer is overwhelmingly "yes"--19, 10 and 150 would withdraw co-components. But there are--there's one each of the two blood bank facilities that said "no," and 10 of the transfusion services that said "no." And, then, of course, we have the ever-popular "other," which is comments that need further evaluation.

[Slide.]

And what about donor notification? "If

you get a positive or unacceptable test results--"--I'm sorry, this is not notification, this is about what do you do about the donor--how will you treat the donor? The blood center response for whole blood platelets is the first column to the right of center, and apheresis platelets is the far-right column.

What do you do about the donor who has a positive test result? And you can see, for whole blood, the answer was they would temporarily defer the donor; for apheresis, five results were that they would temporarily result [sic], one would place them on a surveillance for a whole blood positive, and three would for apheresis platelets. One facility said they would not defer them for whole blood, and four facilities said they would not defer the donor. But the popular answer here, of course, was "it depends on what the culture shows." And, again, I think you've heard some of that discussion. I can't give you further details about that, but it appears as though there is some appreciation for the fact that if it's an apparent

bacteremia, that that might be treated differently from a skin contaminant.

Those were all the slides that we had prepared.

Thank you.

CHAIRMAN SKINNER: Thank you.

Specific just to these slides, is there questions that the committee--Mark?

DR. BRECHER: A factual comment.

In one of the AABB guidances that was put out for everybody, there was an algorithm, principally prepared by Jim AuBuchon, but also that I had input in. And in that, it says that if the organism is an organism likely to be from a bacteremia, or if the organism--or if the donor has been implicated twice, then the donor should be evaluated. And I suspect that's where a lot of people are taking their lead from.

DR. SAZAMA: I agree. I think that's true.

CHAIRMAN SKINNER: Thank you for preparing that so quickly.

Next up, we're going to hear Roger Dodd

present. And, again, I apologize for asking you to keep it tight, but I know we all appreciate the importance of getting to the recommendation phase.

Next Steps Beyond bacterial Testing of Platelets

Extension of Platelet Dating and Pre-Storage

Pooling of Whole Blood-derived

DR. DODD: Thank you. In interests of disclosure, I do sit on an advisory panel to Pall, and under the same conditions of others who have made this kind of disclosure.

I put my talk together on Saturday, and I've been sitting through this meeting and realizing that all I've done is to review things that everybody else has said. So I'm going to run through these rather rapidly. I'd like to draw your attention to a few points. But if a slide goes by, you've seen it before. So don't worry.

[Laughter.]

[Slide.]

I think my message--my take-home message, which I'll give first, is that there's a clear need for the availability of platelets with extended

storage time, and a definite signal that a pre-pooled product would be useful.

There's plenty of evidence from other countries that both of these requirements can be met. But as we heard from the FDA yesterday, there are going to be some significant requirements in establishing the bacteriologic safety of such products.

And it's my believe that these are going to be extremely arduous, if not almost impossible to achieve, and therefore creative solutions will be required.

[Slide.]

I think that we've all see all of this background. I think that I will just draw your attention to a certain amount of regulatory uncertainty in moving ahead toward these two products.

The tests currently in use are really approved only for quality control of products, and not for release. I think that the community's been doing a terrific job of using these tests to

improve the safety of the product, or to generate an appearance of improving the safety of the product.

[Laughter.]

But you heard that a test approved for release is going to be needed, and the pathway to safety validation of these products, in my mind, is not clear.

[Slide.]

This one we've all seen.

[Slide.]

And I think that I just want to point out that everybody you've spoken to has commented that the available shelf-life of the platelets has been decreased as a result of testing, and that we've seen changes in outdating and/or availability patterns for the products. I think that Rick Davey made this point very clearly, and it should still be fresh in your mind.

[Slide.]

The perceived prerequisites for a seven-day platelet in the U.S.: satisfactory

maintenance of platelet properties at day seven in vitro and in vivo. There has been, I think, scientific acceptance of this position, and regulatory approval of at least some containers.

The other issue is the maintenance of product bacterial safety. And, as you heard yesterday, the current thinking of the FDA is that we would need to use a bacterial test approved for release, and demonstrate the equivalence of seven- and five-day platelets after the use of the release test. No attention has been paid to the question of whether a day-seven platelet with a bacterial release test would be as safe as today's day-five platelets--which is another way of looking at this possible requirement.

[Slide.]

There really have been no clear guidances about the way to clear a test for product release. Again, we heard a real-life 50,000 point study of actual products. This would actually differ--and I realize that detection of bacteria differs very much from any of the other tests we do, because of

the problem of subsequent outgrowth, but normally the requirements of a test to be approved for blood screening require definition of sensitivity, specificity, reproducibility, and non-interference.

Sensitivity definition is usually done with known samples in field conditions. And the epidemiologic specificity claims are based upon donor population data. So we're really looking for the proportion of negatives who test negative in these very large studies for routine samples.

But it appears that there will be different standards for bacterial tests; for example, definition of the negative predictive value of a test by re-testing at day five and perhaps day seven.

Would it be possible to do some of these studies by spiking?

[Slide.]

These are data from Dr. Mark Brecher, and I've put them up to show that this is but part of a significant body of spiking studies, and this represents hours to detection with a number of

organisms. You've actually seen this slide before. But I think there's some capability to define the performance of these tests for specific bacteria by spiking studies.

[Slide.]

I remind you that you've heard that seven-day platelets are currently in use in Europe. There has actually been limited emergency use in the U.S. Jim AuBuchon reported on this in his own hospital studies.

The BaCon study suggests that fatalities, in contrast to prior indications, tend to occur early in the life of platelets, rather than late in storage, particularly for SDPs. Now, we've hear that these data are extremely limited and not definitive. And I'll also show you a little piece of data from Hong Kong, relating to day five and day seven.

[Slide.]

We saw the overall results--the BaCon study. The interesting thing from these data that were not shown earlier that the risk of fatality

was much more associated with Gram-negatives. These tend to be fast growing. They tend to come from circulation and not from the skin--and interestingly--that the platelet storage time for fatal cases was about two-and-a-half days, compared to about five days for non-fatal cases. Both of these observations were statistically highly significant.

I think the rest are of relatively importance, other than that the cases were recognized much earlier when there was a fatality--presumably because of the high levels of bacteria present.

[Slide.]

I won't talk about that, but I will introduce another topic, which speaks to the five-versus seven-day experience. There is very limited data about this.

[Slide.]

This came from a study in Hong Kong and relates to whole blood-derived platelets. The have slightly different culturing procedures from us,

but they compared 3,010 culture-negative platelets which were stored for five days, with another 3,010 that were stored for seven days. These were re-cultured at day six or eight, and four additional positive cultures were found in each group; .0133 percent. So these would have been negative at issue.

They were all staphylococci and P. acnes. The only difference was that there was one staph at day five, and two at day seven. But I hardly think that this would be statistically significant. There were significant levels, because they were detectible by Gram stain.

So this is all the data that we have. It does say that there may be more culture detectible bacteria at day five, but in this study we did not see--or the Hong Kong team did not see an increment.

[Slide.]

We talked yesterday--Jaro Vostal talked yesterday, about protocols to assess seven- versus five-day bacterial contamination rates. This was

the other protocol that had been presented to FDA, and Jaro outlined it.

FDA has suggested a total number of 50,000, with bacterial evaluation ingoing--as we've discussed for the last couple of days. In order to do this, we believe that we would have to keep in-house outdates, because the logistics of recovering outdated products from numerous hospitals are not good. And, as Allan Ross showed this morning, that's currently about three to four hundred per week for the Red Cross, which is approximately half of the U.S.

In order to achieve this, and to do the evaluation of outdate on day seven, we'd need 50,000 data points as a minimum--although Steve Wagner pointed out that some statistical assessments which suggest a million might be necessary.

And this is barely feasible, I believe. At current rates, it would take about two years to accumulate the study sample, using all available in-house outdates in the U.S. The resource

requirements we've estimated are certainly more than $5 million, and we are not clear, at this time, what the regulatory response might be to the data that would come out of this.

We don't know whether the cost-benefit of doing these studies compares with alternate collection strategies, such as the Sunday collections that you heard about, or modifications of inventory and usage patterns. These are things that we intend to look at.

[Slide.]

So, I think this is pretty obvious. My point here is that for seven-day platelets, if the bacteriologic safety objectives cannot be met by the proposed approaches, then we're going to have to have creative alternatives. Perhaps we could go to a six-day platelet without any further work. Who knows?

[Slide.]

Pooled whole blood-derived platelets--similarly, you've heard that 25 to 30 percent of therapeutic doses in the U.S. are whole

blood-derived, and in some hospitals it's 100 percent.

One of the values of whole blood-derived platelets, that they can support temporary or long-term needs that cannot be met by increasing donations for single-donor platelets--for apheresis platelets. We can do this manufacturing change, rather than by increasing the number of donors.

You've heard that they're used in pools of five, but that in the U.S., those pools have to be made, essentially, within four hours of usage.

[Slide.]

We've heard about the bacterial testing of whole blood platelets. I would just point out that most of the sensitive methods require a significant volume to be withdrawn from the platelets, and this leads to a loss of the therapeutic content, and therefore it's better to take one sample volume from a pool.

Again, there are perceived prerequisites. We need an approved container--and at least one manufacturer, as you've heard, is developing this.

We need maintenance of in vitro characteristics, in vivo validation; proposed or new FDA criteria will probably be needed.

We had heard concerns in the past about the potential for mixed lymphocyte culture cytokine generation in storage of pooled products. We haven't heard much about that lately.

And the FDA had also raised the issue of the integrity of using multiple sterile connecting devices, but the Blood Products Advisory Committee indicated this was not of concern to them. But, again, we were advised of the issue of bacterial safety in these materials.

[Slide.]

The donor exposure, in terms of number of donors is the same as pools made in the hospital. The real concern is that the large volume of the pool may permit outgrowth to greater total bacterial load, compared to late-stage pooling. And Steve Wagner has data in this.

[Slide.]

In the other direction, we don't know

whether pooling is going to result in self-sterilization, relative to the absence of pooling WE don't know--although we can predict--the impact of dilution on detectibility of products, but we do know that we get a better sample--more sample. But there are implications for co-components. We would have to eliminate five red cells for every pool that came out positive.

Outside the U.S.--as you heard--pre-pooled platelets are the current standard, although they're derived from Buffy-coats. This product does not appear to be associated with excess transfusion reactions, compared to non-leukoreduced products in the U.S., and appears to be similar to leukoreduced products. Bacterial testing has been applied to these products with apparent success, and the seven-day product is routine in some countries. And, as you heard, just to the north--Canada is evaluating implementation of this approach.

[Slide.]

We really don't have guidance on bacterial

safety, although the FDA again reminded us that a release test was needed. Are there regulatory concerns beyond in vitro and in vivo characteristics? We don't know about that this stage?

[Slide.]

How do hospitals feel about this? It certainly lifts a burden from them, and there was brief mention of a potential seven-day product here.

[Slide.]

So, in summary, bacterial detection is an industry initiative to improve patient safety. And I think you've heard a lot of evidence that this is the case. But regulatory approval for product release appears to be desirable or necessary, according to the FDA, because these are now approved only for product quality control--which may account for some of the absence of the full responses to the medical questions that have been raised by this committee in the last couple of days.

[Slide.]

Optimal achievement of patient safety and adequacy of treatment are best obtained through the availability of seven-day platelets, and pre-pooled whole blood-derived platelets. Equivalent products are available in other countries, with no evidence of failures in safety or efficacy. And, finally, there is a need to work with U.S. regulators to develop rational and feasible pathways to validation and approval of these new platelet products.

Thank you.

CHAIRMAN SKINNER: Thank you. And thank you for keeping your presentation succinct.

Questions from the committee?

[No response.]

DR. DODD: It really was a summary. Thank you.

CHAIRMAN SKINNER: I've scared them all.

Moving on to our next presentation, at this time we're going to hear from Dr. Scott Murphy, with the American Red Cross, as well, on

future platelet research.

Future Platelet Research

DR. MURPHY: I, too, have associations with manufacturers. We have research grants with Baxter, Pall and Gambro. So I presume that you should know that.

[Slide.]

I'm the chief medical officer at this blood center--have we got a pointer?--

[Pause.]

--in downtown Philadelphia. I'm going to be giving you my opinions. Although I'm a Red Cross employee, I will--these will be my opinions, not necessarily Red Cross opinions.

And I want to focus on--to some extent--on the problems we have in our blood center, because I think the research that's to come should be based on issues that for which we need resolution.

[Slide.]

We've heard from Allan Ross that, within the Red Cross, about 75 percent of platelet transfusions are a apheresis. We're quite

different from that, with more transfusions from random-donor platelets than we have with apheresis platelets.

[Slide.]

The thing to emphasize, for us--s Dr. Sayers said yesterday--that without having ready access to lots of random-donor platelets we would be in big trouble. And it's not so much that you don't have enough, if you average out the whole year, but when you have declines in donations because of snow, or weather, or holidays, we crank up our random production to meet the need.

[Slide.]

We know that bacterial contamination of platelets and transfusion-related acute lung injury are major causes of concern, in terms of complications with transfusion. There was a recent--to just say a word about TRALI, I think it's an extraordinarily important aim for research to be directed at that. There was a wonderful conference in Toronto last week, which basically asked more questions than providing answers. And I

think we really need to work hard in that area.

However, on a day-to-day basis, I really only fret when we have an example of one or the other. On a day-to-day basis, I'm worried about availability of blood; Group O red cells, and platelets.

[Slide.]

Now, as we've heard--and just to expand on it a little bit--in Western Europe, the percentage of products that are made from apheresis is only 42 percent. And you see that some countries like Denmark, Finland, Holland, Portugal use almost entirely pooled platelets, but they are pooled from Buffy coats.

[Slide.]

And this is just a schema--which you probably can't read, but--and Dr. DeKorte showed us some of this--this is the PRP method. Here we have a hard spin, to put the Buff coat right in the middle. The red cells go out the bottom and the platelets--plasma goes out the top, and then one needs to dilute the Buffy coat--the pooled Buffy

coats in something, so many of the centers are using additive solutions. And that has the added advantage of making more plasma available for transfusion and fractionation. To the extent that we worry about reactions caused by antibodies in the donor, those are diluted.

[Slide.]

I had an opportunity--I've had personal opportunity to work with this technology, and this just shows you briefly--the pre-storage pooled Buffy coats--we found in two in vitro tests shown here--ATP and osmotic reversal--a very striking maintenance of characteristics and quality with both, even out to 15 days of storage, with platelets pooled from Buffy coats. The other lines are control PRP platelets.

I'm personally convinced that this method of making platelets from Buffy coats will allow a prolonged storage beyond seven days. And so I think that research should be done about this method; about what the characteristics of additive solution should be. And just to add on that,

Cheryl Shlichter, at the ASH meetings last December, showed data about extension of pheresis platelet storage to 15 days, and that was based on products made with a Hemonetics, and with 80 percent additive solution--in her case, Plasmalyte. So, I think this is the way things might go.

[Slide.]

Just as one more comment about apheresis versus random--if we have in the United States million donations per year, and if there are two million platelet transfusions per year, there's more than enough platelets in these blood donations to satisfy most of the needs for platelets in the United States, and that's what the countries in Europe are taking advantage of.

So how can--if my major worry is availability, what can we do to increase availability?

[Slide.]

The first, and primary one, probably: improve donor recruitment and retention; obtaining more platelets from whole blood--don't throw away

the give that's already given; extend current storage interval 22 degrees to seven days and beyond.

[Slide.]

And just some new thinking about temperature and platelet storage. In work in the late 60s, we showed that storage in the cold was associated with very short platelet survival, even after about 24 hours. We correlated that with the disappearance of the circumferential band of microtubules. They disappeared after 24 hours in the cold, and they would not be--they can't re-form, and the platelet became an irreversible spherical cell.

And I think that was the dogma for about 30 years. This group of scientists in Boston studied mast platelets and their storage at 4 degrees. And they developed a new concept of the storage elision; that glycoprotein 1Bà on the platelet's surface
was altered, and could then be recognized by the liver and cleared from the circulation.

They developed the novel ability to cover the activated glycoprotein 1Bà with galactose present in uridine diphosphate galactose, and found that these spherical cells survived normally, at least in the mouse. It's a long way from the mouse to man. There are many similar proposals that didn't pan out, but I think this is an extraordinarily good one.

[Slide.]

I think we need research on the storage elisions, but at 22 degrees and 4 degrees.

I think we have to be careful not to waste platelets; adhere to the newly established trigger of 10,000; and find out what the best platelet dose is. I'm happy to say that transfusion medicine, hematology clinical network established by the NIH is going to embark on a study of platelet dose, with a 1,200 patient study, using clinical bleeding as the primary endpoint.

And, as I'll show you, knowing what the dose is is very important, in terms of how you handle pheresis.

[Slide.]

This is from Mark Brecher's work, showing that high-dose therapy gives you a better increment; you have platelets handing around longer. Shorter and more frequent transfusions ad required by low-dose therapy. But, in the end, when you calculate the number of platelets used, one has to use more platelets with high-dose therapy.

I think we should decrease low-yield apheresis collections. We have found over the last five years that our split rate has gone up dramatically due to improved technology from industry, without a substantial decline in what we call "the distribution yield." There's no studies in the literature, that I know of--I think they should be done, obviously--of what the average platelet content of pheresis platelets that are sent to the hospitals.

[Slide.]

There's a very high correlation between the collection yield and the--the average

collection yield per month, and the split rate. I think that this--improving technology to allow consistent production of units that are greater than the split level, I think, would be very important.

[Slide.]

And don't waste platelets to alloimmunization. It was anticipated from the TRAP trial that there would be a decrease in the number of alloimmunized patients, due to the effect of pregnancy. And the TRAP study did show only 50 percent efficacy.

And we, indeed, had a decline in the number of matched platelets we distributed practically to our 1991 level, but in 2003, it's increased again. So I think this is still an important phenomenon that we have to study and deal with.

[Slide.]

This just shows the huge variability within Red Cross blood centers as to how they get platelets--or test them for alloimmunized people.

You see percent cross-match goes from--as opposed to HLA typing--goes from less than 1 in Madison, to 94 in Atlanta.

[Slide.]

There's a new concept about how to match platelets, called the "antibody specificity prediction method," developed by Garrity, Petts and Tarasaki. It's simple conceptually. You perform lymphocytotoxic antibody screen, identify the HLA antigens to which the patient has developed antibody, and treat the patient with platelets which lack those antigens; i.e., antigen-negative platelets. They showed, in a paper in Transfusion two years ago, that this was a quite good way to support patients.

What makes the situation more attractive is that there are now much more precise ways to identify the specificity of the HLA antibodies in patients, based on the fact that the antigens themselves have been cloned and reproduced, so that only one antigen is on this well. If there's an antibody in the patient's serum, it binds.

[Slide.]

Oh, this doesn't project very well.

You then add an anti-human IgG with an enzyme conjugate, and reveal that binding with a typical olizen method.

There are also flowcytometric methods for determining the specificity of HLA antibodies with a unique, single HLA antigen on each bead.

So I would propose that we take advantage of this technology in a clinical trial, to show that our ability to support alloimmunized patients has improved.

[Slide.]

I want to say a word about platelet decontamination, or pathogen reduction. And these slides just show the Baxter Serous technology. And I think that most of you are familiar with S-59 and UV light.

I think, in addition to cleaning up the residual pathogens that we have in blood that have escaped testing, there will be a marked decrease in the concern over CMV transmission, because that

virus is killed easily by this kind of technology.

[Slide.]

The disadvantages of testing--developing a new test over and over each year or so, has its disadvantages. I'll just stress that many donors are eliminated because of reactivity, even though they're perfectly healthy.

And, less important, the lag time between pathogen identification in the development of a screening assay is significant. We know that in 2001, five patients died from West Nile virus, whereas if this technology had been in place, that would not have happened.

[Pause.]

Oh, here we go.

[Slide.]

This slide shows that there are large number of pathogens emerging around the world, and we can expect that new pathogens will come into the blood supply, and perhaps they'd be better dealt with a pathogen-inactivation mechanism.

I wanted to talk, then, about the testing

of platelets. How do we work with the FDA to show that a product is suitable?

The paradigm, in 2002 and 2003, has been to do a paired-study in the same donor, with the experimental method and the control method.

[Slide.]

Now, the control has typically been what I call "regular old platelets"--the oldest platelets that you're allowed to store, and at the very end of the license period for that storage--this is perhaps a worst-case scenario for the control.

We need to develop a line in the sand as to what will be acceptable. And when results in different lab are shown, the "regular old platelets" will vary widely. And there's some potential here for creeping inferiority, where you're 45 percent with your established method, and then you go to 39 percent--that's not statistically significant. Then you go to 32 percent, that's not statistically significant. And pretty soon we're going to have mush in our platelets.

[Slide.]

So the proposal's been made that the control should be fresh platelets and experimental results should be expressed as the percentage of the control. And--well, I propose this, actually--and that recovery should be two-thirds of fresh and survival one-half of fresh.

I think this concept will be discussed at the May 3rd meeting put together by the FDA, "When Platelet Survival's Safe." And I'm hopeful that we can come to some conclusion about how to do these studies. But I know, as we have been studying this, that we continue to see new, specific areas where these radiolabeling studies can be improved.

They're very expensive. They're difficult to do. There's less than 10 labs in the U.S. that can do it. And I think we need to research novel ways to assess, in vivo, novels ways of preparing platelets and storing them.

I think I will stop at this point. I appreciate the chance of making this presentation.

CHAIRMAN SKINNER: Thank you, Dr. Murphy.

Are there any questions from the

committee?

[No response.]

CHAIRMAN SKINNER: Thank you very much.

At this point I just would like to let the committee to know that, in the interest of time, I'm going to defer with the break. So if you need to take a break, feel free to get up and do so.

Public Comment

Chiron

CHAIRMAN SKINNER: We're going to move immediately to the public comment section. And we did have one request for comments.

Ms. Deborah Dodge, with Chiron, wanted to address.

MS. DODGE: Good afternoon. I'm Deborah Dodge, Global Marketing Manager for the Chiron Bacterial Detection Assay for use in screening platelets for bacterial contamination. Thank you for giving me this opportunity to speak to the committee about the issues surrounding the development of this assay.

Chiron, with its partner,

InfectioDiagnostics, is developing a nucleic acid test to detect bacterial DNA in platelet concentrates. The test detects a universal bacterial gene which contains DNA sequences that are highly conserved across all bacterial species. This represents a major multi-million dollar commitment by the company in its effort to rapidly develop a blood safety screening test using a new technology for the identification of bacterial contamination.

Unlike the culture approach, this assay will not be dependent on growth or metabolic byproducts, but rather, only upon the number of genes which are present in the sample at the time the assay is performed. This raises the problem that the sensitivity claims of the current products are based on growth, and are therefore difficult to compare to methods of direct detection.

The sensitivity of PCR is exquisite, and we have been able to demonstrate the detection of less than 1 CFU per ml, which is approximately equivalent to 5 genomic copies per ml. Our current

sensitivity goal is to develop an assay capable of detecting 50 to 250 genomic copies per ml, which is equivalent to 10 to 50 CFUs per ml.

The purpose of my statement is to make three points. The test we are developing uses a new technology which is not based on growth. It will require a rethinking and new definition for the sensitivity standard. We ask that the committee take these critical into account.

Secondly, the costs of the trial for release tests are prohibitively expensive, and it is hard for a commercial manufacturer to justify the cost and risk of such a trial. We would like to ask that the committee consider recommending a reduction in the scope of the trial, or rapidly convene a workshop to discuss the best option for trial design.

Lastly, it would be helpful to know that the FDA will treat a release test for bacterial detection asa public safety standard issue, so that once the test is created, it will be recommended in the guidelines.

Thank you for your consideration of these requests as we work towards developing a nucleic acid test to detect bacterial contamination in platelet concentrates.

CHAIRMAN SKINNER: Thank you very much for your comments.

Committee Discussions/Recommendations

CHAIRMAN SKINNER: At this point what I would like to do is--we have a lot of work ahead of us. It's three o'clock. I know some folks are going to have to leave early. I think we'll skip back to the CMS recommendations.

There were four resolutions that have been suggested. I think they are all on the computer.

It would be my intent--unless there was an objection--just to take them each as stand-alone resolutions, in the interests of time, as opposed to trying to combine them all into one. If, when we get through all four we decide that it really was better to combine them, then we can go back and do it. But I think they are each--at least as I understand them--relatively stand-alone. I believe

there are two that relate to exemption from the competitive bid process. I believe there's one that relates--seeking some clarification as it related to the conference committee agreements on compiling data. And then I believe there is one that Dr. Heaton asked me to bring forward that he drafted before he left, which relates to some data collection on, basically, heading towards reimbursement for safety measures implemented for blood and plasma products.

So--I don't know which one you have.

[Slide.]

That's Dr. Heaton's recommendation. So--he did speak with me, and I'll just briefly explain it, as I understand it, to the committee, and then share with you my brief conversation. And he apologizes for not being here to present it.

I believe what he has presented is largely consistent with previous committee recommendations; that for some time the committee has recommended--or excuse me, has talked about the need for reimbursement to keep pace with the cost

of safety, and for the cost of advances in the products, both whole blood plasma and the recombinant analogues.

What--if the committee can read down through it, towards the bottom of the page--or actually, the "whereases"--the beginning is largely just reciting relevant sections for the different pricing provisions that were explained yesterday; references to the new current provisions in the MMA.

The next section, I think, actually that starts, "The MMA Conference--"--"--the Secretary to compile and clarify data--"--I think actually is going to be the subject of Dr. Sayers' recommendation--resolution. So that might be a stand-alone resolution that I think Dr. Sayer is going to present.

But I think the essence of what he's looking for at the end are some guidance, and perhaps asking HHS to do some studies to determine incremental costs of the various safety measures; data tracking; the AWC for whole blood products

and, I believe, also for plasma products. Although it wasn't mentioned here, he indicated that was his intent. It just didn't get in his draft when he gave it to me--and then asking CMS to do some assessments.

Now, my personal comments on it are that these are all things that were consistent with what the committee's talked about. The dialogue I had with him after he gave this to me was whether or not it might better for the committee to take this as instructive and perhaps for the agenda committee, or the Executive Secretary to look at taking some of these issues and the committee using them to build a future committee meeting around, and flesh out some of these before--if they aren't sufficiently detailed enough for us to ask for studies at this point.

So I guess the question to the committee is: do--is this something that we want to act on at this point and reinforce that we want these kinds of studies to proceed? Or is it something that we would like to spend some more time talking about,

see if we can clarify the requests and then take them forward?

Ms. Lipton?

MS. LIPTON: I guess--well, I have two thoughts about this. I mean, I agree that ultimately we want to get there, but there are a couple of things that are--that would even prevent us, I think, from getting good data.

One of the things that we've heard from CMS is that they don't have the accurate data already in there. That's why we're trying to get them to first change their--clarify their policy so that we can actually bill appropriately so they can get in better data. And I think that's kind of the track we were on.

And I guess I would rather have CMS put its efforts into doing that, and clarifying policies, than doing a long-term study that could take them forever, and then we're sort of in a holding pattern.

So, I'm sorry that Andrew isn't here, and I didn't know about this. I would have said this

to him personally. But I don't know that I necessarily agree with going in this direction.

CHAIRMAN SKINNER: Other committee comments?

Dr. Linden?

DR. LINDEN: I don't feel that we're at a point yet of supporting this. You know, I agree--I think we need to look more at some of these issues. I mean, just one thing I noticed is I don't think we're really talking about initiatives that are actually required in regulation at this point. I think we're talking about things that have really become industry standard, or maybe recommended by FDA.

So--but I think some of these issues are things that we have talked about, in terms of getting industry there. But I agree with what Karen said, and maybe there's other things that need to be looked at, to get at this issue.

CHAIRMAN SKINNER: Am I hearing a sentiment that this resolution, although we don't disagree with the direction it's going, that it should be

more guidance for the committee, or for us to look at areas that need more exploration, and not to take action on it at this time?

MS. LIPTON: That would be my recommendation.

CHAIRMAN SKINNER: Okay.

Dr. Sayers, did I characterize it correctly that your resolution that you drafted is going to capture the item on the MMA?

DR. SAYERS: In this regard, to this resolution--or recommendation--I was just going to agree with Karen. I think we're in a stronger position if we pain with a broader brush stroke. And certainly some of the issues that Andy raised could be for development of agendas, which would enable us to speak with, I think, more strength and more confidence.

CHAIRMAN SKINNER: Okay.

Then unless there's any further discussion on that, we'll move on to the second resolution, which I believe is the one that Dr. Sayers has drafted, and I'll let him speak to it.

It was there.

DR. SAYERS: This was in the interest of being short and sweet.

[Slide.]

Unfortunately, I can't read it and speak into the microphone at the same time.

[Laughter.]

Why don't you read it.

CHAIRMAN SKINNER: I believe the section in the quotes is directly out of Dr. Bowman's presentation yesterday, and that's what you were referencing, is--virtually the last paragraph in his presentation from yesterday.

DR. SAYERS: All right. Triumph of technology here.

So-- whereas a safe, available and affordable blood supply is an essential--that should be "national" resource, and whereas the committee applauds Secretary Thompson's recognition of the importance of a sound policy of reimbursement, the DHHS ACBSA--that's us--one, reiterates the recommendations of their January the

28th and 29th, 2004, meeting; secondly, endorses the MMA Conference Agreement statement--and that is direct from the presentation yesterday, namely "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 blood deductibles." And, three, we urge that a timeline be applied to the above directive.

And the reason I thought short and sweet would be good was I thought we had got off to a flying start, particularly when I read Secretary Thompson's response to Dr. Brecher's letter. That's why I thought it would be worthwhile reiterating those recommendations, which certainly sounded like they--if didn't get a warm reception, at least got some sort of a reception.

And then I thought that if we had a timeline to that directive to the Secretary, it would certainly remind the hospitals that this committee is making attempts to ensure that some of

these reimbursement inequities are addressed.

CHAIRMAN SKINNER: Mark--are there other--Dr. Holmberg?

DR. HOLMBERG: Yes, I just would ask the committee members that are associated with the plasma community whether this would include them also?

MR. HEALEY: Well, that's a direct quote out of the MMA, I believe. And as written, it does not cover plasma or recombinant therapies.

The watchwords there usually are "blood and blood products," or "blood components." And it simply says "blood." So--my reading of it is that it would not include that.

Now, whether we sought to recommend that it be expanded, I guess that would take some more consideration. So I would need to think about that and confer with--

DR. SAYERS: You know, the recommendations of the 28th and 29th, in Item 3, did specifically mention plasma-derived therapeutics and their recombinant analogues. So that's why I referred

back to the recommendations of that meeting.

CHAIRMAN SKINNER: Is there--in that vein, then, would there be a suggestion that an item three be added? That this statement be expanded to include plasma-derived products and the recombinant analogues, and then have your existing three as an item four?

MR. HEALEY: Dr. Sayers, is what you're saying that the 28th and 29th recommendations, they do include plasma and recombinant therapies.

DR. SAYERS: You know, that recommendation said, "Address funding needs at all levels of the blood system to support safety, availability--"--and essentially it was the Gerry Sandler section, saying that there should be appropriate reform of the CMS reimbursement system for blood and blood products, including plasma-derived therapeutics and their recombinant analogues.

MR. HEALEY: I mean, I guess, inasmuch as this paragraph really is just seeking some clarification, you know, that's kind of

mom-and-apple-pie. So I can't imagine anyone's going to oppose that. So I guess I wouldn't object to expanding it to include plasma and recombinant therapies.

DR. LINDEN: But if you're saying that basically the recommendations that we're endorsing already include plasma-derivatives and the recombinant analogues, I don't think we want to suggest that we're modifying those. Perhaps we just want to, in number one, expand the language a little bit to reiterate them--what they are, instead of just cross-referencing them, to make clear that it covers all of those things.

MR. HEALEY: I think that's an--

DR. LINDEN: Because we're not changing them, from what I'm hearing.

MR. HEALEY: That's right. And so what you're saying is: under one, that reiterates the recommendations of the January 28th--

DR. LINDEN: Yes, relevant to this, that and the other thing.

MR. HEALEY: --which includes--

DR. LINDEN: Yes.

MR. HEALEY: --blood products, and plasma, and--

DR. LINDEN: Right Exactly. Just include some of that language.

MR. HEALEY: Mm-hmm.

CHAIRMAN SKINNER: So, in essence, what you're saying then is that we're interpreting this language to be all-inclusive, like our statement was, and we're--because if we just state ours, and then we accept theirs, and their's doesn't mention it by reference, then it sounds like we're saying we're okay with this much, and then come back and do the other.

And it seems to me we have to repeat--

DR. LINDEN: Well, but I thought that Merlyn was saying that their language does, in fact, specifically include that language.

CHAIRMAN SKINNER: The 28th and the 29th is--

DR. LINDEN: Can be--

CHAIRMAN SKINNER: --the BSA committee recommendations--

DR. LINDEN: --I mean, is there not a specific chunk of their language that we can just throw in there and cross reference?

DR. SAYERS: Do you have that technicolor three-ring binder?

[Laughter.]

Because that--our recommendations of the 28th and 29th are under the first blue plastic sheet, and they're Item 3.

CHAIRMAN SKINNER: Let me see if I can attempt to clarify.

There is--item one refers to this committee's specific recommendation, in which we mentioned plasma-derived products and their recombinant analogues. Item number two refers to the MMA, which does not mention plasma-derived products and the recombinant analogues.

I think the question before us is: do we also want to ask, if this study goes forward, that it parallel our recommendation, thus really expanding upon what was in the conference committee report for the MMA. And if we want them to do this

in a timely fashion, then do we also want them to do the balance of our recommendation from January 28th and 29th in a timely fashion?

[Laughter.]

MR. HEALEY: I guess my concern is, you know, that's language straight out of the statute. And to start suggesting that the language ought to be interpreted differently or changed or something like that is perhaps presumptuous, and maybe inappropriate for the committee.

I think the point--the first point, reiterating our recommendations and drawing attention to the fact that it includes, you know, plasma therapies and the recombinant analogues is totally appropriate. And then in number three, if we say "urge that a timeline be applied to the above provision of the MMA and the recommendations of the committee," then you sort of capture it all.

CHAIRMAN SKINNER: Is there consensus that that captures it?

VOICE: Yes.

CHAIRMAN SKINNER: Any other comments on

that point, then?

Karen?

MS. LIPTON: No, not that one. I was just concerned that when we talk about a timeline, that I'm more concerned, actually, I think, with the timeliness. I mean, we could have a timeline that goes on for--five years. So, I'd somehow like to capture the sense that we'd like something that recognizes, you know, the urgency of--you know, of doing this, so that we can somehow make sure that reimbursements are timely, and--

DR. SAYERS: Well, it urges a timely response to the directive; directive and to the recommendations of the 28th and 29th meeting.

CHAIRMAN SKINNER: We're seeking a timely response to the committee? Or a timely action in developing a timeline?

DR. SAYERS: It's a timely response to the directive.

COL. SYLVESTER: But they could still develop the timeline quickly that dragged out for five years.

CHAIRMAN SKINNER: So then there will be two modifications to item three: one to insert "urge a timely response in developing a timeline--"--

DR. SAYERS: Well, just a timely response to the directive.

CHAIRMAN SKINNER: "Urges a timely response to the directive--"--and then the language that Chris suggested needs to go at the end of item three. Okay--so--

DR. HOLMBERG: Okay. So--"urges a timely response--"--then delete "that a timeline be applied." Then, before the period, add--what did you say, Chris?

DR. SAYERS: And the recommendations of the January 28th and 29th--

MR. HEALEY: [Off mike]--the aforementioned recommendations of the committee.

DR. SAYERS: Right.

DR. HOLMBERG: "On the aforementioned recommendations of the committee."

[Pause.]

CHAIRMAN SKINNER: Does this capture everybody's thoughts? No.

Dr. Linden.

DR. LINDEN: No--we always get a timely response. We get a letter back that says, "Yes, thank you very much for your comments."

[Laughter.]

The idea of having a deadline, or a timeline, I think was a very new idea. And Merlyn had an excellent suggestion there.

CHAIRMAN SKINNER: Could we change it to "urges timely action on the above directive?"

DR. LINDEN: Umm--

CHAIRMAN SKINNER: Or we could say "timely action in development of a timeline."

[Laughter.]

[Pause.]

DR. HOLMBERG: Urges a prompt response?

MS. LIPTON: I don't think it's a response we're looking for. I think we're looking for the action to be timely. And that's--we don't care about a "timeline," we care about a deadline for

action.

So I think "urges timely--"--what is that?

CHAIRMAN SKINNER: I think take out the "a"--urges timely action?

MS. LIPTON: "In response to the above directive and the aforementioned recommendations of the committee."

So, Gerry, after "action," it would be "in response to".

CHAIRMAN SKINNER: And then change the "in"--

MS. LIPTON: Change the "in" to "and."

CHAIRMAN SKINNER: Any other comments or suggestions?

Dr. Linden.

DR. LINDEN: Switching back to item one, the language that we used last time, if we would like to be consistent, is: "Blood and blood products, including plasma-derived therapeutics and their recombinant analogues."

CHAIRMAN SKINNER: Okay. He'll be working on that.

Any other comments or suggestions?

[No response.]

CHAIRMAN SKINNER: All of those in favor, aye.

[Chorus of ayes.]

CHAIRMAN SKINNER: Opposed?

[No response.]

DR. HOLMBERG: Wait a minute--let me go back--"blood and blood products--"--

CHAIRMAN SKINNER: Oh, I have to take a hand count? I'm sorry.

DR. LINDEN: "including plasma-derived therapeutics--"--

DR. HOLMBERG: "--including plasma--"--

DR. LINDEN: "--derived therapeutics"--with no hyphen, for some reason.

CHAIRMAN SKINNER: I'm sorry, I understand I actually have to record a vote.

So, all those in favor, raise your hand?

[Show of hands.]

CHAIRMAN SKINNER: There are nine affirmative votes, and the Chair votes aye as well.

So the resolution passes--unanimously.

Okay, the third resolution, please.

[Pause.]

Chris, can you explain your resolution?

MR. HEALEY: Yes, this came out of the discussion yesterday where Dr. Bowman gave us a great report on the new Medicare legislation, and we noted that clotting factors--blood clotting factors--were not excluded from the competitive bid process under the MMA. And it was our clear understanding that they indeed were intended to and that, for whatever reason, that was not captured in the final legislation, but that the conferees had agreed that it would be excluded.

So, in reading the statute, we realize that the Secretary has authority, has discretion under the statute to exclude products from the competitive bid or competitive acquisition process under two circumstances: one, where to do otherwise would not assure access to those therapies; and, two, where there would be no cost savings from the competitive acquisition process.

So this resolution, if you scroll down just a little bit, simply asks--after a bunch of "whereases"--that the Secretary exercise his jurisdiction under the statute to exclude blood clotting factors from that competitive acquisition clause.

CHAIRMAN SKINNER: Any questions or comments?

[No response.]

Are we ready for a vote?

DR. HOLMBERG: I can certainly read through it--

CHAIRMAN SKINNER: read it all. I'm sorry.

DR. HOLMBERG: "Whereas blood clotting factors are life-saving biological therapies; whereas it is crucial that individuals with hemophilia have access to and choice of the full range of blood clotting factors available on the market; whereas inappropriate reimbursement methodologies can have a significant and detrimental impact on Medicare beneficiaries' access to these therapies; whereas the competitive

bidding process under Medicare Part B, Sec. 1842(o)(I)(C) of the Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA) would not assure access to blood clotting factors; whereas Congress has recognized the unique access challenges facing beneficiaries that rely on life-sustaining plasma protein therapies through an exclusion of intravenous immunoglobulin therapies from competitive acquisition provisions of the MMA, the committee recommends that the Secretary exclude blood clotting factors from competitive acquisition under the exclusion authority granted in Sec. 1847 B(a)(I)(D)."

My comment to the committee, again, is that with this clotting factors, we've been consistent in the past about the recombinant analogues, and is it the desire of the committee to include that?

MR. HEALEY: We can certainly add that language. I think, in the past what we've done is made sure that we called that "the recombinant analogues" when we refer to plasma therapies, or

plasma-derived therapies, because recombinant therapies are not derived from plasma.

I think this references blood clotting factors only, and when it does not, it refers to intravenous immunoglobulin. So--but perhaps I'm incorrect about that. "Life sustaining plasma protein therapies"--I suppose that could also say plasma-derived and recombinant analogues.

DR. LINDEN: Well, what was in the law, though? Didn't it refer to clotting factors?

MR. HEALEY: It said "blood clotting factors," it did not distinguish between plasma-derived and recombinant.

DR. LINDEN: right, so I think we should use the same language that--

MR. HEALEY: Yes.

DR. LINDEN: --the law did.

MR. HEALEY: Right.

CHAIRMAN SKINNER: Any other questions or comments?

Dr. Linden?

DR. LINDEN: This is trivial, but in the

last "whereas" can we just change the second line: the "that" to "who" so that we make these beneficiaries people?

CHAIRMAN SKINNER: I appreciate that.

Any other questions?

Dr. Sayers?

DR. SAYERS: Sorry--this is also trivial.

In that second bullet, would anyone object to leaving out "and choice?"

VOICE: Yes.

DR. SAYERS: Okay. You know, my concern is that almost sounds like an opportunity to exempt physicians from their contribution from deciding. "Given access to the full range"--physicians deciding what's appropriate for the patient. How's that for professional arrogance.

MR.WALSH: Yes, except that you can't get a product without a prescription, and you can't get a prescription without a physician. So there has to be some negotiation, at least there.

CHAIRMAN SKINNER: Any other comments, suggestions or amendments from the committee?

[No response.]

CHAIRMAN SKINNER: Is the committee ready to vote?

All those in favor, please raise your hands?

[Show of hands.]

The motion passes unanimously. Ten votes aye. I didn't ask for negative votes, but I saw all the voting members voting.

And I believe that there is a fourth resolution. I haven't seen it, but I understand there's one similar that relates to blood.

Ms. Lipton, you're going to speak to that?

MS. LIPTON: Yes, I am.

CHAIRMAN SKINNER: Okay. Thank you.

MS. LIPTON: It's a similar issue, although we would like to see it, I think, operate in a slightly different way because there is presently an exclusion permissible for situations where you have--thanks--this will allow me to read without turning my head 180 degrees.

It says--it requires--it may require the

establishment of quality standards and accreditation bodies. And we actually already have those in place and they are effective. So we're asking that the Secretary use his authority to exclude all blood products and transfusion medicine services from the establishment of quality standards and competitive acquisition processes of the MMA.

CHAIRMAN SKINNER: Questions? Comments? Suggestions? Amendments?

[No response.]

CHAIRMAN SKINNER: Has everyone had an opportunity to read and digest the resolution?

Dr. Lipton--Linden, I'm sorry?

DR. LINDEN: Can you explain what this really would mean?

MS. LIPTON: It just means we would be exempt from the competitive acquisitions sections. We don't necessarily think we are, but we want to verify that we aren't, and this is a good way--do you want to--Theresa, go ahead.

CHAIRMAN SKINNER: Identify yourself,

please.

MS. WIGMAN: I'm sorry--Theresa Wigman, from the AABB.

There is some confusing language within the bill passed last year within the competitive acquisition section; a different competitive acquisition section, not the one that the plasma-derivatives are under, but for different medical equipment--durable medical equipment and other things.

There's a provision in that section that would require certain products to be subject to quality standards and be accredited by outside parties subject to these quality standards. And in the list of products that they say could be subject to these quality standards it includes blood products and transfusion medicine.

It's our understanding from discussions with Congressional staff that this was put in inadvertently and that we should work with the agency to just have them use their exclusion and their own authority to clarify that blood shouldn't

have been subject to that provision.

So it's within the section of the bill that deals with competitive acquisition, there's this section that deals with quality standards, and that's the one part of the existing Act that we think we need to make clear that blood--it's not appropriate to have blood products or transfusion medicine services subject to these provisions.

DR. LINDEN: So they would be excluded, period--

MS. WIGMAN: Right.

DR. LINDEN: --not just if the particular entity involved were AABB accredited, or anything like that.

MS. WIGMAN: Yes. Yes. We're just saying--

DR. LINDEN: You're just excluded, period.

MS. WIGMAN: Yes, we're just saying that there's no need--it's not appropriate to require blood products to--or transfusion services to undergo a separate quality standards and accreditation system for purposes of the Medicare

law, and that this was just an inadvertent mistake--as we have been told by Congressional staff. And they just think it's too minute of an issue for Congress really to deal with at this time; that we should just deal with the Agency on clarifying that this was a mistake.

But we do--as the blood banking and transfusion medicine community--think that it's important for the Agency to act in correcting this, just so that there's never a precedent down the road, where someone says, "Well, really, you're in competitive acquisition clause here, and why don't we apply it more broadly."

CHAIRMAN SKINNER: Dr. Haas?

DR. HAAS: I suggest we do the same with this motion as in the previous one, that we editorially get the right section number written in there so that when it's read, it's read in the context of the explanation.

I don't think we need to have that this moment. That can be added.

CHAIRMAN SKINNER: Is the committee

comfortable allowing the staff to fill in the relevant statutory cites?

[No response.]

CHAIRMAN SKINNER: Okay.

Any other discussion?

MR. HEALEY: I fully support this. I just note that the competitive acquisition issue kind of comes in at the very tail end there. I just didn't know whether you wanted--I know that's difficult to explain in sort of a preamble fashion because of the posture of that thing, but I just didn't know whether you needed any more context for it to make any sense to the Secretary, or whomever ends up reading it.

MS. WIGMAN: You could say something along the lines of, "Whereas, in the competitive--"--"--in competitive acquisition provisions of the MMA--"--or--"--a competitive acquisition section of the MMA--"--and then I can give you--at the very top, in the "whereas," and I can give you the appropriate statute's provision, but something along the lines of "Whereas, in the

competitive acquisition section of the MMA--"--and then I'd put in parentheses "Section" such-and-such-- "there is language that may require--".

Or you could just say--get rid of the "in" in the beginning. "Whereas a competitive acquisition section of the MMA contains language that may require--."

DR. HOLMBERG: But you'd want to put "Sec." here?

MS. WIGMAN: Yes--I can actually give it to you right now: Sec. 302. And then I think that would work.

CHAIRMAN SKINNER: Other discussion?

[No response.]

CHAIRMAN SKINNER: are we ready for a vote?

All those in favor, please raise your hand.

[Show of hands.]

The motion passes with 10 affirmative votes.

CHAIRMAN SKINNER: We have a fifth

resolution, relating to the CMS matters.

DR. SAYERS: Well, actually there was--the one I'm looking for was the resolution relating to platelet storage and shelf-life.

CHAIRMAN SKINNER: And we were. I was going to close out this part of the subject, and then I was going to move into what I thought would be the longer discussion, and spend the balance of the meeting on it.

Are there any other suggestions or recommendations coming out of the MMA or CMS presentations yesterday?

[No response.]

Okay. Then at this point we'll spend the balance of the meeting looking at what was the primary topic. And the committee's very thankful for Dr. Bowman's presentation from CMS. It actually was very helpful and helped the committee in making these recommendations. And we appreciate the time.

Okay. Just to get a sense of the committee--I know some committee members have

flight schedules, but just so we can think about how we want to move through this--are there committee members that have to leave before four o'clock or 4:30?

Before 4:30? Is there anybody that's leaving before 4:30? Anybody leaving before 4:00? At 4:30. Okay.

So we have about an hour. And there's been--the suggestion was made to simply work through the questions, or to attempt to start with a resolution. I know Dr. Sayers drafted a resolution which was up on the screen, which perhaps could move us to a conclusion. But I also know that Dr. Holmberg, the secretary, would like, you know, some specific response to some of the questions.

The adoption of the resolution actually would require a vote of the committee, and I want to be mindful of maintaining a quorum, ore we could--if for some reason we didn't have a quorum--actually discuss the questions.

Dr. Sayers, do you want to discuss your

resolution, and then we'll get a sense of the committee, how they want to process?

DR. SAYERS: Thanks. This was also in the tradition of a broad brush stroke. I think some of the agencies might feel understandably resentful if the committee came across with specific instructions. So this is how this one reads.

"Whereas our committee recognizes the importance of methods to reduce the risk of bacterial contamination in both apheresis and whole blood-derived platelets; and whereas the committee also recognizes the potential for limited availability of platelets, particularly whole blood-derived platelets, the committee encourages dialogue between the DHHS agencies, blood programs and manufacturers to ensure the prompt development of technology, design and completion of clinical trials, and satisfaction of licensing requirements to permit both the pre-storage pooling of whole blood-derived platelets and extension of platelet dating."

[Pause.]

Well, there's a conversation killer.

[Laughter.]

CHAIRMAN SKINNER: So--well, I'm just looking at--I was looking at the structure of the resolution. You have two "whereas" clauses, and then the actual recommendation starts midway down where--"the committee encourages."

DR. SAYERS: Criticisms about layout should be directed at Dr. Holmberg.

[Laughter.]

CHAIRMAN SKINNER: I mean, so there's two findings, and then there's an actual recommendation. Okay.

MR. HEALEY: Mark, I had a comment about that.

I just--I think it's, you know, very well worded and very well put together. I guess two things: one is, kind of be careful what you ask for, because if you ask for dialogue that may be all you get. And you maybe want something a little more concrete, in terms of action.

DR. HOLMBERG: Well, let me just go back

and reiterate what I said earlier, and that is that the intent of the agencies--and also Dr. Biato is, or was--for us to have this public forum, and then to move from this public forum into a roundtable discussion which will probably take the--we would like to work, definitely with the AABB's task force and bring the agencies together with the task force so that we can have this roundtable discussion--and make sure that we have a strategy. And that's one thing that Dr. Biato was very serious about, is that we do need to come down to the details of a strategy on how do we move this ahead.

CHAIRMAN SKINNER: Karen?

MS. LIPTON: I was actually going to suggest use of that word--"strategy"--in the second part: "--to ensure the development of a strategy that facilitates the prompt development--". I don't know what we can ensure, because we have to get the manufacturers to the table, too, and somebody has to want to invest in this.

But I really like the use of--Gerry's use of the term "strategies"--and "strategies," because

I think it's not just one strategy.

DR. HOLMBERG: So help me out there.

MS. LIPTON: I would say "--to ensure the development of strategies for the prompt--"--what is it?--"to facilitate the development of--"--I can't read this. I'm sorry. I can't read and talk here at the same time.

[Pause.]

It was "to facilitate the development of strategies to--"--where are we now?

"--development of strategies to facilitate the prompt--"--and I guess we need another word other than "development."

DR. HAAS: Well, can we take the first "development" out? I mean--it's the second development you want.

MS. LIPTON: Yes.

[Pause.]

Yes, it's got something grammatically funning going on there. But I guess--"To ensure strategies that facilitate--"--I don't know. Jean, you're out--

DR. KUEHNERT: Mark?

CHAIRMAN SKINNER: Dr. Kuehnert?

DR. KUEHNERT: Could I just get a little clarification? You mentioned the task force. Who is the task force composed of?

MS. LIPTON: In our--I think we mentioned earlier that we are putting together an AABB task force that includes a number of experts in the fields, and representatives of our committee. You actually have also been requested to be on that task force, although--

DR. KUEHNERT: So it includes government and non-government.

MS. LIPTON: Well, yes--and in speaking with--I think what Dr. Holmberg was suggesting that if we were to lead the initiative it would actually make it easier to have this dialogue, because you don't have to be concerned--or as concerned--about advisory committee rules. We can actually--we can have the task force and ask the government to join us at the table.

DR. KUEHNERT: Okay--yeah. I just wondered

about that, if we were saying, you know, form a group that would be separate from the task force. It sounds like what we're saying is that it could be the task force. But--

MS. LIPTON: I don't think we want to mention the task force in there. I just think we just want to say we want to have a dialogue.

DR. KUEHNERT: Right. Right. Right. But that's what we're thinking, is that it would be. Is it, in reality, that's what we're thinking, is that it would--it could--what we're asking for here could essentially be what you're talking about.

MS. LIPTON: It could, if you would answer the letter and come to the meeting [laughs].

[Laughter.]

MS. LIPTON: If you'll accept.

DR. KUEHNERT: The other concern I had echoed the earlier sentiment about "encouraging dialogue." And that's sort of--you know, there's--well, even just about the dialogue, there's nothing in here about public health concerns that I saw. There is "development of

technology," there is "design and completion of clinical trials," and there's "satisfaction of licensing requirements."

So we've got the, you know, "develop new methods," and "clinical trials," and regulatory stuff, but we don't have the issues on, you know, public health in there.

MR. HEALEY: [Off mike.] It's in the first "whereas" isn't it?

DR. KUEHNERT: Ahh--the first "whereas?"

MR. HEALEY: I read the first "whereas" as to kind of cover the public health issue, there. It's--you know, it's implicit that the importance of it is a public health--maybe if you add those words up there you cover it.

DR. HOLMBERG: But I think--not to put words in Dr. Kuehnert's mouth--but I think where he's going is with the donor and recipient notification, and some of those issues that were addressed earlier.

DR. KUEHNERT: I mean, I think people are going to, hopefully--you know, maybe I'll be an

optimist and say everyone's going to do the right thing because we've asked, you know, numerous speakers, you know, "What about organism speciation?" And the answers were either, "Yes, not right now," or "We're thinking about it." And so I just didn't know if the committee wanted to have a little bit stronger push for including some things that they thought were important for public health or not.

Certainly, you know, it would be couched in that--again, that it's under the "encourages dialogue" about it, rather than, you know, prescribing something. But I just wondered if that--

CHAIRMAN SKINNER: Perhaps, Dr. Kuehnert, if you want to try to craft a few words, and I can come back to you in a moment--

DR. KUEHNERT: Okay.

CHAIRMAN SKINNER: --and then we can add it to the action part of the recommendation?

DR. KUEHNERT: Okay.

CHAIRMAN SKINNER: Or we can stay on this

topic and discuss it, or--

MS. LIPTON: Well, I actually wanted to respond, because I would not like to see an issue like that at this point. I don't think we have any idea--and I think we are still in a fact-finding mode, even in terms of the operation of these tests and what we're going to find. And I don't want to put the cart before the horse, and have everyone establishing a donor notification and a whole bunch of policies around this before we even have tests that we even understand what we're looking at.

So I--this is something that I think naturally falls out of that, but I think our most important thing is coming up with a reliable method, specifically to test whole blood-derived platelets.

DR. KUEHNERT: I think what I was getting at was not exactly seeing even the words "organism identification." I mean, more saying that there should be minimal criteria to allow for adequate quality control and public health interests, basically. I mean, I wasn't even necessarily

suggesting that we even go as far as describing specific things.

But maybe it doesn't need to be there. I don't know.

CHAIRMAN SKINNER: Dr. Linden?

DR. LINDEN: Yes, I mean, I'm not clear on what we're trying to do with this entire resolution. And I think we have a difference of opinion. That's why Dr. Kuehnert is coming up with certain issues that are really different from what's in there.

I mean, I think whoever wrote this is addressing certain issues that are perceived to perhaps have barriers right now that can be addressed by the agency, versus--I think Dr. Kuehnert is coming up with issues that he's hearing are things that are not perhaps adequately being addressed by the blood agency that, you know, maybe more could be done there from a public health perspective as opposed to necessarily done by HHS.

And--you know, I think we need to figure out what we're doing here. And my perspective,

reading this, is it's not clear to me whether the reference to development of "technology" is, in general, technologies to facilitate testing of whole blood platelets, technology to facilitate bacterial detection of platelets in general, or--the first time I read this, I thought it was specifically referring to the last two items: the pre-storage pooling of whole blood-derived platelets and the extension of platelet dating. I thought it was focusing only on those two items.

So I think it needs to be clarified, regardless. And, unfortunately, I'm one of the early leavers, so I'm not going to be able to participate in a lot of word smithing.

But I think, one, our purpose needs to be clarified and then, secondly, the wording really needs to be clarified, because I think it's open to interpretation as to what is really meant by this. Are we intending to mean, broadly, that the agency should facilitate various technologies, or are we focusing only on these two as specific things that have been identified, you know, clearly during this

meeting as issues.

CHAIRMAN SKINNER: And, obviously, it's the committee's pleasure what kind of recommendation they want to make. I think that was why Dr. Holmberg had perhaps suggested that we work through the questions and answer them.

I think--we don't have to pass any resolution unless there are specific things that we're looking for action on at this point. If what the Secretary is looking for at this point is some guidance, and our conclusions on these questions is they move forward into the task force, then we could operate by consensus without actually crafting a resolution as to what our sense is on these answers. Because there's clearly items that were on this list of questions that aren't covered in this resolution. And whether or not it's our intent to jump to the end, reach the conclusions and package everything, and say these are the things that we're ready to recommend on, or whether we need to go through them piece by piece.

And there were certainly presentations

that were made on subjects that questions weren't asked on; you know, including the public health aspects.

I'm at somewhat of a loss on which direction the committee wants to go: if we want to continue on this vein, I'm happy to do it. We probably won't get through all the questions, but I don't know which is most important.

DR. SAYERS: Let me just respond to Dr. Linden before she goes.

I came away with, I think, four messages. We can't discount the value of whole blood-derived platelets. We could be facing shortages of platelets in general. We need to be looking at pre-storage pooling. And we also need to be looking at prolonging the shelf life. And all this recommendation was meant to do was address specifically that.

You know, I think, as a blood bank, I look to AABB for the sort of other issues that have to do with are you going to identify the organism? What are you going to be telling the blood donor?

What do you do with the other products?

This was just meant to be a broad brush stroke.

CHAIRMAN SKINNER: Karen?

MS. LIPTON: I'd really like to echo what Merlyn said. I mean, I was--I understand that we may want to answer these questions, but I would submit to you that we don't have enough data to answer these questions.

I think what we consistently heard was that there are availability issues, and that those availability issues can be somewhat addressed by those two strategies, and that we currently do--and I hate to say this--but we do have barriers to this at the FDA level. We do need some creative thinking about how we're going to design studies that allow us to sort of have a rational different approach to getting some of these strategies licensed.

I think much of the other data will fall out, and much of the other things that we need to do.

This is a critical need now. I think it's perfectly appropriate to revisit some of these issues the next time the committee meets. We'll have a much better handle on what's going on out there. But it's premature for us to jump in any other direction, other than the four--I mean, I absolutely agree. I heard the same thing that Merlyn heard over and over and over again. And that's what the critical need right now is to address those two pieces.

CHAIRMAN SKINNER: Other comments?

Dr. Lopez.

DR. LOPES: Does this commit us to the particular clinical trial strategy we've been hearing about that would require the 50,000 to a million data points?

[Comment off mike.]

DR. HOLMBERG: Let me just comment on that.

I think that, you know, we from the government have heard a lot of information. I think that we also need to be able to go back--all of the agencies of HHS--to go back and to talk

about this, and then to reconvene with the task group to be able to work out the details.

So, you know, I don't think anybody can give you that answer today, whether things are going to be changed. But, definitely, we have heard comments, and we will take those comments.

MR. WALSH: I think this recognizes the importance. I think it identifies a vehicle to take the next step. And it's specific enough for a resolution right now. And if we want to do another resolution more specific to data points, then make that another resolution. But I think this resolution spells it out: we need the government to work with industry, to work with the blood banking community, to get it done. And we need to state that.

CHAIRMAN SKINNER: Dr. Linden?

DR. LINDEN: Yes, it's helpful. Because when I read this, I thought the focus was only on those two issues. So that's the way I first read it. But it has not been clear to everybody.

It might be helpful to add either another

"whereas," or to one of the existing "whereases," that the current shelf-life and lack of availability to pool pre-storage is--you know, are current issues that have been identified by the committee; you know, to make it clear that we're identifying and referring to those two issues. That might help make things clearer.

You also might consider, in referring to the clinical trials, putting in the word "feasible"--you know, "completion of feasible clinical trials." Because I think the issue came up that what's been proposed is not feasible. A possible suggestion there.

Otherwise, I agree. I think this is very appropriate to focus on these two issues. And I think it does say what we want to say.

DR. HOLMBERG: Does somebody want to draft that third "whereas?"

DR. LINDEN: "--and inability to pool platelets prior to storage has been identified as--

COL. SYLVESTER: "--as barriers to--"--you know--ahh-- "--the wholesale use of bacterial

detection methodologies--"--or there are barriers--or cost effective--

MS. LIPTON: "--the effective implementation of--"

COL. SYLVESTER: Yes--"--full scale implementation, particularly for whole blood-derived platelets"--because that seems to be the biggest challenge.

CHAIRMAN SKINNER: Dr. Angelbeck?

DR. ANGELBECK: Just a comment. I would concur with Karen that if you look at the questions, this was just implemented a short while ago--perhaps less than 30 days ago. And I do not think that there is sufficient data to really answer these questions. I think that that needs to come back to the committee after a longer period of implementation, where we can see the response to this.

I would concur with this resolution. And the only other thing I would emphasize is, as a manufacturer, the sooner the manufacturers can participate in the process the better. And we

would certainly welcome that opportunity.

CHAIRMAN SKINNER: Karen?

MS. LIPTON: Can I just offer one small, also word, amendment? In the third "whereas," we talk about "have been identified as barriers to implementation." We actually have had implementation. I think we want to say "barriers to the optimal implementation." Because people have implemented by using dipsticks, glucose--the optimal implementation is a culture method.

CHAIRMAN SKINNER: Other comments? Suggestions?

MS. LIPTON: That's "optimal" not "optimum."

DR. HOLMBERG: Oh--sorry.

MS. LIPTON: That's okay. No, I mean, that's why I said it. It's fine.

DR. HOLMBERG: It's like being at the blackboard and everything goes blank.

DR. SAYERS: Can I just go to the screen and point to Gerry where two "the"s are needed?

DR. LINDEN: And it should be "whole

blood-derived platelets."

DR. HOLMBERG: What is this now?

DR. LINDEN: In the third "whereas." Right--because we're talking about whole blood-derived platelets here.

[Pause.]

DR. HOLMBERG: And--Jeanne? Where?

DR. LINDEN: In the third "whereas," the last couple words: "whole blood-derived platelets."

[Pause.]

DR. LINDEN: Just say "platelets." Forget "products." We actually don't like to use the word "products." They're actually components.

CHAIRMAN SKINNER: Other questions? Comments?

DR. LINDEN: Can I vote yes before I go?

[Laughter.]

DR. HOLMBERG: Thank you, Dr. Linden.

DR. MIDTHUN: Gerry, maybe I'm just confused, but that third "whereas"--"whereas the current five-day shelf-life and inability to pooled platelets pre-storage"--I think something is

missing there, or--

VOICE: [Off mike.] How about "restrictions on pre-storage pooling," rather than "inability?"

DR. MIDTHUN: Yes, I think that would be better. Yes.

CHAIRMAN SKINNER: Dr. Kuehnert?

DR. KUEHNERT: I know we're word-smithing here, but I just want to bring up two other broad concepts. One is the importance to monitor; whether anybody wanted to add any language to that effect, that there's a need to monitor availability while this implementation is going on.

And the other is about cost issues. But, you know, I'll leave that to voting members of the committee to decide whether those are necessarily elements.

CHAIRMAN SKINNER: One option to address that would be simply to have this put back on the agenda for the next meeting. And if we learned some new data at that point, we could obviously amend the recommendation.

MS. LIPTON: And we will commit--we will

maintain our study. You know, we have a survey document out there, and we will periodically run that. We can bring back new data.

CHAIRMAN SKINNER: And other questions or comments--from committee members first?

MR. HEALEY: I think Karen point out earlier, there's something a little hinky about the language there in the last paragraph: "To ensure strategies to facilitate the prompt--"--something doesn't quite work there. I don't be a stickler about it, but there might be a better way to phrase it.

MS. LIPTON: I would suggest "Ensure strategies that facilitate," or "which facilitate," as opposed to "to."

VOICE: [Off mike.] Shouldn't it be "build strategies" or something like that? Rather than "ensure."

MR. HEALEY: The point is that you want dialogue that's going to result in strategies--right? I mean, that's the--and there's sort of like no verb there. There's a verb

missing, I think.

DR. SAYERS: You know, we could get around this by having "to ensure" then bullet "strategies that facilitate," then bullet "design and completion of feasible clinical trials," and then bullet "satisfaction of licensing."

MR. HEALEY: Okay--wait. Go back again? To--bullets where?

CHAIRMAN SKINNER: Colon after "ensure," and then a bullet, an then create three bullets.

DR. SAYERS: Yes.

MR. HEALEY: I don't think that's right. I think it's "to ensure strategies that" --"that," colon, bullet, "facilitate the prompt development--"--

CHAIRMAN SKINNER: Could you go to the screen and point again, please?

[Pause.]

CHAIRMAN SKINNER: We're going to lose a quorum very quickly. So I want to make sure that everybody's had their change.

I know there were two quick comments.

Mike, did you have something that you needed to--that you wanted to add for a clarification?

DR. FITZPATRICK: Mike FitzPatrick, and thanks for recognizing me, Mark.

I just would suggest that the committee put something at the end of this--a last bullet or something--to say something about research and development of other methods, and not imply that this is the be-all and end-all if this is completed.

CHAIRMAN SKINNER: What's the pleasure of the committee? Is there agreement to add a catchall phrase encouraging other research and development?

[No response.]

CHAIRMAN SKINNER: Perhaps someone could craft some language quickly.

And I believe there was someone else that had a comment--yes. Steve?

DR. WAGNER: Thanks for recognizing me. Steve Wagner, Red Cross.

I'd like to somehow improve the third

whereas to be able to include apheresis platelets with the extension of the storage time from five to seven days.

CHAIRMAN SKINNER: Can you put it at the end there?

[Pause.]

MS. LIPTON: We would--I think that's right. We were just talking about that. We do need to--it does need to platelets--pheresis, too, or single-donor.

And I think we have a potential fix to that little thing that's going on in the end.

CHAIRMAN SKINNER: Okay. So staying the pheresis--stay on the pheresis for a moment, which is where he's crafting.

MS. LIPTON: Under the third--"detection in whole blood-derived--"--oh, I see. So, what did you say?--"--and extend the shelf life of--"--I don't know what--this is factual, Mark. Help us out, here.

[Pause.]

MS. WIGMAN: I still think, actually, it's

a barrier to the optimal implementation, because--and it affects the availability of--

VOICE: [Off mike.]--instead of--actually word-smithing--instead of putting it down here, why don't you just put parentheses "single-donor apheresis and whole blood-derived platelets"--[inaudible]--shelf life.

Clinical trials--sometimes [inaudible]

MS. LIPTON: And one other thing, to address Mike's issue, perhaps we could say "facilitating the prompt development of technologies"--you know--understanding that we may have totally different approaches to this issue that we would be interested in exploring.

CHAIRMAN SKINNER: And so the only other item that's not yet captured was the suggestion to change the reference to clinical trials to "studies?" Or "clinical trials and studies?" "And/or"?

MS. LIPTON: "Completion of studies and feasible clinical trials" maybe.

VOICE: [Off mike] [inaudible].

CHAIRMAN SKINNER: What's the committee's--"-studies and--"--?

VOICE: [Off mike] [inaudible].

CHAIRMAN SKINNER: Any other substantive comments or issues at this point?

DR. GOMPERT: Are we sure the third "whereas" is correct?

MS. LIPTON: Yes, and then in the "whereas," instead of there, we could just say "in platelets"--or just "in platelets," I guess--right? We don't have to say--

COL. SYLVESTER: It would be "restrictions on pre-storage pooling of whole blood-derived platelets" and then at the end you could just say "platelets."

MS. LIPTON: Okay.

COL. SYLVESTER: Because it's the five-day shelf-life on both, and the fact that we can't do pre-storage pooling on whole blood-derived.

VOICE: [Off mike] [inaudible].

CHAIRMAN SKINNER: In Item 3, after "the detection." Period.

Any other edits? Corrections? New issues?

Dr. Haas?

DR. HAAS: Again, a really minor thing: the first bullet, to have parallel structure it should read, "The facilitation of--"--instead of a gerund there.

DR. HOLMBERG: Where is this?

DR. HAAS: First bullet: "The facilitation of--"--you just can take out "the."

DR. HOLMBERG: But is that third "whereas" correct? Yes?

CHAIRMAN SKINNER: Other comments?

COL. SYLVESTER: You can either "apheresis and whole blood" in parentheses, or you could just say "five-day shelf life of apheresis and whole blood-derived" and take the parentheses off.

CHAIRMAN SKINNER: And delete the--at the end.

Chris, did you have a comment?

MR. HEALEY: It should be dialogue "among" not "between."

VOICE: [Off mike] [inaudible].

CHAIRMAN SKINNER: Other comments? Questions? Has the committee had a chance to read it?

[Laughter.]

Are we ready for a vote? All those in favor, raise your hand.

[Show of hands.]

The resolution passes. Eight affirmative votes--unanimously.

MR. HEALEY: Mark, I think you need to ask for abstentions.

CHAIRMAN SKINNER: Oh, I'm sorry. Abstentions?

DR. BRECHER: [Raises hand.]

Dr. Brecher will be recorded as abstaining.

Do we need to vote again?

MS. LIPTON: Yes, maybe you should vote again. I'll abstain.

CHAIRMAN SKINNER: We're going to vote one more time?

VOICE: Do we have a quorum?

VOICE: Quick before I leave.

CHAIRMAN SKINNER: Yes.

[Laughter.]

All those in favor, raise your hand.

[Show of hands.]

CHAIRMAN SKINNER: Seven affirmative votes.

All those opposed?

Abstentions?

[Show of hands.]

CHAIRMAN SKINNER: Karen Lipton and Mark Brecher recorded as abstaining. So the motion passes unanimously.

Any other--we don't have a quorum, we can't transact any additional business, but we can certainly have comments.

Dr. Lopes?

DR. LOPES: I just wanted to suggest that we plan on another--on touching this on another meeting, both as concerns the information that will be coming into existence over the next few months, and also the public health aspects of the problem.

DR. HOLMBERG: Thank you. I'll take those for consideration for the next meeting, which will be in August--I believe it's the--it's the end of August. It's on the website.

Also, the next meeting will be located at the other Hyatt. We lost this one for the August meeting but, hopefully, we'll be back to this one for the next year.

Also, at the August meeting we will give you the dates of all the meetings fro the next fiscal year, so everybody can get those on their calendars.

CHAIRMAN SKINNER: Colonel Sylvester?

COL. SYLVESTER: If the meeting's going to be at the end of August then I need to inform the committee that I will be retiring and I will be replaced by Commander Michael Libby, who will be taking over as director of the Armed Services Blood Program on August 15th.

CHAIRMAN SKINNER: Well, thank you very much.

Any other discussion?

DR. HOLMBERG: Can I make one comment?

CHAIRMAN SKINNER: Dr. Holmberg.

DR. HOLMBERG: Okay. I want to thank you all for going through the last two days of this issue. And Dr. Biato appreciates all your comments. Clearly, there has been a data cap, and we really appreciate the information.

I also want to thank my staff for all the hard work they've done in getting this meeting going. And if you feel likewise, please let them know that you appreciate their hard work.

Also, you'll notice that there is a Lieutenant Commander Hemry that's been floating around here--up here at the podium. And he is newly promoted to Lieutenant Commander from Lieutenant. So you--yes the stripes are eight days old.

[Applause.]

CHAIRMAN SKINNER: Thank you. The committee is adjourned.

[Whereupon, at 4:15 p.m. the meeting was adjourned.]